The effect of stress, FKBP5 gene methylation and immune factors on Psychiatric Phenotypes of patients with 22q11DS

by

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To Asiye Gültekin İzgi, my mother,
will always be with me.
Thank you for helping me become who I am…
To my father, Fatih İzgi, who has endless love and support for me.
To my husband, Samet Ağca, who taught me what love is.
To my nephew, Ela Duru, who has endless love and makes me Vavaa.
To my sisters, Begüm and Betül, amazing sisters more than I could ask for.

ABSTRACT

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22q11.2 deletion syndrome (22q11.2DS) is a disorder that is associated with many psychiatric disorders and has been the focus of studies on copy number variations (CNV). The present study aims to investigate the lifetime stress factors and the epigenetic mechanisms of psychiatric phenotypes in individuals diagnosed with 22q11.2DS, in order to shed light on the gene-environment interaction on psychiatric phenotypes. 32 individuals (17 patients with 22q11.2DS and 15 matched controls) participated in the study. Structured clinical interview for DSM-5 (SCID-5), self-report psychopathology and stress scales, and The Stress and Distress Inventory (STRAIN) were used to evaluate psychiatric symptoms and stress levels throughout the participants' lifetime. Cognitive performance of the participants was measured with The Pennsylvania Computerized Neurocognitive Battery (PennCNB) and The Probabilistic Reward Task (PRT). For biological biomarkers, immune factors (C-Reactive Protein level, total white blood cell (WBC) counts, lymphocyte, neutrophil counts, and neutrophil- lymphocyte ratio) were measured. PBMC samples were used to analyze the methylation level at the cg00130530 region with using pyrosequencing method. Our results revealed that there was a high prevalence of anxiety disorders in the 22q11.2DS population. Participants with 22q11.2DS had lower performance in PennCNB (depending on the overall summary score for battery), episodic memory, and social cognition than control groups. They had also lower discriminability score but not difference in response bias in PRT task. When evaluated in terms of immune factors, only lymphocyte cell count was found to be lower in the 22q11.2DS population. They had significantly lower methylation levels at the promoter-associated region, but neither the effect of stressors nor the cg00130530 methylation was found to be associated with the development of psychiatric phenotypes. The methylation level of cg00130530 in the 22q11.2DS population was correlated with legal/crime stressors. It was observed that CNV on chromosome 22 plays a significant role in the determination of psychiatric phenotypes instead of psychological stressors. For future research, additional FKBP5 gene methylation regions, genetic variations, and complex stressor variables (type x count x severity x duration) should be analyzed.

ÖZETÇE

22q11.2 Delesyon Sendromlu Hastalarda Psikiyatrik Fenotip üzerinde Stres, FKBP5 Gen Metilasyonu ve İmmün Faktörlerin Etkisi
Büşra İzgi
Sinirbilim Doktora Programı
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22q11.2 delesyon sendromu (22q11.2DS), birçok psikiyatrik bozuklukla ilişkili olan ve kopya sayısı varyasyonları üzerine yapılan çalışmalara öncülük eden önemli bir bozukluktur. Bu çalışma, 22q11.2DS teşhisi konan bireylerde yaşam boyu stres faktörlerini ve psikiyatrik fenotiplerin epigenetik mekanizmalarını araştırmayı amaçlamaktadır. Çalışma, bu şekilde psikiyatrik fenotipler üzerinde gen-çevre etkileşimine ışık tutacak bulgular sağlamaktır. 32 kişi (22q11.2DS'li 17 hasta ve 15 eşleştirilmiş kontrol) çalışmaya katılmıştır. Yaşamları boyunca görülen psikiyatrik semptomlarını ve stres düzeylerini değerlendirmek için DSM-5 için yapılandırılmış klinik görüşme (SCID-5), psikopatolojik ve stres öz bildirim ölçekleri ve Stress and Distress Inventory (STRAIN) kullanıldı. Katılımcıların bilişsel performansı Pennsylvania Computerized Neurocognitive Battery (PennCNB) ve Probabilistic Reward Task (PRT) ile ölçüldü. İmmün faktörler de (C-Reaktif Protein düzeyi, toplam beyaz kan hücresi (WBC) sayısı, lenfosit, nötrofil sayıları ve nötrofil-lenfosit oranı) incelendi. PBMC örnekleri ile cg00130530 alanındaki metilasyon seviyesi, pyrosequencing kullanılarak analiz edildi. Sonuçlarımız 22q11.2DS popülasyonunda anksiyete bozukluklarının yüksek bir prevalansı olduğunu gösterdi. 22q11.2DS'li katılımcılar, PennCNB'de (pilotta toplam özet puanına göre), episodik bellek ve sosyal bilişsel performans bakımından kontrol gruplarından daha düşük performans gösterdiler. PRT görevinde discriminability puanları daha düşük olmasına rağmen response bias'de farklılık yoktu. İmmün faktörler açısından değerlendirildiklerinde sadece lenfosit hücre sayısı 22q11.2DS popülasyonunda daha düşük bulundu. Promotörle ilişkili bölgede önemli ölçüde daha düşük metilasyon seviyelerine sahiptiler, ancak ne stres faktörlerinin etkisi ne de cg00130530 metilasyonunun psikiyatrik fenotiplerin gelişimi ile ilişkili olduğu bulunamadı. 22q11.2DS popülasyonundaki cg00130530'un metilasyon seviyesi, yasal/suç stres faktörleriyle ilişkilendirildi. Psikiyatrik fenotiplerin belirlenmesinde çevresel psikolojik streslerden ziyade kromozomdaki kopya sayısı değişikliğinin rolünün oldukça yüksek olduğu gözlemlendi. Gelecekteki perspektifler için, ek FKBP5 gen metilasyon bölgeleri, genetik varyasyonlar ve kompleks stres etkeni değişkenleri (tip x sayı x şiddet x süre) analiz edilmelidir.

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ABBREVIATIONS

₺	Turkish Lira
22q11.2DS	22q11.2 deletion syndrome
ACTH	Adrenocorticotropic hormone
ADHD	Attention Deficit Hyperactivity Disorder
ANS	Autonomic nervous system
APR-DRG	All Patients Refined Diagnosis Related Groups Severity of illness
AR	Androgen receptor
ASD	Autism spectrum disorder
ASRS	Adult ADHD Scale
BAI	Beck Anxiety Inventory
BD	Bipolar Disorder
BDI	Beck Depression Inventory
BPRS	Brief Psychiatric Evaluation Scale
CNV	Copy Number Variation
CPF	Penn Facial Memory Test
CPFD	Late version of face memory test
CPT	Penn Continuous Performance Test
CRH	Corticotropin-releasing hormone
CRHBP	Corticotropin-releasing hormone binding protein gene
CRHR1	Corticotropin-releasing hormone receptor 1
CRHR2	Corticotropin-releasing hormone receptor 1
CTAP	Computerized Finger Tapping Test
CTQ	Childhood trauma Questionnaire
ER	Estrogen receptor
ER-40	Emotion recognition task
FKBP5	FK506 binding protein 51
FSIQ	Full Scale Intelligence Quotient
GABA	Gamma-aminobutyric acid
GAD	General anxiety disorder
GC	Glucocorticoid

GR	Glucocorticoid receptor
GRE	Glucocorticoid response element
GxE	Gene x Environment Interaction
HPA	Hypothalamic-Pituitary-Adrenal
IQ	Intelligence Quotient
kb	Kilobase
LNB	Letter-And-Back task
MNP	Major neurocognitive psychosis
MR	Mineralocorticoid receptor
MSPSS	Perceived social support scale
NLR	Neutrophil-to-lymphocyte-ratio
NR3C1	Nuclear Receptor Subfamily 3 Group C Member 1
NR3C2	Nuclear Receptor Subfamily 3 Group C Member 2
OCD	Obsessive-compulsive disorder
PBMC	Peripheral Blood Mononuclear Cell
PCET	Conditional exclusion task
PennCNB	Pennsylvania Computerized Neurocognitive Battery
PNS	Parasympathetic nervous system
PR	Progesterone receptor
PRS	Polygenic risk score
PRT	Probabilistic Reward Task
PSS	Perceived stress scale
PTSD	Post-traumatic stress disorder
PVN	Paraventricular nucleus of hypothalamus
SAD	Social anxiety disorder
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SCID-5	Structured Clinical Interview for DSM-5
SCL-90	Symptom checklist-90
SCZ	Schizophrenia
SHR	Steroid hormone receptors
SIPS	Structured Interview for Psychosis-Risk Syndromes
SNP	Single Nucleotide Polymorphism

SNS	Sympathetic nervous system
STRAIN	The Stress and Distress Inventory
SVOLT	Visual object learning task
SVOLTD	Late version of visual object learning tasks
TD	Typical developing
TSS	Transcription start site
UHR	Ultra high-risk for psychosis
WHODAS	World Health Organization Disability Assessment Schedule short self-report form
WISC-IV	Wechsler Intelligence Scale for Children – Fourth Edition

Chapter 1

INTRODUCTION

1.1.22q11.2 Deletion Syndrome

Copy Number Variations (CNV) are submicroscopic genetic variations. The length of these submicroscopic genetic variations can be 1 kilobase (kb) or more, and the number of variations may differ (Almal & Padh, 2012). These variations are caused by various mechanisms such as deletion, duplication, translocation, and the addition of specific chromosome regions (Almal & Padh, 2012). These changes can affect the gene expression level in specific regions, thereby increasing or decreasing transcription levels (Hastings et al., 2009). In addition, extra copies of genes may affect the gene expression and mechanisms and functioning as well.

Phenotypes of individuals with copy number variations may depend on the gene expression dose change and their effects on regulatory mechanisms (Almal & Padh, 2012; Giovanoli et al., 2019). In addition, environmental factors may play an important role in determining the phenotypes of individuals (Almal & Padh, 2012; Giovanoli et al., 2019). Carrying more than one CNV, having homozygous or heterozygous deletions, ethnic origins, and stressful events are good determinants for diagnosis (Girirajan et al., 2012; Nowakowska, 2017).

As one of the significant phenotypes related to CNVs, being a CNV carrier was associated with many psychiatric disorders such as autism, schizophrenia, bipolar disorder, and major depression (Consortium, 2008; Ingason et al., 2011; Malhotra et al., 2011; O'Dushlaine et al., 2014; Szatmari et al., 2007). Phenotypes of complex diseases can occur due to disorders in genes with a large effect size, as copy number variations, as well as the combination of many genes with a narrow effect size. In CNVs, a large number of candidate neurodevelopmental genes may play a role in forming these patients' phenotypes (Jensen & Girirajan, 2019).

Thanks to the developing genetic detection methods, the importance of CNVs on the phenotype is better understood (Nowakowska, 2017). Although some individuals with

a copy number variation may show no abnormal phenotype, 15-20% of children with unexplained mental disability, developmental delay, and congenital anomalies have pathogenic CNVs. Another group of CNV carriers may show no abnormal phenotype in childhood but may develop other disorders, such as Parkinson's disease or schizophrenia, in adult life (Nowakowska, 2017). Understanding the determinants of different phenotypic presentations in this context is important.

The major specific copy number variations strongly linked with neurodevelopmental disorders, can be listed as follows: 1q21.1, 2p16.3, 3q29, 7q11.23, 9q34.3, 15q11.2, 15q11-13, deletions and copies, 15q13.3, 16p11.2 (breakpoint 4-5), 16p11.2 distal, 16p13.11, 17q12 and 22q11.2.

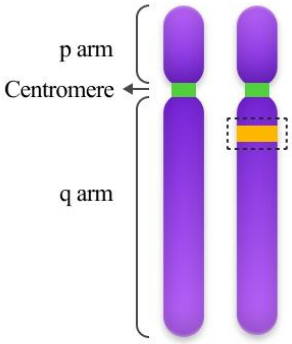

Figure 1.1. Chromosome 22 (Adapted from (McDonald-McGinn et al., 2015)

An approximately 1.5–3 million base pairs (Mb) in size hemizygous microdeletion on the long arm (q) of chromosome 22 causes the 22q11.2 Deletion Syndrome (22q11DS; OMIM #192430), also known as DiGeorge Syndrome (OMIM #188400) (Figure 1).

22q11.2 Deletion Syndrome is a neurogenetic disorder that Dr. Angelo DiGeorge first explored (DiGeorge, 1965). The 22q11.2 deletions were discovered as the most prevalent reason of DiGeorge syndrome in the early 1990s by FISH investigations utilizing probes inside the often-deleted region (Scambler et al., 1991). This technique simplifies detecting copy number variations and correlates patients' genotypes and phenotypes. 22q11.2DS was found responsible for several disorders with seemingly unrelated phenotypic characteristics, such as; conotruncal anomaly face syndrome, velocardiofacial syndrome, subgroups of people with Opitz G/BBB and Cayler cardiofacial syndromes (Giannotti et al., 1994; Kinouchi, 1976; Shimizu, 1984; Takao, 1980).

Regarding the prevalence, with an estimated frequency of 1 per 4,000 live births, 22q11.2 DS is one of the most prevalent deletion syndromes (Jonas et al., 2014). In

addition, studies carried out between the early 1990s and the early 2000s, in which few population screening utilizing FISH technology with a diagnosis of newborns with serious birth abnormalities, the incidence of this condition has been reported to vary between 1 in 3,000 and 1 in 6,000 live births (Botto et al., 2003; Devriendt et al., 1998; Goodship et al., 1998; Oskarsdottir et al., 2004). According to literature, there is considerable uncertainty about the prevalence of 22q11DS due to (Hacıhamdioğlu et al., 2015; Kobrynski & Sullivan, 2007) likely underreporting in the studies. The fact that familial incidence is one of the most common reasons for adult diagnoses in many genetic centers can be shown as a finding supporting that the incidence rate may be higher than the stated rate (Vogels et al., 2014). Clinical phenotypes can vary, and people without congenital heart defects frequently experience a delay of several years before their diagnosis is given. Clinical referral is an important factor in determining the incidence of the disorder, as patients are directed to research by clinical referral, but patients with unusual or limited phenotypes may be unnoticed in clinics. Although the deletion is mostly a de novo mutation, it can be inherited in an autosomal dominant manner. Nearly 8% to 28% of mutations are believed to be inherited from a parent, according to estimates from a small number of studies that examined asymptomatic parents for the mutation's existence (Digilio et al., 1997; McDonald-McGinn et al., 1999; Ryan et al., 1997).

There is no difference about the incidence of the disorder in different biological sexes. With considering ethnic groups, 22q11.2DS is observed in Hispanics more than other ethnic groups (Asians, African Americans, and Caucasians) (Kobrynski & Sullivan, 2007). 22q11.2 region has large blocks of identical low copy repeats (LCRs) and it makes structurally complex region and vulnerable to meiotic error (Babcock et al., 2003; Bailey et al., 2002; Edelmann, Pandita, & Morrow, 1999; Saitta et al., 2004; Shaikh et al., 2000). There are four types of LCRs; LCR22A, LCR22B, LCR22C and LCR22D. Deletion occurs with de novo mutations during fetal development mostly and it can be also inherited in an autosomal dominant manner. During fetal development, non-allelic homologous recombination between LCRs causes the 22q11.2 deletion syndrome (Donna M McDonald-McGinn et al., 2015). According to LCRs in homologous recombination,

phenotypic features may vary. Affected genes and the related LCRs in the 22q11.2 deletion are seen as in Figure 2 (Donna M McDonald-McGinn et al., 2015).

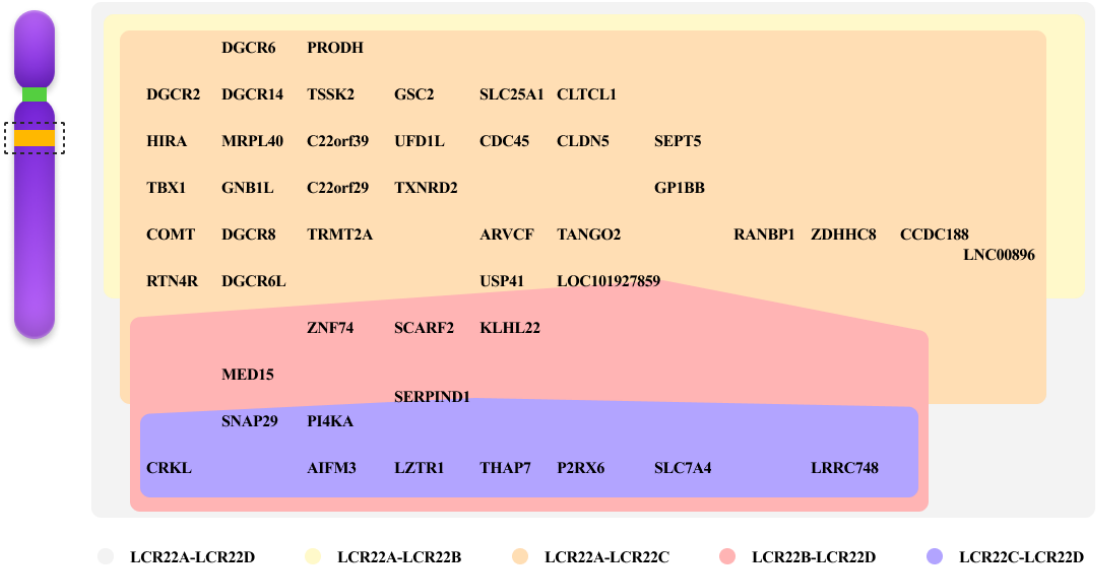

Figure 1.2. Affected genes in the 22q11.2 deletion (Adapted from (McDonald-McGinn et al., 2015))

Genes in LCRs in q arm of the chromosome 22 are affected by deletion. It has been observed that Tbx1 from these region plays an important role in cognitive and behavioral disorders (Paylor et al., 2006). The thymus and parathyroid glands, as well as the development of the face and neck's bone structure and major arteries that transport blood away from the heart, are all influenced by TBX1 gene (Cortés-Martín et al., 2022).

In the study, the behavioral manifestations of ASD caused by constitutive heterozygosity of the 22q11.2 gene Tbx1, level of mRNA and protein were investigated in animal model, researchers showed that TBX1 gene may be reason for the ASD phenotypes in 22q11.2 (Hiramoto et al., 2011). In line with that, the gene interaction-based machine-learning classifier found top 10% of all genes to be linked with autism included 4 genes within 22q11.2 (Krishnan et al., 2016). DGCR8, another gene region that has been subjected to deletion, has been observed in the development of

neuropsychiatric diseases and related phenotypes associated with 22q11.2 deletion (Brzustowicz & Bassett, 2012; Earls & Zakharenko, 2014).

The COMT gene encodes for catechol-O-methyl transferase, which breaks down catecholamines (epinephrine, norepinephrine, and dopamine). In the literature, the relationship between a common polymorphism of the COMT gene associated with variable enzyme activity and cognitive mechanisms and schizophrenia has been investigated. There are controversial findings about this relationship in the studies with adult patients (Bassett et al., 2007; Gothelf et al., 2013; Murphy et al., 1999). The importance of the COMT gene is also associated with changes in expression level depending on the gene's activity in the prefrontal cortex (Donna M McDonald-McGinn et al., 2015).

RANBP1 gene is examined about 22q11.2DS-related diseases due to its role in the neurogenesis mechanism in cortical networks; examples include attention deficit disorders, autism, and schizophrenia (Meechan et al., 2015).

PRODH encodes the enzyme proline dehydrogenase, which degrades proline. Pathogenic mutation in the gene can cause increasing the proline levels (Goodman et al., 2000). High level of proline can cause convulsions and intellectual incapacity in extreme cases (Magnee et al., 2011; Paronett et al., 2015; Raux et al., 2007; Vorstman et al., 2009). In the 22q11.2DS population, proline levels are elevated in around one-third of patients. There are some contradictory results for the relation between proline level and some indicators for schizophrenia and intellectual disability (Philip & Bassett, 2011).

22q11.2DS is generally characterized by multiple organ dysfunction, including cardiovascular, endocrinologic, gastrointestinal, immunologic, genitourinary, skeletal, and biochemical, as well as neurological symptoms , like developmental delays, cognitive deficits, and neuropsychiatric disorders (Bassett et al., 2000; Drew et al., 2011; Edelmann, Pandita, Spiteri, et al., 1999; Murphy, 2002). Due to the pharyngeal arch system's defective embryonic development, the DiGeorge syndrome (DGS) is characterized by conotruncal CHD, hypoparathyroidism, dysmorphic facies or palatal

deformities, and T cell lymphopenia (Conley et al., 1979; Donna M McDonald-McGinn et al., 2015; H. H. Yu et al., 2022).

Clinical signs may vary depending on the disease's severity and the patient's developmental stage. During childhood, congenital heart problems, infections, hypernasal speech, hypocalcemia, feeding issues, delays in speech and development, learning deficiencies, and behavioral disorders are commonly observed. Cognitive prognosis may change depending on the medical condition of the children with 22q11.2DS (Cheung et al., 2014). In contrast to the standard IQ range of 85-115 (mean: 100) in the typically developing population, the mean IQ is only 70, with almost two-thirds of people falling in the IQ range of 55-85 (De Smedt et al., 2007; Swillen et al., 1997). Across the lifespan, cognitive development follows different paths (Duijff et al., 2012; Swillen & McDonald-McGinn, 2015) and that the level of intellectual capacity is not always the same.

Learning difficulties are thus quite prevalent in preschool and primary school, particularly in the fields of mathematics (De Smedt et al., 2009; Wang et al., 2000) and language comprehension (Glaser et al., 2002). In accordance with the prevalence of neurodevelopmental disorders (NDDs) and intellectual disability, children with 22q11.2DS have developmental delay. Motor difficulties, language deficits and speech problems are observed among 22q11.2 deletion carriers beginning in infancy (Gerdes et al., 2001; Gerdes et al., 1999; Goodship et al., 1998; Klaassen et al., 2013; Donna M McDonald-McGinn et al., 2015; Roizen et al., 2007; Swillen et al., 1999). According to Kortanek (Kortanek et al., 2022), early detection for the development of the 22q11.2 CNVs phenotype can be missed by families and clinicians but it is really important to interfere development of 22q11.2CNV phenotype with early interventions. Kortanek emphasized the need for close monitoring of neurodevelopment in individuals with 22q11.2 CNVs, as this group has a high rate of developmental issues. This is particularly relevant for identifying potential delays and increased risk of autism.

1.1.1.22q11.2DS & Psychiatric Disorders

Many psychiatric disorders may be seen in individuals diagnosed with 22q11DS, which can be summarized as anxiety disorder, major depressive disorder, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD) and schizophrenia (Antshel et al., 2006; Green et al., 2009; Kates et al., 2015). According to the population-based cohort study, stress-related disorders, somatoform disorders, and childhood developmental disorders may be cited as other psychiatric disorders in patients with 22q11.2DS or 22q11.2 duplication syndrome (Hoeffding et al., 2017).

In a study of 1402 patients with 22q11.2DS, mean age 18.78 ± 10.66, the most common condition in children (represented by 37.10%) was ADHD (M. Schneider et al., 2014). At all ages, but particularly in children and adolescents, anxiety disorders were more frequent than mood disorders. Psychotic disorders, diagnosed with validated diagnostic tools, were prevalent in 41% of people over 25 years old (M. Schneider et al., 2014). Following that, there are common clinical features in the 22q11DS diagnosis and schizophrenia diagnosis (Demily & Franck, 2016). In the study, in which researchers investigated whether differences in the clinical significance of ultra-high risk (UHR) symptoms and criteria in 22q11DS were related to age, 111 patients with 22q11.2DS (age between 8 and 30 years, mean =15.7 4.7) were included (Marco Armando et al., 2017). The exclusion criteria for participants were having a past or present psychotic disorder. Structured Interview for Psychosis-Risk Syndromes (SIPS) was used to detect UHR symptoms, positive symptoms (unusual thought content, perceptual abnormalities, e.g.), negative symptoms (decreased emotion expression, social anhedonia, e.g.), disorganized symptoms (problems of attention and concentration, bizarre thinking, e.g.) and general symptoms (sleep disorders, dysmorphic mood, e.g.) (Marco Armando et al., 2017). Because 38.8% of individuals with 22q11DS have psychotic symptoms (Marco Armando et al., 2017) and 30-40% of adult patients are diagnosed with schizophrenia, it is concluded that there is strong relationship between 22q11DS and schizophrenia (M. Schneider et al., 2014). However, it is unknown why psychotic symptoms are not

observed in approximately 60% of the remaining cases and to what extent this resilience is related to environmental factors.

In another study, which included the cohort (individuals with 22q11.2DS (n = 172, from Israel and Western Europe) aged 5 to 54 years) of Green et al. (2009), investigated the relation between cognitive decline and psychotic disorders, 13% of the patient with 22q11.2DS sample was diagnosed with a psychotic disorder (mean age 16.1± 6.2, n=411). Researchers found that early cognitive decline could be a strong predictor of the development of psychotic disorder in those with 22q11DS (Vorstman et al., 2015). They suggested that 22q11DS could be used as a genetic model for clarifying the neurological processes underlying the onset of psychosis (Vorstman et al., 2015). According to the Green et al. (2009), monitoring these patients' mental symptoms during adolescence and young adulthood is very important because psychosis and depression are reared up in these critical periods.

When patients diagnosed with 22q11DS between the ages of 18-25 was studied, it was found that 24% had anxiety disorders, 18% had mood disorders, and 23% had schizophrenia spectrum disorders (Kates et al., 2015; Maude Schneider et al., 2014). With increasing age, the frequency of schizophrenia spectrum disorders can reach 41.3%, anxiety disorders can reach 27.5%, and the frequency of mood disorders exceeds 20% (Kates et al., 2015; Maude Schneider et al., 2014). Considering with sexes, ADHD is more prevalent in male than female (Niarchou et al., 2017; Maude Schneider et al., 2014). On the other hand, anxiety disorders and mood disorders have high prevalence in females (Maude Schneider et al., 2014).

According to Niarchou et al. (2017), a study with 331 individuals with 22q11.2DS (mean age 16.9 ± 8.7), when psychiatric symptoms in this population were examined for the spectrum of psychopathology, psychiatric symptoms could be divided into four specific dimensions as psychosis, attention deficit hyperactivity disorder, mood disorders, and anxiety disorders, which are loaded to the factor general psychopathology. Specially psychosis symptoms were strongly loaded to the general psychopathology factor. This demonstrates that psychosis significantly impacts the predisposition for psychopathology

in 22q11.2DS. This study suggests that the highly linked nature of psychopathology in 22q11.2DS is not being sufficiently captured by the diagnostic classification methods in use today. The impact of the "general psychopathology" factor may contribute there is no interplay between the biological markers and other factors and psychiatric disorders in this patient and nonpatient populations (Caspi et al., 2014). They suggested that psychiatric nosology should be updated to a new version, which represents the dimensions of psychopathology. Limitation of this study was not included these psychiatric disorders: social phobia, specific phobia, ASD and antisocial behavior. Authors also pointed that these disorders symptoms probably change the dimensional structure of the psychopathology.

Genetic factors, neural connections, neurotransmitter systems, cellular functions and common environmental factors can be shown among the causes of comorbidity. In a recent study evaluating the psychiatric comorbidities in inpatients with 22q11.2DS, 6563 patients, mean age 30.40 ± 0.14, anxiety disorders (16.4%) and mood disorders (24.7%) had the highest prevalence rates, followed by schizophrenia and other psychotic conditions (14.0%), and also intellectual disability was present in 16.5% of the sample but this study did not assess for autism spectrum disorder (ASD) (Patel et al., 2022). The likelihood of having mental comorbidities was higher in females than males (Patel et al., 2022). In this study, psychiatric comorbidities were seen in 45% of the large sample without any relation to the severity of the syndrome, and a few of the patients got psychiatric admissions (13%) (Patel et al., 2022). The reason for the difference between the literature findings and Patel et al. (2022) findings may be that the patients with 22q1.2DS included in this study were inpatients and 70% of the patients had a high and severe level of loss of function according to All Patients Refined Diagnosis Related Groups Severity of illness subclass (APR-DRG). The severity of an illness is determined by the degree to which a person's physiological functions have declined or the extent to which their organs are no longer functioning properly. On the other hand, etiology of the psychiatric disorders observed may depend on not only the CNV's genetic effect, but due to psychosocial factors as increased medical burden, bullying experienced during adolescence and social challenges. People with 22q11DS are often thought of as shy and socially withdrawn compared to those without the condition (Shprintzen, 2000; Swillen

et al., 1997). People with 22q11DS often have difficulty with social interactions and may be isolated from their peers (M. Schneider et al., 2014; Schonherz et al., 2014; Swillen et al., 1997). Additionally, children with 22q11.2 deletion syndrome may be more likely to be bullied or mistreated by their peers because of their differences (Mayo et al., 2019). This can become more pronounced during adolescence and can lead to long-term negative consequences (Kates et al., 2015). According to Mayo et al. (2019), bullying as a form of early trauma encourages a changed developmental trajectory especially in children who are genetically more susceptible. In this manner, they discussed how differ cognitive, social, and developmental functioning of patients with 22q11.2 DS from the typically developed individuals considering the short- and long-term effect of bullying. They proposed that bullying may increase the likelihood of maladaptive functioning and increasing the risk for psychotic disorders (Mayo et al., 2019). This can cause additional emotional distress and further exacerbate their feelings of shyness and anxiety. It is important for the parents and family members of children with 22q11.2 deletion syndrome (spouses, siblings, and other relatives) to provide support and understanding, and to help child develop coping skills and build self-esteem (Donna M McDonald-McGinn et al., 2015). Moreover, considering the social skills of 22q11.2DS patients, half of the married adult patient have children however only few adults get married (Mosheva et al., 2018).

Exposure to stress increases the risk of psychiatric disorders, and coping skills play an important role in the prognosis of the disease. In light of this knowledge, individuals with 22q11.2DS may be experiencing the dual neurobiological effects of psychosocial stress and CNV, and also CNV may be altering the stress responses that CNV carriers experience, compared to controls.

1.2. Psychological Stress

The effects of stress on healthy individuals and the effects on individuals with copy number variations can vary significantly depending on biological and environmental factors. At this point, it can be thought that individuals with 22q11.2DS may show biological differences in terms of stress responses since they are often thought of as shy

and socially withdrawn. The healthy stress response mechanisms should be detailed first to understand and find the difference.

Three basic interrelated systems are activated in response to psychological stress in our body. First the amygdala, which allows us to evaluate the stress factors captured by the sense organs from our environment and recognizes these factors as stressors. This information transferred to the hypothalamus from amygdala activates the autonomic nervous system (ANS). ANS is responsible for homeostasis in the body against stress via the sympathetic (SNS) and parasympathetic nervous system (PNS). The hypothalamus activates SNS to deliver messages to the adrenal glands via the autonomic nerves. In response, these glands release the catecholamine hormone epinephrine (adrenaline) into the circulation. Catecholamines (epinephrine, norepinephrine, and dopamine) are rapidly released against stressors when adrenal glands are activated by SNS. They function as both hormones and neurotransmitters that are essential for maintaining homeostasis. Catecholamines increase heartbeat and blood pressure and direct blood from the skin and abdomen to skeletal muscles; it also initiates the breakdown of glycogen in the liver into glucose and allows it to enter the blood. After the stressor disappears, PNS dimishes the stress response to maintain homeostasis. Moreover, there is another crucial system, Hypothalamus-Pituitary-Adrenal (HPA) axis, which is the main stress response mechanism in the body.

1.2.1. The Hypothalamus-Pituitary-Adrenal HPA Axis

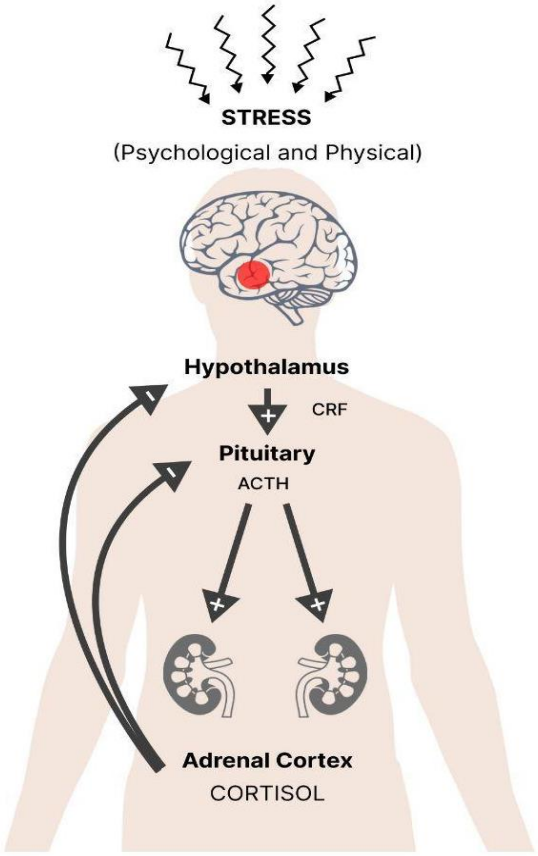

Figure 1.3. Hypothalamus-Pituitary-Adrenal Axis

The axis comprises the hypothalamus, the pituitary gland, and the adrenal glands. The HPA axis uses several hormonal signals to control the sympathetic nervous system. The paraventricular nucleus of the hypothalamus (PVN) releases corticotropin-releasing hormone (CRH), which binds to its receptors on the pituitary gland and causes the production of adrenocorticotropic hormone (ACTH). The adrenal glands are targeted by ACTH, which stimulates releasing cortisol from zona fasciculata (adrenal gland cortex) into the circulatory system (Smith & Vale, 2006). It is a neuroendocrine system involved in the adrenal glands' stress hormone production. It could affect the immune system, sympathetic and central nervous system, and metabolism (glucose, fat, and bone) (Frodl & O'Keane, 2013). To mobilize or store energy to meet the demands of the stress challenge, cortisol, a glucocorticoid, changes the way many tissues functions (de Kloet et al., 2005). As a result, the body remains energized and vigilant. Cortisol (GC) also negatively affects pituitary ACTH production and CRH secretion via cortisol receptors in the hypothalamus/hippocampus (Frodl & O'Keane, 2013).

1.2.2. Glucocorticoids

According to a study, glucocorticoids (GC), which regulate physiological changes depending on intracellular receptors, are downstream effectors of the HPA axis (Munck

et al., 1984). They could also function as transcriptional factors (Frodl & O'Keane, 2013). Glucocorticoids have a significant role in the HPA axis' duration and intensity (Keller-Wood & Dallman, 1984). With continued stress exposure, glucocorticoids can block the HPA axis at the hypothalamic and pituitary gland levels via negative feedback regulation, and GC can control the HPA axis independently.

Glucocorticoids use also genomic pathways to restrain the HPA axis (Smith & Vale, 2006). Brain functioning could be affected by the GC activation via two nuclear receptors: glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). Through transcriptional changes, glucocorticoid receptors (GRs) in stress-responsive brain areas control negative feedback regulation (Reul & de Kloet, 1985). Glucocorticoids have a low affinity for GRs and a high affinity for mineralocorticoid receptors; therefore, glucocorticoids bind to mineralocorticoid receptors at the baseline level of GC production (Reul & de Kloet, 1985). MRs control the HPA axis at baseline, while GRs control the HPA axis' negative feedback after exposure to stress. The PVN and the hippocampus are two regions of the brain that have been particularly identified for negative feedback (Smith & Vale, 2006). High numbers of GRs are found in PVN, and local GCs reduce PVN neuronal activity, resulting in ACTH decrease (Watts, 2005). The hippocampus has a high level of GRs and MRs, so GC administration cause inhibition of releasing GC at the basal and high-stress levels (Buckley & Schatzberg, 2005).

HPA axis regulation, which has been linked to a variety of psychopathology, is affected by the negative feedback loop mechanism (Marques et al., 2009), SCZ (Bradley & Dinan, 2010), post-traumatic stress disorder (PTSD) (Morris et al., 2012), and alcohol dependence (Stephens & Wand, 2012).

GCs are biologically adaptive; however, insufficient or extreme activation of the HPA axis may play a role in the development of diseases. If stressors cause abnormalities in HPA axis regulation, chronic GC release affects brain anatomy and function. Memory and learning are controlled by the hippocampus, a brain area located on the medial section of the limbic cortex that is abundant in GRs (Goosens & Sapolsky, 2007). The negative feedback mechanism for HPA axis, via the cortisol, and learning and memory function

depend on the hippocampus. According to research conducted on humans, learning and memory are negatively impacted by artificially increasing or decreasing cortisol levels (Lupien et al., 2002). Chronic release of glucocorticoids increases prefrontal inflammation and basal cortisol levels (especially in patients with schizophrenia). It causes pathologies such as damage to the nervous system, immune system problems, depression, and anxiety.

Sapolsky et al. (1986) proposed the "glucocorticoid cascade theory," which states that excessive glucocorticoid exposure causes a loss in the negative feedback regulation, this causes more cortisol releasing and hippocampal injury. This theory is generally accepted as a pathophysiological route leading to brain alterations linked with severe and long-term stress. According to Sapolsky et al. (1986), similar process happens with increasing age, in which gradually reduces cognitive functions mediated by the hippocampus and results in a decrease in the hippocampus's capacity to govern the HPA axis. This theory explains how persistent stress may alter the brain in a way that impairs the HPA axis's ability to operate, which in turn can cause pathologies (Frodl & O'Keane, 2013).

GRs with binding glucocorticoid response elements (GREs) or GRs that may directly bind to transcription factors of HPA axis components control the transcription of the HPA axis genes (Bamberger et al., 1996). Individual differences in the HPA axis response to stress may be caused by genetic variations in the key genes involved in HPA axis function. There are some specific genes to regulate HPA axis. Corticotropin-releasing hormone (CRH) gene encodes a member of the corticotropin-releasing factor family, corticotropin-releasing hormone binding protein gene (CRHBP) gene encoding CRH binding protein, corticotropin-releasing hormone receptors 1 and 2 (CRHR1 and CRHR2) genes encode the CRH receptors. There are also widely studied genes: Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1) and FKBP5. NR3C1 and NR3C2 gene encodes glucocorticoid receptor end mineralocorticoid receptor, respectively. In addition, FK506 binding protein 5 gene encodes the FKBP5 protein which is regulation HPA axis via glucocorticoid pathway.

The glucocorticoid receptor (NR3C1) gene is one that has been extensively researched in connection to stress and mental health. NR3C1 serves as a transcription factor or as a regulator of other transcription factors since it is the main receptor for cortisol and other glucocorticoids (Herbert et al., 2006). With the role in the HPA axis regulation via feedback mechanism NR3C1 physiological feedback mechanism enables modulation of the protein and the adaptability to stressors exposed (Binder, 2009; Herbert et al., 2006). Similarly, NR3C1's co-chaperone and regulator, FKBP5, controls glucocorticoids (Castro-Vale et al., 2016; Klengel et al., 2014). Due to their control over glucocorticoids and activation of the negative feedback loop via the GR, NR3C1 and FKBP5 are essential in both initiating and ending the stress response following exposure to trauma (Binder, 2009).

1.3. FK506 binding protein 51 (FKBP5)

FK506 binding protein 51 (FKBP5) was discovered in the studies about purifying the steroid hormone receptors and identifying novel receptor-associated proteins by Smith et al. (1990). The FKBP5 gene encodes the FKBP5 protein. This gene, is located on the short arm of chromosome 6 (6p21.31; chr6:35,573,585-35,728,583) (Zannas et al., 2016) and it contains 13 exons and 12 introns (Fries et al., 2017).

1.3.1. Transcription of FKBP5 and Regulation Mechanisms

Transcription regulation mechanisms could be controlled by steroid hormone receptors (SHRs) as transcription factor, genetic variations (single nucleotide polymorphisms), epigenetic mechanisms (DNA methylation). All these regulation are depending on tissue-specific manner (Galat, 2004; Hubler & Scammell, 2004; Torsten Klengel et al., 2013; Magee et al., 2006; Ong & Corces, 2014; Paakinaho et al., 2010; Pelleymounter et al., 2011; Scharf et al., 2011; U et al., 2004).

Steroid Hormone Receptors

The transcription mechanism of FKBP5 can be affected by the activation of steroid hormone receptors (the mineralocorticoid receptor (MR), the androgen receptor (AR), the estrogen receptor (ER), the progesterone receptor (PR), and the glucocorticoid

receptor (GR)) (Hubler et al., 2003; Hubler & Scammell, 2004; Magee et al., 2006; Smith et al., 1993; Smith et al., 1990; U et al., 2004). Different types of SHRs have diverse functions in the transcription mechanisms.

Glucocorticoid receptors have specific functions in FKBP5 gene regulation and since GRs are related to the HPA axis. GR-induced transcription of the FKBP5 gene is one of the most studied regulation mechanisms related to stress and psychiatric disorders and these studies showed that the presence of functional glucocorticoid responsive elements (GREs), which form an intracellular negative feedback loop, is the most crucial characteristic of the FKBP5 gene (Hubler & Scammell, 2004; Paakinaho et al., 2010; Rein, 2016).

To glucocorticoid receptors, there are two ways to affect the transcription regulation of FKBP5 gene. One way is binding of its homodimer to glucocorticoid response elements (GREs) on regulatory regions of the gene. Another one is interacting GR monomer with other transcription factors via GRE-independent.

In the FKBP5 gene, many glucocorticoid response elements (GREs), enhancer elements, are located upstream of the promoter region, intron 2, intron 5, and intron 7 (Paakinaho et al., 2010). These enhancer elements are critical in determining the gene's glucocorticoid response (Hubler & Scammell, 2004; Paakinaho et al., 2010). The promoter region is expected to be the location for binding transcription factors, but surprisingly intronic regions and distal regions of the gene have many binding sites (Pelleymounter et al., 2011) and they have been found to be more responsive than a promoter to glucocorticoids (Hubler & Scammell, 2004). GREs can interact directly with RNA polymerase II and the transcription start site (TSS) through three-dimensional chromatin loops forming, thereby initiating transcription (Jääskeläinen et al., 2011; Torsten Klengel et al., 2013) (Figure 1.4). According to Klengel, these interactions could be changed depending on the genomic location of the GREs, genetic variations, and epigenetic mechanisms (Torsten Klengel et al., 2013).

Genetic Variations

Owing to the studies in which different methods were applied, more than 600 single nucleotide polymorphisms (SNPs), >50 insertions and deletions, and >250 rare variants in the FKBP5 gene have been discovered (Ellsworth et al., 2013; Pelleymounter et al., 2011). Among all SNPs, some affect the expression and functions of the FKBP5 protein (Binder et al., 2004; Ellsworth et al., 2013; Scharf et al., 2011). According to Zannas et al. (2016), SNPs in strong linkage disequilibrium are responsible for increasing glucocorticoid receptor-induced transcription. These are some common SNPs: rs3800373, rs9296158, or rs1360780. In the literature, rs1360780 is the main SNP related to stress-related disorders. This SNP can be protective or risk allele, it may affect the transcription mechanism according to the methylation level and the chromatin structure. There are studies to decide which CpG sites' methylation level is related to stress-related (Mihaljevic et al., 2021; Saito et al., 2020; Tozzi et al., 2018). In these studies, researchers found that the allele type (protective or risk) on rs1360780 is an important factor defining the chromatin structure and the expression of the gene The relation between rs1360780 and the GR-induced transcription mechanism was shown by Torsten Klengel et al. (2013). This study, in which lymphoblastoid cells were used, showed that rs1360780 causes the binding GRE in intron 2 of TSS directly via conforming three-dimensional chromatin structure. The haplotype containing rs1360780 has a possibly higher affinity for TATA-box protein (TBP) than other alternatives so that conformational change of the DNA could be promoted Klengel, 2013 #78}. According to Zannas and Binder (2014), the relationship between GR and FKBP5 is altered by rs1360780 via inducing

transcription and causes more likely GR resistance, especially during GR-mediated negative feedback of the hypothalamic-pituitary-adrenal (HPA) axis.

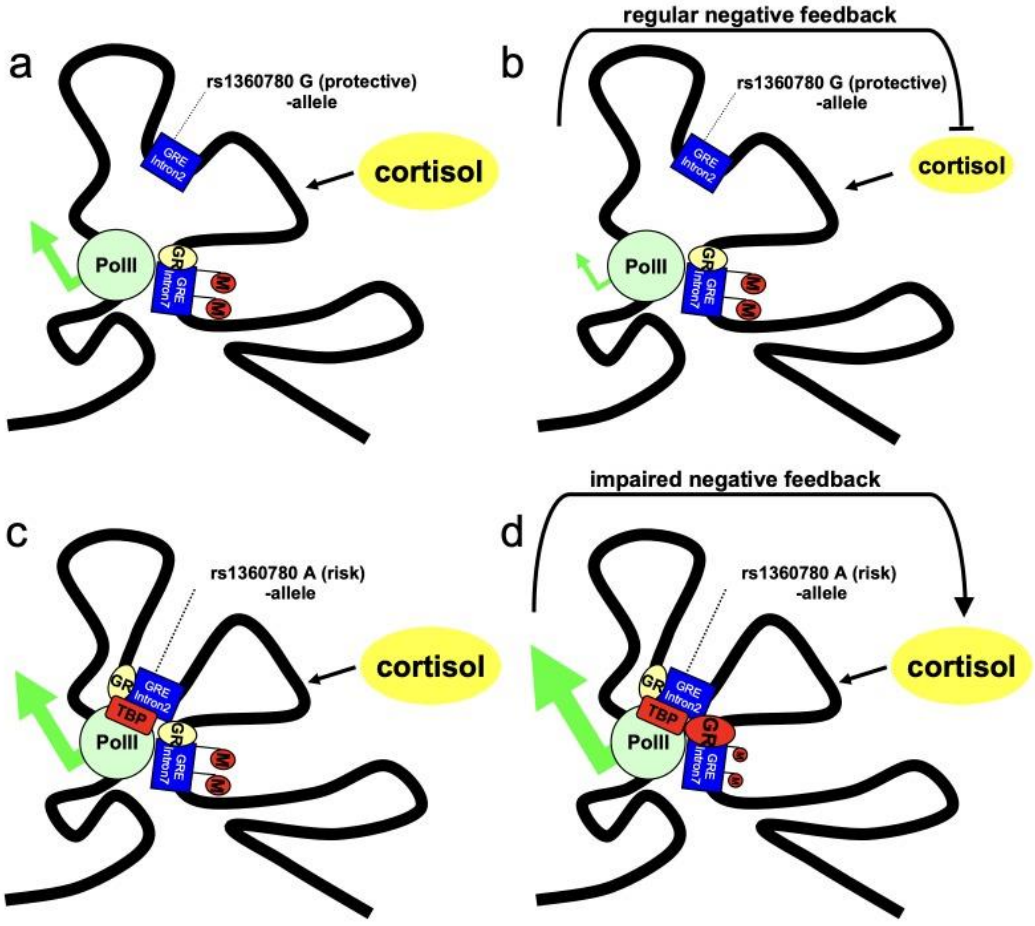

Figure 1.4. The long-distance interaction of Glucocorticoid Responsive Elements in FKBP5 may involve a suggested by Klengel et al. (2013) epigenetic mechanism of trauma-induced demethylation (Figure is directly used from original article.)

DNA Methylation

One of the reasons for the relationship between exposure to stress and FKBP5 gene regulation in the context of psychiatric disorders is epigenetic mechanisms (Matosin et al., 2018). DNA methylation, one of the epigenetic mechanisms, has an effect on the transcriptional regulation of the FKBP5 gene via changing the functions of transcription factors and conformational changes of the chromatin. This effect may also vary depending on SNPs, the location and direction of methylation, and exposure to stress (at what time of development stage and how long the stress is exposed is an important factor) (Fries et al., 2017; S. H. Parade et al., 2021).

One of the most important studies about the relationship between childhood adversities and the methylation level in the FKBP5 gene proved that many other factors, such as SNPs and environmental factors, should be considered during the transcription process (Torsten Klengel et al., 2013). This remarkable study found that functional polymorphism could be a risk for stress-related psychiatric disorders since this polymorphism could change the interaction between TSS and GREs of the FKBP5 gene. This interaction can cause various GR-induced transcriptional activation of FKBP5 in response to childhood abuse (Torsten Klengel et al., 2013).

Zannas et al. (2016) stated GR-induced transcription mechanism model of FKBP5 depends on the literature. According Zannas et al. (2016), the glucocorticoid receptor complex is activated by entering glucocorticoids into the cytoplasm. When FKBP5 binds to the complex, glucocorticoids have less affinity for the GR, and the GR's translocation to the nucleus is delayed. However, GR translocation to the nucleus happens when FKBP5 is switched out for FKBP4.

In one way, the GR may form a homodimer to bind to DNA at GRE sites. In another way, it can interact with other transcription factors. Many genes are transactivated or transrepressed as a result of GR activities. FKBP5 polymorphisms and methylation status affect how the FKBP5 gene responds to GR responsively. The cytoplasm is where the newly generated FKBP5 mRNA is translated into FKBP5 protein. Then, FKBP5 reduces GR activity via influencing several other biological processes and creating an

extremely short intracellular negative feedback loop of GR signaling (Zannas et al., 2016).

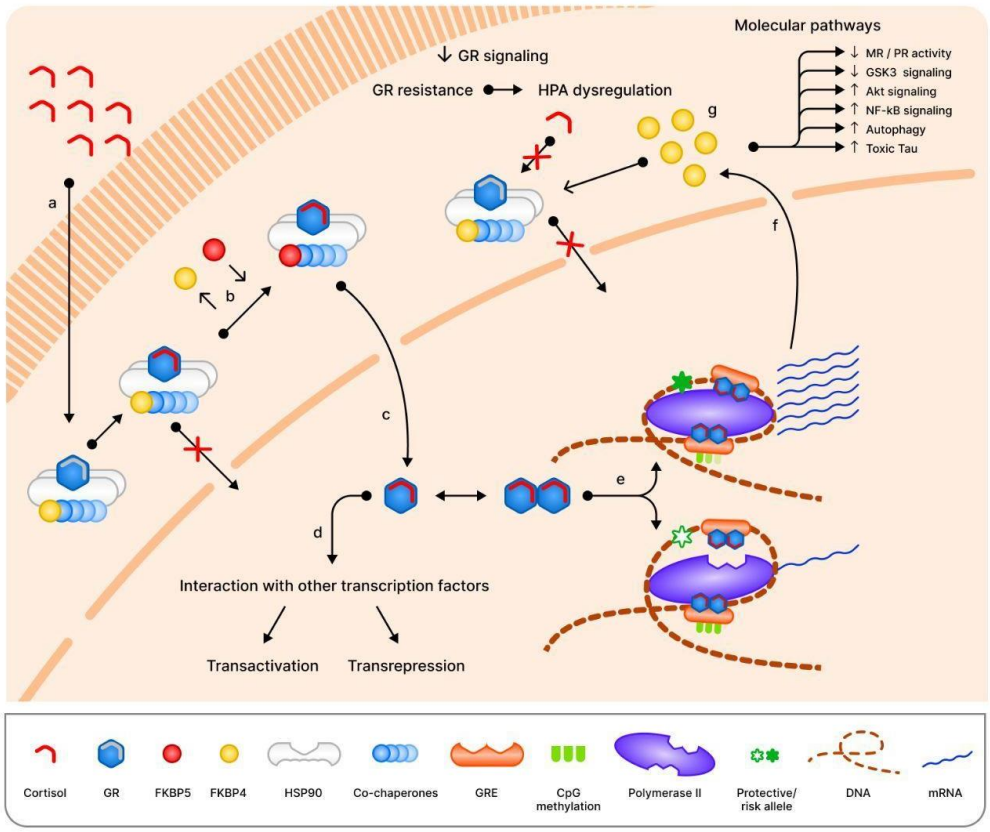

Figure 1.5. A visual diagram of the molecular events that lead to the induction of FKBP5 by glucocorticoids and the subsequent negative feedback loop within cells. The diagram also shows how this process impacts other biological processes (Adapted from Zannas et al. (2016)).

Tissue-Specific Manner of Transcription

In different tissues, FKBP5 transcription mechanisms could be affected differently. In research using mice, FKBP5 expression is reported in the whole brain but there are differences in regions (Galat, 2004). They found that glucocorticoid exposure (GC) affected the expression depending on the tissue-specific manner (Galat, 2004). In the hypothalamus, the PVN (low expression at the baseline) is more affected by GC exposure rather than the hippocampus (high expression at the baseline).

The expression level of FKBP5 and the demethylation level of the gene show that GC exposure has an important effect on the FKBP5 transcriptional regulation (Menke et al., 2013). In mice, researchers showed that all these changes could be found in different tissues; peripheral blood cells, neuronal tissues, and pituitary tissue in different ways (Lee et al., 2010; Yang et al., 2012). Moreover, GR-mediated regulation of FKBP5 transcription is also tissue-specific (Lu & Cidlowski, 2005; Nicolaides et al., 2014). In addition to all these studies in the literature, there are also findings that the transcription and translation of FKBP5 are rapidly induced by GR activation in various tissues (Jääskeläinen et al., 2011).

In line with the function of the FKBP5 on the HPA axis via GR, a change in the level of FKBP5 expression is expected. FKBP5 is the functional regulator of GC receptors that play a role in the HPA axis feedback system.

1.3.2. Relation Between Hypothalamic-Pituitary-Adrenal (HPA) Axis and FKBP5 Gene

As the GC system has a regulatory role in the function of the HPA axis, this system also has a functional regulator. FKBP5 is the functional regulator of GC receptors that play a role in the HPA axis feedback to end the stress response after the disappearance of the stressor. Functional impairment in this system has been observed in psychiatric disorders due to stress, and childhood traumas have been shown to impair the function of this system in the long term (Torsten Klengel et al., 2013). FKBP5 inhibits ligand binding to glucocorticoid receptors, preventing translocation of the receptor complex within the nucleus (Wochnik et al., 2005). FKBP5 can also regulate the activity of glucocorticoid receptors as part of a rapid short negative feedback loop; FKBP5 transcription is induced as a result of limited activation of GC receptors (Torsten Klengel et al., 2013).

Torsten Klengel et al. (2013) found that the extent to which FKBP5 is transcribed in the body can interact with early traumatic experiences or childhood abuse to predict the likelihood of an individual developing adult post-traumatic stress disorder, attempting suicide, and experiencing major depression. For this reason, FKBP5 gene methylation

will be examined in the participants as a variable that can explain the variation in the biological effects of stress (Saetre et al., 2007; Weinberger et al., 2002).

1.4. Immune System

Another system affected by stress is the immune system. Immunological and inflammatory differences between the case and control groups were found in stress-related psychiatric disorders**.** To demonstrate the importance of gene dosage in neurodevelopmental disorders, researchers have shown that changes in inflammatory processes may be associated with the duration of stress exposure by using postmortem brains of schizophrenic patients in the research (Saetre et al., 2007; Weinberger et al., 2002). Moreover, they also showed that the limbic system reduces stress, and the sensitivity to stress might be a sign of abnormal frontal lobe function (Saetre et al., 2007; Weinberger et al., 2002). Acute, intense, or chronic stress stimulates natural immunity, creating a sterile inflammation. Different types of stress can have positive and negative effects on the immune system, like all other stress-related situations. For example, chronic stress may increase autoimmunity, susceptibility to infections, delay in wound healing, chronic and low inflammation, change in immune cell activities, and increase in inflammatory markers in the blood (Seiler et al., 2020). Since acute and short-term non-traumatic stressors are function controlled by natural inflammatory processes, they can have a strengthening and mature effect on natural immune systems.

Psychological stress may disrupt the activities of regulatory T cells, preventing T cells from reaching the maturation to fulfill their function in the immune system (McCray & Agarwal, 2011). After acute stress, the immune system is activated at the cellular level, along with processes; this can also be considered a process of adaptation and recovery after the effects of a stressor (Miller & Prinstein, 2019). This adaptive immunity affects the signaling mechanisms within the cell, initiating transcription that is effective in proinflammatory activity, thereby releasing cytokines; as an example of these, tumor necrosis factor-alpha (TNF-αlpha) and interleukin-1beta (IL1B) can be given (Raison et al., 2006). A meta-analysis stated that the levels of cytokines such as IL-6 and IL-10 increase with the effect of chronic stress (Steptoe et al., 2007). It has been reported that

this effect is higher, especially in depressive disorders, and even depressive symptoms decrease by blocking these cytokines (Howren et al., 2009).

In the 22q11.2DS population, immune system deficits are common (Donna M McDonald-McGinn et al., 2015; Sullivan et al., 1998). Immunodeficiency caused by thymic hypoplasia in patients varies from no production of T cells to normal T cell production with typical thymus (Jawad et al., 2001). Clinical phenotypes of 22q11.2DS patients, depending on the immune deficits, also vary depending on the production of T cells (Piliero et al., 2004).

In a longitudinal study of 195 patients with 22q11.2DS (0-9 years), researchers found that T cell production deficits are common in this population, and there is no common life-threatening infection condition, but these patients may have chronic infections (Jawad et al., 2001). According to the literature, impaired T cell production and immune function are common in patients with deletions of chromosome 22q11.2. The presence or severity of immunocompromise cannot be predicted based on any particular phenotypic phenotype features (Sullivan et al., 1998). Therefore, it is important for each child to be individually assessed for immune function, specifically the investigation of peripheral T cells by flow cytometry (Donna M McDonald-McGinn et al., 2015).

Investigation relation between the immune system and psychiatric conditions, neutrophil-to-lymphocyte-ratio (NLR) is used as a basic and cheap method in clinics (Gibson et al., 2007; Karageorgiou et al., 2019; Mazza et al., 2018). NLR level, the ratio of the number of neutrophils and the number of lymphocytes, includes both innate and adaptive immune cells since this variable is less vulnerable to other environmental factors (e.g., physical exercise) than other immunological markers. NLR level is related to psychiatric conditions and physical conditions, and increasing NLR levels cause more inflammation in the system (Brinn & Stone, 2020). Brinn's study included 13888 patients with psychiatric conditions in a survey. They found that some psychiatric conditions are directly related to NLR level, specifically schizophrenia, bipolar affective disorder, depression, non-phobic anxiety disorders, dementia, alcohol dependence, and mild mental retardation.

According to a recent study, genetic risk variants responsible for psychiatric disorders were significantly enriched at epigenetically active promoters, and enhancers in adaptive immune cells, particularly stimulated T cells (Lynall et al., 2022). In line with that, cells from the peripheral blood are a good choice for use during the epigenetic mechanism analysis.

1.5. Objectives & Hypotheses

22q11.2 deletion syndrome (22q11DS) is an important disorder that has been associated with many psychiatric disorders and pioneered research on copy number variation. This study will reveal the relationship between the psychiatric phenotypes developing in individuals with 22q11DS, and the stress factors exposed to lifetime. The research specifically examines the effects of environmental factors in individuals with 22q11DS. It also aims to shed light on the contribution of gene-environment interaction to the neurobiology of psychiatric disorders.

Hypothesis 1: Individuals diagnosed with 22q11DS have higher psychiatric diagnosis compared to general population.

Hypothesis 2: 22q11DS individuals are exposed to more adverse life events than controls and psychiatric disorders and symptoms observed in adult life in this group are also partially associated with exposure to negative life events.

Hypothesis 3: Individuals with 22q11DS show higher peripheral biological markers for life adversities compared to controls and biological markers for stress partially explain adult psychiatric symptoms of individuals with 22q11DS.

With this study, many scientific outputs will be obtained, the psychiatric characteristics of individuals with 22q11DS, the multidimensional analysis of how stress mechanisms are affected by environmental and genetic factors, and the role of the neurobiological mechanisms of stress in psychiatric diseases. It is aimed to create an enlightening guide in the field of psychiatry for the future, to better identify the phenotypes of individuals with 22q11DS and to direct the protocols in multi-center research.

1.6. Original Value of This Project

In this project, the neurobiology of stress, clinical effects of copy number variations, and effects of copy number variations on the brain will be examined in the evaluation of clinical phenotypes of individuals with 22q11DS. This aspect of the study will investigate the extent to which environmental factors, which have not been adequately explored in the literature, influence the phenotypes of individuals with copy number variations and the neurobiological basis of this effect.

Psychiatric disorders are observed in a significant part of patients with structural chromosome abnormalities. This study aims to examine the relationship between lifetime stress factors, epigenetic mechanisms, and psychiatric phenotypes in individuals diagnosed with 22q11.2DS, to better understand the role of gene-environment interactions in the development of psychiatric disorders. In this context, it is to fill the gap in the literature about the relationship between gene-environment interaction.

It is thought that, with the findings, it will contribute to the understanding of the neurobiology of psychiatric disorders in general, not only for individuals with CNVs. It is believed that the study has many unique values and will make significant contributions in both basic and clinical sciences.

Chapter 2

MATERIALS & METHODS

2.1. Participants

Participants with 22q11.2DS and controls formed the study groups. Patients were provided through genetics, pediatric cardiology and immunology departments of hospitals. Both patients older than 18, diagnosed through childhood and registered at these hospitals were accessed, in addition to relatives known to be 22q11DS carriers. None of the patients included in the study were related to each other. Patients and relatives, whose contact information were received, were informed on the study, procedures, the right to participate and leave, and privacy. Inclusion criteria for patients; were being between the ages of 18-65, being able to give informed consent, having received a score of 70 and above from the intelligence test applied in childhood, being a minimum primary school graduate, and being able to use a computer. control group composed of volunteers matched to the clinical group in the study in terms of age, gender, and educational background. Inclusion criteria for controls; being between the ages of 18-65, being able to give informed consent, having a score between normal range from the intelligence test, minimum primary school graduate, the absence of individuals diagnosed with schizophrenia spectrum disorder near the first degree, to be able to use a computer. As compensation for their time and efforts, 500 ₺ (Turkish Liras) for patients or 300 ₺ for controls, was given.

This study was approved by the Koc University Ethics Committee on Biomedical Researches with the IRB number 2019.117.IRB2.036. All procedures were in accordance with the Declaration of Helsinki. Thirty-two participants' data were included in the study, and all participants gave informed consent. The study's sample size was calculated as 17 patients and 15 controls based on the studies with 22q11.2DS.

2.2. Materials

2.2.1. Psychiatric evaluation

Structured clinical interview (SCID-5): Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview guide to establish major DSM-5 diagnoses. SCID-5 was applied by Dr. Hale Yapıcı Eser. An approved Turkish version of SCID-5 was used in the study (Elbir et al., 2019). It is an interview that can be held for about 40 minutes to an hour.

In addition, the following scales were filled in by the clinician with a psychiatric interview and mental state examination:

1. Brief Psychiatric Evaluation Scale (BPRS): This scale has 18 items; it is mostly used to evaluate psychotic and depressive symptoms as well as functions such as attention; usually applied to psychosis patients. Each question can be scored between 0 and 6 points and the total score can reach 108. It was originally developed Overall and Gorham (1962). It has been adapted to Turkish by Soykan (1989).

2. SANS (Scale for the Assessment of Negative Symptoms): In this scale that includes 24 items; there are 5 subscales such as alogy, apathy, anhedonia, attention deficit and affective blunting. Each item can be scored between 0 and 5 points and the total score can reach 120. It was originally developed by Andreasen (1983).

3. SAPS (Scale for the Assessment of Negative Symptoms): In this scale, which includes 35 items, has 4 sub-scales as delusions, hallucinations, strange behavior and formal thought disorder. Each item can be scored between 0 and 5 points and the total score can reach 175. It was originally developed by Andreasen (1983).

SANS and SAPS have been adapted to Turkish and the reliability study of the Turkish version of the positive and negative symptoms assessment scales were performed by Erkoc et al. (1991) Erkoç et al. (1991).

2.2.2. Self-Report scales

After the first psychiatric evaluation participants were asked to fill in the self-report scales. The purpose of selecting these tests is to evaluate participants 'current symptoms of depression, anxiety and attention deficit hyperactivity disorder, evaluation of positive and negative symptoms associated with a possible psychotic diagnosis, as well as measurements of participants' stress and resilience-related variables. The participants filled these measurements using the Qualtrics program on a tablet or desktop computer. Attention and motivation check questions, as 'Please select the 57 option in this question,' and 'Please select option C in this question.', were interspersed to ensure the participants carefully filled out the scales. The scales were applied to the participants are listed below:

1. Sociodemographic data form: It was used to collect data about the characteristics of the participants such as age, education status, marital status, socio-economic status, current medical diagnoses, medications used, alcohol and substance use and family history.

Psychopathology Measurements

2. Beck Depression Inventory (BDI): This scale was originally developed by Beck et al. (1961). In this scale that includes 21 items; there are four sub-longitudes interpreted as hopelessness, negative self-feelings, physical anxieties, and feelings of guilt. It is a 4-point likert-scale and each item can be scored between 1 and 3 points. Total score can reach 63. It has been adapted to Turkish by Hisli (1989).

3. Beck Anxiety Inventory (BAI): This scale, which contains 21 items, is used to measure the degree of anxiety experienced by the individual. This 4-point likert-scale was originally developed by Beck et al. (1961). Each item can be scored between 1 and 3 points and total score can reach 63. It has been adapted to Turkish by Ulusoy et al. (1998).

4. Adult ADHD Rating Scale (ASRS): This scale was developed by Kessler et al. (2007). It contains 18 items and consists of two subscales: attention deficit and hyperactivity. Each item can be scored between 0 and 4 points. It has been adapted to Turkish by Doğan et al. (2009).

5. Symptom checklist-90 (SCL-90): This scale, 5 point likert scale, was originally developed by Derogatis et al. (1976). Each item can be scored between 0 and 4. It has ten subscales containing 90 items related to somatization, obsessive-compulsive disorder, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid thought, psychoticism, as well as sleep and appetite disorders and feelings of guilt. It has been adapted to Turkish and is a scale used to measure psychological distress symptoms (Kılıç, 2016).

6. WHODAS (World Health Organization Disability Assessment Schedule) short self-report form: This scale was originally represented by World Health Organization. It contains 12 items and 5- point likert scale. It includes cognition, movement, self-care, getting along with people, life activities, and social participation. Turkish version of the scale was adapted by Uluğ et al. (2001).

Stress-related Measurements

1. Childhood trauma Questionnaire (CTQ): It was originally developed by Bernstein et al. (2003). This scale consists of 28 items; the total score can be 25 and 125.It covers five subscales: emotional abuse, physical abuse, physical neglect, emotional neglect, and sexual abuse. It also has a minimization subscale. It has been adapted to Turkish by Şar et al. (2012).

2. Perceived stress scale (PSS): This scale was originally developed by Cohen et al. (1994). It contains 14 items with a 5-point scale. Total score can be between 0 and 56 points. A higher score means higher perceived stress. It consists of two main dimensions inadequate self-efficacy and stress/discomfort perception. Turkish version has been validated by Eskin et al. (2013).

3. Perceived social support scale (MSPSS): This scale was originally developed by Cohen and Wills (1985). This scale consists of 12 items. There are three subscales: support of family, friends, and special people. The scale has a Turkish validity and reliability study (Eker & Arkar, 1995).

4.The Stress and Distress Inventory (STRAIN) aims to measure 55 different types of acute and chronic stress exposure, which can affect physical and mental health, and their response to these stress factors, including a flow of questions that takes place in face-to-face interviews. According to the participants' responses, this lifelong stress identification system asks new questions related to stress exposure and responses to new questions. The design aims to combine the reliability and complexity of an interview-based stress measure with the simplicity of a self-reporting tool.

To accomplish this goal, STRAIN include the questions related all of its main habitats (e.g. health, intimate relationships, children, friendships, childhood, education, work, financing, housing, living conditions, crime, etc.) and its various social-psychological features (e.g. interpersonal loss, physical danger, role change, trap, etc.) (Table 2.1). Users answer all questions which are asked in Turkish language, they can also be read out to users. Users record their answers by tapping them if they are using an iPad, or by clicking if they are using computer monitor. For each confirmed stressor, users are asked a series of short follow-up questions that determine the stressor's severity, frequency, timing, and duration. Using this sophisticated logic, the STRAIN system can guide users in a matter of 20 minutes for a 157-page interview. This is used in 2 main variables analysis from the inventory, one of which is the cumulative number of life stressors (obtained by summing the frequency of the stressors), the other is the cumulative stressors is the degree of difficulty (obtained by adding up the perceived difficulty levels against stressors). The number of stressors can be between 0 and 159, and the stressor difficulty level can be between 0 and 275. Moreover, these stressors can be documented separately as childhood and adult life stressors. In addition to producing general lifetime stress exposure indices, Adult STRAIN can calculate 20 subpoints. These sub-scores include stressors occurring in two time periods of a person, two types of stressors, 11 habitats, and five socio-psychological features, and the difficulty levels of stressors for each category. The validity of this inventory has been demonstrated in the context of predicting many different health outcomes, including mental and physical health complaints, sleep difficulties, cognitive impairment, and general health problems and autoimmune disorders diagnosed by the doctor, and has been validated in many languages (Slavich & Shields, 2018).

Table 2.1. The Stress and Distress Inventory (STRAIN) Variables (Directly taken from (Slavich et al., 2019))

Stressor Types	
Acute Life Events	Stressors that typically last a few days and that exceed the impact of "daily hassles," such as learning of a death, getting fired, or being physically attacked.
Chronic Difficulties	Stressors that typically last a minimum of one month (although most are present for longer), such as persistent educational, housing, or financial problems.
Primary Life Domains	
Housing	Frequent moves, unsafe neighborhood, poor housing conditions, etc.
Education	Overwhelming workload, failed a class, suspended, dropped out, etc.
Work	Laid off, fired, discriminated against, overwhelming workload, inadequate support, etc.
Treatment/Health	Revelation of poor prognosis, hospitalization, ongoing caregiving duties, etc.
Marital/Partner	Infidelity, major argument/fight, chronic conflict, serious break-up, etc.
Reproduction	Pregnancy, accidental pregnancy, abortion, etc.
Financial	Difficulty paying for rent, basic needs, clubs/sports teams, school, etc.
Legal/Crime	House break-in, car break-in, robbed, arrested, court appearance, etc.
Other Relationships	Discrimination or exclusion (outside of work), dissolution of important friendship, bullying by peers, difficultly socially connecting with peers, etc.
Death	Death of key people from acute illness, chronic illness, accident, suicide, etc.
Life-Threatening Situations	Serious car accident, physically attacked, sexually attacked, etc.
Core Social-Psychological Characteristics	
Interpersonal Loss	Parental divorce, parental death, long-term separation from parents, serious relationship break-up, dissolution of important peer friendship, etc.
Physical Danger	Unsafe neighborhood, maltreatment, ongoing physical or sexual abuse/neglect, physically/sexually attacked, life-threatening diagnosis, etc.
Humiliation	Revelation of infidelity, public shaming, peer bullying, social isolation, rejection, or exclusion at school or work, etc.
Entrapment	Chronic caregiving responsibility, overwhelming demands at work or school, overcrowded or unsafe housing, persistent financial or food insecurity, etc.
Role Change/Disruption	Residence change, starting a new job, moving to a new school, etc.

2.2.3. Assessments of cognitive functions with objective tasks

It is known that there are impairments in many areas of cognition in patients diagnosed with 22q11DS. Although individuals with an IQ score of 70 and above were included in this study, participants were evaluated using objective tasks to determine cognitive variation according to controls and to understand the effect of stress on adult cognitive functions. In this context, PennCNB cognitive test battery and "Probabilistic Reward Task (PRT)" developed in Turkish by our laboratory were used for evaluation purposes.

Probabilistic Reward Task (PRT)

It is a signal perception task used to measure hedonic capacity and reward learning. It was developed by Pizzagalli et al. (2005) as a way to objectively assess a person's tendency to modulate their behavior in response to rewards. In each trial of the PRT, participants are presented with two stimuli that are difficult to distinguish. These stimuli consist of simple cartoon faces (diameter 25 mm, eyes 7 mm) with either short or long mouths presented in the center of the monitor. At the beginning of the trial, the face has no mouth, and after a certain delay, a straight mouth of 10 mm ("short mouth") or 11 mm ("long mouth") is presented for 100 ms. Participants are asked to press a button to indicate which mouth they see. The correct identification of a stimulus ("rich stimulus") is rewarded three times more often ("Correct! You earned 25 kuruş") than the other ("lean"), but they are not aware that one stimulus is rewarded more often than the other. In controls, this strengthening method causes response bias and the more frequently rewarded alert is preferred. Response bias towards the alternative option, which is awarded more frequently, will be used to operationalize sensitivity to rewarding.

There are two important data outputs in the analysis of the test; discriminability, which means understanding bias and understanding the difference between the two lips. For their participation in this test and validity of the test, participants were given 20 TL regardless of performance. Turkish version of the test is developed by Dr.Hale Yapıcı Eser in counseling with Pizzagalli and is currently used in our lab for reward-related learning and automated measurement of anhedonia. The work of this task is done via E-prime software. The data passed through quality control by Pizzagalli and his team can

be used in the research. Long lip and short lip pictures used in the program are presented as examples in Figure 2.1.

Figure 2.1. Faces with long and short lips

Pennsylvania Computerized Neurocognitive Battery (PennCNB)

The neuropsychological test battery was developed by Prof. Dr. Rachel Gur at the University of Pennsylvania and is currently intended for use in the United States for many large-sample and multi-center studies. This battery has been translated into Turkish by Dr. Hale Yapıcı Eser after collaboration with researchers at this university, and it is still used in many clinical and translational research by Dr. Hale Yapıcı Eser and her research team. After this neurobiological test was translated into Turkish, a validity and reliability study were performed. It was observed that the neurobiological test battery made accurate and reliable measurements (Izgi et al., 2022). It has also been shown that IQ scores and CNB accuracy scores correlate in patients with 22q11.2DS. Researchers suggested that CNB results can be used instead of IQ results to investigate the particular domains of the brain and behavior (R. E. Gur et al., 2021).

In Penn-CNB, emotion recognition and discrimination, working memory, visual-spatial perception and memory, motor praxis, impulsivity, and attention are evaluated in a structured way. Below is a list of the tests selected to be applied within the battery. Some of these tests are used to obtain information about reaction time and motor capacity, while other tests aim to evaluate different aspects of cognition, attention, short and long-term memory, executive functions, visual-spatial perception, and emotion recognition.

Motor praxi task: This task is designed to measure the participant's sensory-motor skills and the ability to use the computer mouse, the response input tool used in almost all PennCNB tasks. They are asked to follow the green box, which is getting smaller in time, and be as quick as possible.

Figure 2.2. Penn Motor Praxi Task

Penn Facial Memory Test (CPF) and Delayed Version (CPFD): It is a measure of face memory. PennCNB includes two versions of face memory, immediate and delayed. In the first step, 20 faces are shown to participants to be asked to remember later. In the face memory immediate response task, participants see 40 photos, 20 of which are new faces and 20 of them old faces. The participant's task is to decide whether they have seen the face beforehand. They have four options to answer the question: “definitely not,” “probably not,” “probably yes,” or “definitely yes.” During the delayed recall, the same task is repeated after a certain period.

Figure 2.3. Penn Facial Memory Test (CPF)

Penn Continuous Performance Test (CPT): It measures visual attention, alertness, and impulsivity. In this task, a series of red vertical and horizontal lines (in 7 segments) flash in a digital numerical frame in the first half of the task and a digital letter in the other half. Participants must press the space key when these lines form whole numbers or whole letters. In each trial, participants see the stimulus for 300 msec and then see a black screen for 700 msec. The task is divided into two parts: participants search for integers (Continuous Performance Test- Number) for 3 minutes and letters (Continuous Performance Test- Letter) for 3 minutes.

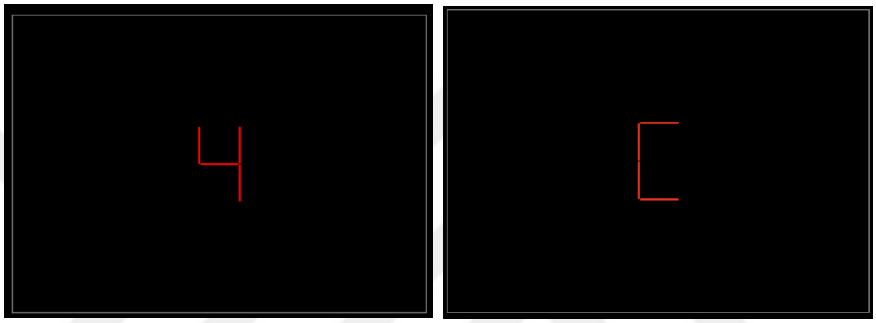

Figure 2.4. Penn Continuous Performance Test (CPT)

Penn Computerized Finger Tapping Test (CTAP): It is used to measure dexterity and motor speed. In this task, there are trials for each hand before starting the task. Participants are asked to press the spacebar with their forefinger as much as possible with both their dominant and non-dominant hands while they see "GO" on the screen. If the screen presents "STOP", participants should not tap. It consists of 10 attempts, each of which takes 10 seconds. Number of taps during "GO" screen is recorded by programme. This task is designed to measure the ability to use the spacebar, the response input tool used in almost all PennCNB tasks, and reaction times.

Figure 2.5. Penn Computerized Finger Tapping Test (CTAP)

Conditional exclusion task (PCET): It is a measure of abstraction in the executive function. Participants should select the object that they think is not related to the other trio among the four objects. There are three criteria throughout the task to select an object (line thickness, shape and size). For example: one of the shapes, line thickness or size of the one's shape can be different than others. Participants select one of the shapes in each trial and task gives feedback as correct or incorrect. Depending on the feedback, participants determine the right criteria for exclusion. When the participant receives 10 consecutive correct answers for each policy, the applied criteria changes and adaptation of the participant to the new strategy is expected.

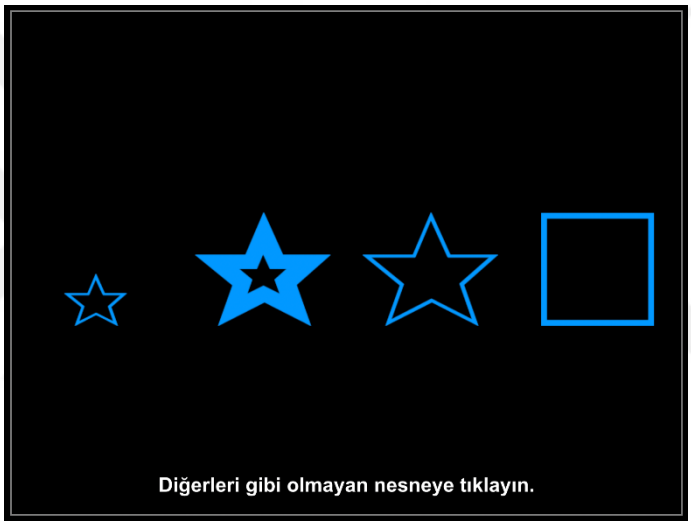

Figure 2.6. Conditional exclusion task (PCET)

Visual object learning task (SVOLT) and delayed version (SVOLTD): It is a measure of visual object learning and episodic memory. In the first part of this test, a variety of three-dimensional Euclidean shapes are shown, which participants will be asked to identify for immediate and delayed recalls. During instant recall, participants are shown a series of 20 three-dimensional Euclidean shapes - 10 are new shapes that they must memorize before. The task of the participant is to decide whether s/he saw the shape before. They have four options to answer the question: "definitely not", "probably not",

"probably yes" or "definitely yes". During the delayed recall, the same task is reapplied after a certain period.

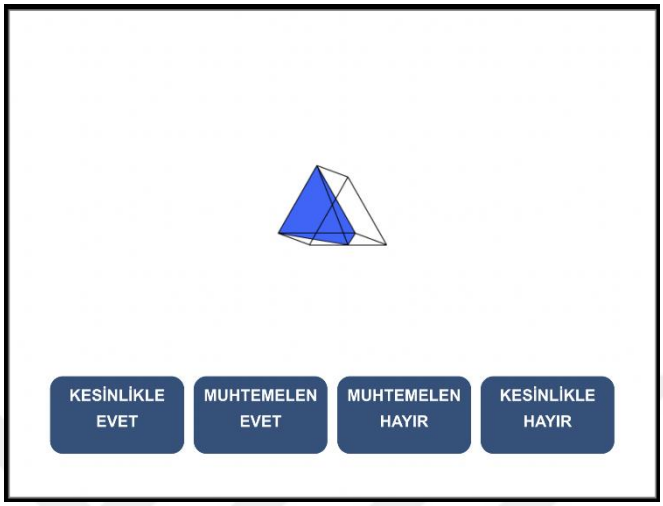

Figure 2.7. Visual object learning task (SVOLT) and delayed version (SVOLTD)

Emotion recognition task (ER40): This task is the measure of emotion identification. Participants see Ekman's 40 facial series one by one. Participants should determine which emotion the faces show. There are five answer options: happy, sad, anger, fear, and no emotions. For each option, there are eight different faces, half of it as male and another half as female.

Figure 2.8. Emotion recognition task (ER40)

Letter-N-Back task (LNB): This task is the measure of attention and working memory. In this task, participants are asked to pay attention to the letters flashing on the computer screen and press the spacebar according to three different rules: 0 back (LNB0), 1 back (LNB1) and 2 back (LNB2). In each trial, stimulus is seen for 0.5 seconds and time

between the stimuli is 2.5 seconds. During the 0-back, the participant must press the space key when the letter X appears on the screen. During 1-back, they are asked to press the spacebar when the letter on the screen is the same as the previous letter (e.g., in the "A", "C", "C" series, the participant must press the spacebar immediately after the second "C"). During 2-back, they are asked to press the spacebar when the letter on the screen is not the same as the previous letter, but the letter before it (i.e., in the "A", "C", "A" series, the participant must press the spacebar just above or after the second "A"). If a participant is answering wrong in trial sessions of the 2-back, participants will be guided by task. 2-back task is described as a sandwich model (“T”, ”A”, “T”) and one example is given step by step to participants to make it easy to understand what the requirement is in the 2-back task. This example can be seen in Figure 2.8.

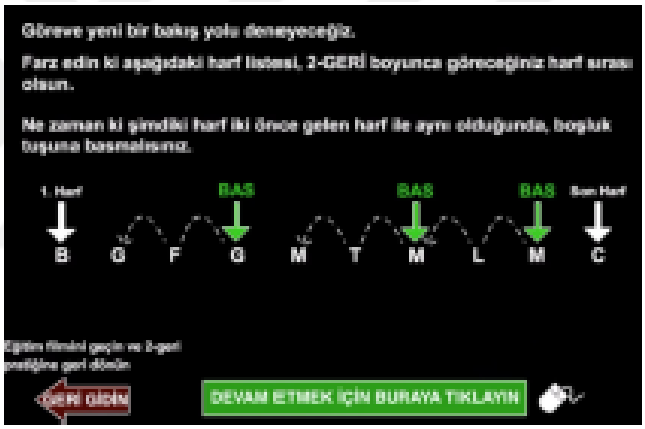

Figure 2.9. PennCNB Letter N-Back Task- Trial Phase

For each test performed with this battery, the test results are automatically calculated by the system. The reaction time, correct and incorrect answers, and efficacy data are presented in an analyzable data format. With this program, data can be presented by performing arithmetic calculations, automatically and objectively. All variables from PennCNB can be found in Table 2.2.

Table 2.2. Pennsylvania Computerized Neurocognitive Battery variables

CPF_TP	True Positives for Face Memory Test	SVT_TP	True Positives for SVOLT
CPF_FP	False Positives for CPF	SVT_TN	True Negatives for SVOLT
CPF_TN	True Negatives for CPF	SVT_FP	False Positives for SVOLT
CPF_FN	False Negatives for CPF	SVT_FN	False Negatives for SVOLT
CPF_CR	Total Correct Responses for CPF	SVOLTD	Total Correct Response for SVOLTD
CPFD_TP	True Positives for CPFD	SVOLTD_TP	True Positives for SVOLTD
CPFD_FP	False Positives for CPFD	SVOLTD_FP	False Positives for SVOLTD
CPFD_TN	True Negatives for CPFD	SVOLTD_TN	True Negatives for SVOLTD
CPFD_FN	False Negatives for CPFD	SVOLTD_FN	False Negatives for SVOLTD
CPFD_CR	Total Correct Responses for CPFD	CPN_TP	True Positive Responses for CPN
SVOLT	Total Correct Response for SVOLT	CPN_FP	False Positive Responses for CPN
CPN_TN	True Negative Responses for CPN	PCET_ER	Number Incorrect Responses for PCET
CPN_FN	False Negative Responses for CPN	PCET_PER_ER	Number of Perseverative Errors for PCET
CPL_TP	True Positive Responses for CPL	PCET_PER_RES	Perseverative Errors Plus Correct Perseverative Responses for PCET
CPL_FP	False Positive Responses for CPL	LNB_TP	True Positive Responses for LNB
CPL_TN	True Negative Responses for CPL	LNB_FP	False Positive Responses for LNB
CPL_FN	False Negative Responses for CPL	LNB_TP0	True Positive Responses for 0-Back Trials
CPT_TP	Total True Positive Responses for CPT	LNB_FP0	False Positive Responses for 0-Back Trials

CPT_FP	Total False Positive Responses for CPT	LNB_TP1	True Positive Responses for 1-Back Trials
CPT_TN	Total True Negative Responses for CPT	LNB_FP1	False Positive Responses for 1-Back Trials
CPT_FN	Total False Negative Responses for CPT	LNB_TP2	True Positive Responses for 2-Back Trials
PCET_CR	Number Correct Responses for PCET	LNB_FP2	False Positive Responses for 2-Back Trials

In the article published in 2015 by Moore et al., a single 'g cognition score' was calculated based on the correct responses of the applied the cognitive tests (Moore et al., 2015). Thus, comparison of the participants with a general cognition score can be provided. g factor was calculated with converting the selected variables (mean of total correct response of CPF and CPFD, mean of total correct response of SVOLT and SVOLTD, correct response of CPT, LNB and accuracy score for PCET) to Z scores. After converting, all Z scores were summed and then convert Z score again to get the g factor.

Detailed cognitive assessments were conducted both to analyze the g factor difference between the patients and controls and also the analyze the effect of stress exposure and biological stress markers on the cognitive assessments.

2.3.Protocols

Volunteer participants for the patient group and controls were invited to the hospital in the morning without having a breakfast. An informed consent was obtained. Considering that stress-related questions to be asked during interviews may affect blood levels of stress-related variables blood samples were taken before the clinical evaluation and before they ate. After collecting blood samples, the clinician applied a structured clinical interview. Third, participants came to the laboratory to complete cognitive tasks and fill out the self-report scales and STRAIN battery. The protocol of our study is illustrated in Figure 2.9. In addition, the participants' blood count and CRP values were checked for

confirmation of infection, and a questionnaire that asks the signs of infection was administered. Infection checklist can be found in Appendix A.

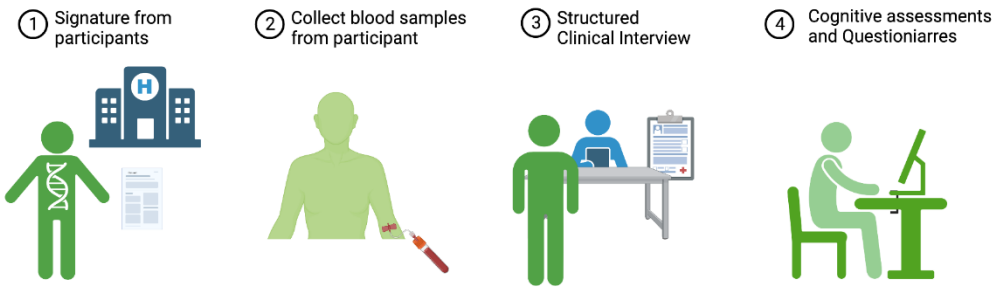

Figure 2.10. The protocol of the study (Created in Biorender.com)

2.3.1. FKBP5 methylation assessment protocol

Pyrosequencing method

To provide detailed information about the FKBP5 gene and how the methylation level change of the FKBP5 gene affects the HPA axis, specific CpG sites should have been selected accordingly. To determine the related CpG site to stressors in the FKBP5 gene, all studies from PubMed and Web of Science databases were identified using keywords: “FKBP5,” or “FK506 binding protein 51,” and “methylation.” All CpG sites investigated with related psychiatric disorders, stress universe, and stress exposure and intervention were analyzed, and decide which CpG sites should be studied for further experiments. After analyzing the literature, CpG sites were decided. In this step, we decided designing two primers for analyzing these CpG sites and used primers, designed and used in T. Klengel et al. (2013). From five primers for promoter region (2 sites), intron 2, intron 5 and intron 7; only one passed the quality criteria. Pyrosequencing primer for the CpG site (cg00130530) was validated (results for the validation steps can be found in Appendix B (Table 6.1.). Details about the validated primer can be found in Appendix C (Table 6.2.). Since the result of the validation analysis for the primer is greater than 0.95 ($R^2 > 0.95$), this primer was used for further analysis. Others will be used to after passing validation steps.

Peripheral Blood Mononuclear Cell (PBMC) isolation

Blood samples were taken into anticoagulated blood collection tubes and mixed by inverting and waiting for 15 minutes before the procedure. A 9 mL blood sample was mixed with 11 mL of 1X PBS. Blood and PBS mixture was transferred into another 50 mL falcon tube which contains 20 mL Lymphoprep. Then, the sample was centrifuged at 500g with maximum acceleration and minimum deceleration for 30 minutes. After the centrifuge stopped the mononuclear cells from the interphase were collected and transferred into a 50 mL falcon tube. The cells were centrifuged at 500g with maximum acceleration and deceleration for 5 minutes. Next, 15mL of 1X PBS was added into a falcon tube and centrifuged with the same configuration for 10 minutes. The supernatant was discarded, and cells were resuspended with a freezing medium (10% DMSO in FBS). Finally, the cells were transferred into labeled cryovials and stored in a -80°C freezer for at least 24 hours. Then, PBMC samples were stored in a nitrogen tank.

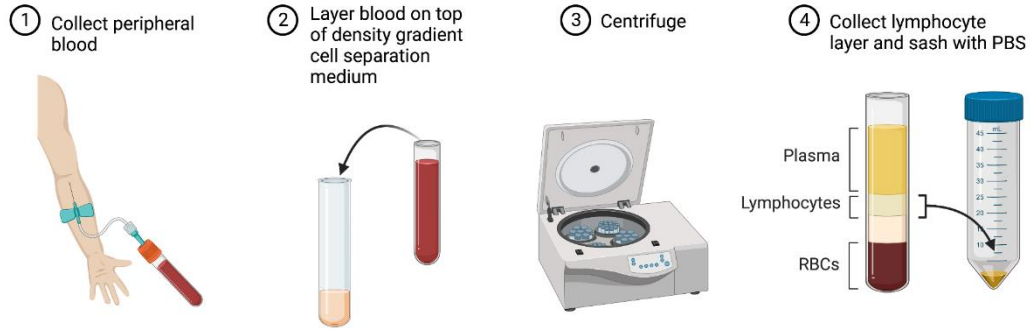

Figure 2.11 PBMC isolation (Created in Biorender.com)

DNA isolation

DNA samples were isolated from peripheral blood mononuclear cells (PBMCs) using the QIAamp DNA Blood Mini Kit, depending on the manufacturer's instructions. DNA samples were treated with lysis buffer (AL or ATL) and proteinase K. With smoothly shaking, samples were incubated at 56°C for 10 minutes. Following that, 50 µl of pure ethanol was then added, and it was immediately vortexed. At room temperature, samples were incubated for three minutes. The whole lysate samples were transferred to the QIAmp MiniElute columns. At 8000 rpm, the columns were centrifuged for a minute. Wash buffer (500 µl) was added to each sample. At 8000 rpm, the samples were centrifuged for a minute again. The samples were centrifuged for three minutes at

maximum speed to dry the membrane thoroughly. After this step, new 1.5 ml eppendorf tubes were used to transfer the MiniElute columns. To the center of the membranes, Elution buffer was added. The samples were incubated at RT for a minute. Then, for eluting DNA samples, samples were centrifuged at maximum speed for a minute.

Bisulfite Modification

In a PCR tube, 1 µg DNA was introduced along with 130 µg of CT conversion reagent. Under the following conditions: 98°C for 10 minutes, 64°C for 2.5 hours, and 4°C storage up to 20 hours, the sample was put into a thermal cycler.

Following the addition of 600 µl of M-binding buffer to the zymo-spin column. The sample was put into an M-binding buffer-containing zymo-spin column, and the column was repeatedly inverted. The sample was centrifuged for 30 seconds at maximum speed. After adding 100 µl of M-wash buffer to the column, the centrifuge was run at top speed for 30 seconds. The sample was mixed with 200 µl of M-desulphonation buffer. At room temperature for 17 minutes, the sample was incubated.

The sample was centrifuged for 30 seconds at maximum speed following incubation. After adding 200 µl of M-wash to the column, the centrifuge was run at maximum speed for 30 seconds. There were two repetitions of this washing process. The 1.5 ml eppendorf tube containing the column was filled with 10 µl of the M-elution. To elute BMDNA, the sample was centrifuged for 30 seconds at maximum speed.

PyroMark-PCR

The BMDNA was amplified using FKBP5-pyrosequencing forward and reverse primers after the DNA sample had been modified with bisulfite. The Qiagen PyroMark-PCR kit was used to create PCR reactions (The information about reagents can be found at Table 2.2). The prepared PCR reaction was put to the thermal cycler; Table 2.3. shows the conditions.

All of the samples were placed into 1.5% agarose gel. At 100 volts, the samples were run for 30 minutes. This step was done to check whether the samples were suitable

or not to follow the procedure in pyrosequencing. The pyrosequencing analysis was processed only after being checked for band intensities.

Table 2.2. PyroMark PCR reaction

Reagents	Volume (for 1x Reaction)
PyroMark-PCR Master Mix	12.5 µl
Coral Load	2.5 µl
Q solution	-
Primer Mix	2 µl
Nuclease-free water	6 µl
BMDNA	2 µl

Table 2.3. Optimized pyro-pcr cycling protocol for FKBP5 primer

Step	Temperature	Duration	Cycle(s)
Initial PCR activation step	95°C	15 minutes	1
Denaturation	94°C	30 seconds	50
Annealing	55°C	30 seconds	
Extension	72°C	30 seconds	
Final Extension	72°C	5 minutes	
Cooling	4°C	∞	

Pyrosequencing

A binding mixture including 10 µl of PCR product, 2 µl of streptavidin coated magnetic Sepharose beads, 38 µl of binding buffer, and 30 µl of high purity water was added. For 15 minutes, the PCR-bead mixture was shaken at 1400 rpm. Filter probes were used to collect the biotinylated PCR product, which was then washed with 70% ethanol for 5 seconds, denaturation buffer for 5 seconds, and 1x wash buffer for 10 seconds.

Sequencing primers were then applied to the DNA product-bead mixture, which was then annealed at 80 °C for two minutes before cooling for seven minutes at room temperature. Each run included a control sample of unmethylated and methylated EpiTect DNA as well as a negative control. Substrate, enzyme, and nucleotides were added to the

PyroMark Q96-ID cartridge. The PyroMark program was used to calculate DNA methylation percentages.

2.4. Statistical Analysis

2.4.1. Data quality

Variables from PennCNB results were selected to analyze depending on the study of the reliability of the Turkish version of PennCNB (Izgi et al., 2022). After deciding which variables were used, outliers for each task were chosen depending on the criterion in the same study (Izgi et al., 2022). Previously we claimed that 3.5 SD was removed from the data to determine if it was greater or less than the mean (Izgi et al., 2022). This criterion was not taken into account for this study because only a non-clinical population was included in the previous study. Since this test could not be applied to only 1 patient, all analyzes were performed with the data of 16 patients. For blood variables, only one patient's CRP data was excluded. Based on infection checklist, chronic checklist score was created. If participant had been experiencing the same symptom chronically since the last months, it was recorded as chronic infection symptom.

In PRT task, response bias, discriminability and overall performance were calculated. While deciding which participants' data could be used for further analysis, the reaction time (150 ms < RT < 2500 ms) and the natural log transformation for all blocks. Since several participants could not pass the quality criteria for block 1, response bias and discriminability scores for block 2 and block 3 were used for analysis. 22 participants' data (11 patients and 11 controls) pass the quality criteria for block 2 and block 3.

2.4.2. Analysis

The Statistical Package for Social Sciences (SPSS; Version 28.0) and GraphPad Prism (Version 9.4.1) were used in data analysis. Since the sample size of our study is small, we used nonparametric tests for age and education year differences between groups and Chi-square tests to analyze demographic characteristics, marital status, working status, and gender differences. To investigate differences in all other dependent variables between groups, a nonparametric Mann-Whitney U test was used. Bivariate correlation

analysis was applied to carry out the relation between the methylation level on cg0013050 site and the stressor factors in each group, separately. Predictors of cg0013050 methylation level was analyzed with using multivariate linear regression model. In the regression models, age, SES, group, gender and NLR were used as cofounding variables since SES and age were related the cg00130530 methylation level in the literature and NLR is related to immune system related differences between groups.

Chapter 3

RESULTS

3.1. Comparison of the groups for sociodemographic variables

Thirty-two participants (17 patients with 22q11.2DS and 15 controls) were included in the study. There is no difference in age (U = 78.5, p = .055) and education year (U = 109.5, p = .495) between patients with the 22q11.2 DS group and the control group. The mean age of the control group was 28.07 ±8.9 (min-max: 18–48), and the mean age of the patient group was 26.47 ±8.54 (min-max: 18–47).

Based on their self-report sociodemographic forms, there is no statistical difference in the working status (p = 0.71), marital status (p =0.169), and gender (p = 0.811) between the two groups. In addition, there is no statistically significant difference in the total score of the infection checklist between groups depending on the scale. All sociodemographic data is listed in Table 3.1.

Table 3.1. Sociodemographic Information

GROUPS	**22q11.2DS patients (n= 17)**	**Controls (n=15)**	**p**
Gender (female %)	5 (29%)	5 (33%)	χ^2 = 0.57, p = 0.811
Working status (Have a job %)	7 (41%)	11 (73%)	χ^2 = 5.285, p = 0.071
Marital status (married %)	4 (24%)	7 (47%)	χ^2 = 1.891, p = 0.169
	Mean±S.D. (Min-Max)	**Mean±S.D. (Min-Max)**	**p**
Age	26.47±8.54, 18-47	28.07±8.9, 18-48	p = 0.507
Education (year)	10.29±2.78, 5-14	12.13±3.48, 5-16	p = 0.055
Infection Checklist Score	0.82 ± 1.38, 0-5	0.73±0.88, 0-3	p = 0.692
Chronic Infection Score	0.76±1.30, 0-5	0.47±0.74, 0-2	p= 0.615

3.2. Psychiatric Symptomatology and Self-report Scales for Psychopathology and Stressors in Lifetime

3.2.1. Clinical Evaluation for Psychiatric Symptomatology

Based on clinical evaluation by a psychiatrist, current and lifetime psychiatric diagnoses of participants were analyzed. For patients, current psychiatric medication, diagnosis time for 22q11.2DS, and any significant medical disorder in childhood were also analyzed. The data is represented in Table 3.2. In addition, the results of the data analysis for differences between groups for psychopathology are listed in Table 3.3.

Table 3.2. Clinical evaluation of all psychiatric disorders in all participants

Clinical Evaluations	22q11.2DS patients (n=17)	controls (n=15)
Childhood Medical disorder	13 (76.47%)	-
22q11.2DS diagnosis in childhood	10 (58.82%)	-
Current Psychiatric medication	5 (29.41%)	-
Autism diagnosis in childhood	3 (17.65%)	-
Psychotic Disorder	1 (5.88%)	-
Current depressive disorder	4 (23.53%)	-
Current GAD	7 (41.18%)	-
Current SAD	4 (23.53%)	-
Current OCD	5 (29.41%)	-
Current Specific Phobia/Agoraphobia	5 (29.41%)	-
Lifetime GAD	8 (47.06%)	-
Lifetime SAD	6 (35.29%)	-
Lifetime OCD	5 (29.41%)	-
Lifetime Specific Phobia/Agoraphobia	5 (29.41%)	1 (6.67%)
Lifetime mood disorder	7 (41.18%)	4 (26.67%)
Lifetime any anxiety disorder	13 (76.47%)	1 (6.67%)
Lifetime suicidal ideation	9 (52.94%)	2 (13.33%)
Lifetime depressive disorder	6 (35.29%)	4 (26.67%)

Note. Abbreviations: GAD, general anxiety disorder; SAD, social anxiety disorder; OCD, obsessive-compulsive disorder. (n=17 for patients with 22q11.2DS, n=15 for controls).

Patients were diagnosed significantly more than controls ($p < 0.05$) for lifetime psychiatric disorders; general anxiety disorders ($p = 0.002$), social anxiety disorders ($p =$

0.011), obsessive-compulsive disorder (p = 0.022), any anxiety disorder (p < 0.001), and suicidal ideation (p = 0.019).

Table 3.3. Clinical evaluation of all psychiatric disorders differences between groups

Clinical Evaluations	22q11.2DS patients (n=17)	Controls (n=15)	p
Lifetime GAD	8 (47.06%)	-	**0.002**
Lifetime SAD	6 (35.29%)	-	**0.011**
Lifetime OCD	5 (29.41%)	-	**0.022**
Lifetime Phobia	5 (29.41%)	1 (6.67%)	0.100
Lifetime Mood disorder	7 (41.18%)	4 (26.67%)	0.388
Lifetime Any anxiety disorder	13 (76.47%)	1 (6.67%)	**< 0.001**
Lifetime Suicidal ideation	9 (52.94%)	2 (13.33%)	**0.019**
Lifetime Depressive disorder	6 (35.29%)	4 (26.67%)	0.599

Note. Chi-square test was applied to data. Abbreviations: GAD, general anxiety disorder; SAD, social anxiety disorder; OCD, obsessive-compulsive disorder. (n=17 for patients with 22q11.2DS, n=15 for controls).

Scores of anxiety (p = 0.004), emotional withdrawal (p = 0.002), tension (p = 0.023), suspiciousness (p = 0.030), motor retardation (p = 0.048), unusual thought content (p = 0.006), blunted affect (p = 0.022) subscales and total score of BPRS (p = 0.001) were significantly higher in patient group than control group. The results of the analysis of group differences for BPRS were listed in Table 3.4.

Table 3.4. Brief Psychiatric Rating Scale differences between groups

	GROUPS				
	22q11.2DS (n=17)		Controls (n=15)		p
	Mean±S.D.	Min-Max	Mean±S.D.	Min-Max	
Somatic Concern	1.29±1.61	0-5	0.47±0.64	0-2	0.201
Anxiety	2.41±1.5	0-6	1±0.93	0-3	**0.004**
Emotional Withdrawal	1.47±1.28	0-3	0.2±0.56	0-2	0.002
Conceptual Disorganization	0.35±1.06	0-4	0±0	0	0.177
Guilt Feelings	0.59±1.06	0-3	0.13±0.52	0-2	0.108
Tension	1.59±1.37	0-4	0.53±0.99	0-3	0.023

Mannerism and Posturing	0.24±0.97	0-4	0±0	0	0.348
Grandiosity	0.18±0.73	0-3	0±0	0	0.348
Depressive Mood	1.41±1.33	0-4	0.73±0.8	0-2	0.153
Hostility	0.29±0.85	0-3	0.07±0.26	0-1	0.576
Suspiciousness	1±1.22	0-4	0.2±0.41	0-1	0.030
Hallucinatory Behavior	0.12±0.49	0-2	0±0	0	0.348
Motor Retardation	0.41±0.8	0-2	0±0	0	0.048
Uncooperativeness	0.24±0.75	0-3	0±0	0	0.177
Unusual Thought Content	0.65±0.93	0-3	0±0	0	**0.006**
Blunted Affect	0.71±0.99	0-3	0.07±0.26	0-1	0.022
Excitement	0.76±1.15	0-3	0.33±0.72	0-2	0.272
Disorientation	0±NA	0	0±NA	0	1.000
BPRS	13.71±8.36	0-31	3.73±3.63	0-10	**0.001**

Note. Mann-Whitney U test was applied to data. Abbreviations: M, Mean; BPRS, Brief Psychiatric Rating Scale. (n=17 for patients with 22q11.2DS, n=15 for controls).

Scores of delusions (p = 0.025), bizarre behavior (p = 0.006), and total score of SAPS (p = 0.001) were significantly higher in patient group than control group. Scores of affective flattening or blunting (p = 0.001), alogia (p = 0.049), avolition - apathy (p= 0.005), anhedonia- asocialty (p= 0.028), attention (p=0.002) and total score of SANS (p = 0.000) were significantly higher in patient group than control group. The results of the analysis of group differences for SAPS and SANS were listed in Table 3.5.

Table 3.5. Scale for the Assessment of Positive and Negative Symptoms differences between groups

	GROUPS				
	22q11.2DS (n=17)		**Controls (n=15)**		**p**
	Mean ± S.D.	**Min-Max**	**Mean ± S.D.**	**Min-Max**	
Hallucinations	0.65±1.97	0-8	0±0	0	0.093
Delusions	1.94±4.12	0-15	0±0	0	**0.025**
Bizarre Behavior	2.24±3.29	0-10	0±0	0	**0.006**
Positive Formal Thought Disorder	0	0	0	0	1.000
Inappropriate Affect	0.18±0.53	0-2	0±0	0	0.177
SAPS	5±7.64	0-30	0±0	0	**0.001**

Affective Flattening or Blunting	5.47±6.73	0-21	0±0	0	**0.001**
Alogia	1.82±3.92	0-13	0±0	0	**0.049**
Avolition - Apathy	2.71±3.53	0-11	0.13±0.52	0-2	**0.005**
Anhedonia - Asociality	4.29±5.28	0-13	0.6±1.3	0-4	**0.028**
Attention	3.65±3.81	0-9	0.07±0.26	0-1	**0.002**
SANS	17.94±19.67	0-65	0.8±1.52	0-4	**0.000**

Note. Mann-Whitney U test was applied to data. Abbreviations: SAPS, Scale for Assessment of Positive Symptoms; SANS, Scale for Assessment of Negative Symptoms. (n=17 for patients with 22q11.2DS, n=15 for controls).

3.2.2. Self- report Scales for Psychopathology

Based on the self-report scales for psychopathology, Beck Depression Inventory, Beck Anxiety Inventory, Adult Attention Deficit Hyperactivity Disorder Rating Scale and its subscales, Symptom checklist-90 and its subscales, patients with 22q11.2DS did not report significantly different than controls ($p > 0.05$). Only the WHODAS score ($p=0.027$) and additional scales of SCL-90 ($p= 0.045$) were reported higher by the patient group than the control group. The results of the analysis of group differences for psychopathology self-assessment were listed in Table 3.6.

Table 3.6. Self-report scales for psychopathology in patients with 22q11.2DS and controls

	GROUPS		
	22q11.2DS patients (n=17)	**Controls (n=15)**	**p**
	Mean ± S.D.	**Mean ± S.D.**	
BDI	13.18 ± 12.63	5.73 ± 6.3	0.091
BAI	7.12 ± 7.4	5.8 ± 7.94	0.301
ASRS-A	6.35 ± 3.92	7.6 ± 3.27	0.191
ASRS-B	12.94 ± 5.75	13.53 ± 5.91	0.924
WHODAS	24.71 ± 7.37	20.73 ± 7.3	**0.027**
SCL90_TOT	0.67 ± 0.47	0.52 ± 0.42	0.308
SCL90_OCD	0.88 ± 0.55	0.77 ± 0.58	0.483
SCL90_ANX	0.62 ± 0.58	0.46 ± 0.45	0.447

SCL90_INT	0.81 ± 0.66	0.7 ± 0.61	0.532
SCL90_ANG	0.54 ± 0.6	0.53 ± 0.61	0.893
SCL90_DEP	0.78 ± 0.63	0.67 ± 0.53	0.65
SCL90_PAR	0.68 ± 0.61	0.67 ± 0.53	0.954
SCL90_SOM	0.54 ± 0.43	0.37 ± 0.48	0.123
SCL90-PBI	0.45 ± 0.51	0.27 ± 0.32	0.348
SCL90_FOB	0.44 ± 0.71	0.21 ± 0.25	0.572
SCL90_ADD	0.82 ± 0.54	0.45 ± 0.41	**0.046**

Note. Mann-Whitney U test was applied to data. Abbreviations: SD, Standard Deviation; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; ASRS-A and B, Adult Attention Deficit Hyperactivity Disorder Rating Scale; WHODAS, World Health Organization Disability Assessment Schedule; SCL-90, Symptom Checklist-90; SCL90_OCD, Obsessive-compulsive; SCL90_ANX, Anxiety; SCL90_INT, Interpersonal Sensitivity; SCL90_ANG,Hostility; SCL90_DEP, Depression; SCL90_PAR, Paranoid Ideation; SCL90_SOM, Somatization; SCL90-PBI,Psychoticism; SCL90_FOB,Phobic Anxiety; SCL90_ADD,Additional Scales (n=17 for patients with 22q11.2DS, n=15 for controls).

3.2.3. Self-report Scales for Stressors

Based on self-report measurements for stress-related issues, PSS, MSPSS, and CTQ and its subscales, patients with 22q11.2DS were not significantly different than controls ($p > 0.05$). Only the minimization score ($p=0.024$) was higher in the patient group than in the control group. The results of the analysis of group differences for stress-related measurements were listed in Table 3.7.

Table 3.7. Self-report scales for life adversities in patients with 22q11.2DS and controls

	GROUPS		
	22q11.2DS patients (n=17)	**Controls (n=15)**	**p**
	Mean ± S.D.	**Mean ± S.D.**	
PSS	19 ± 9.05	21.8 ± 9.73	0.416
MSPSS	67.53 ± 14.88	64.27 ± 18.82	0.733
CTQ	32.53 ± 7.63	35.87 ± 6.2	0.21
CTQ-Emotional abuse	6.29 ± 1.9	6.53 ± 1.96	0.685

CTQ-Physical abuse	5.35 ± 1.06	5.33 ± 0.9	0.921
CTQ-Physical neglect	6.12 ± 1.54	7.2 ± 2.08	0.066
CTQ-Emotional neglect	9.76 ± 4.98	11.33 ± 3.66	0.329
CTQ-Sexual abuse	5 ± 0	5.47 ± 1.3	0.057
CTQ-Minimization	1.41 ± 1.23	0.47 ± 0.74	**0.024**

Note. Mann-Whitney U test was applied to data. Abbreviations: S.D., Standard Deviation; PSS, Perceived Stress Scale; MSPSS, Perceived Social Support; CTQ, Childhood Trauma Questionarre (n=17 for patients with 22q11.2DS, n=15 for controls).

3.2.4. Comparison of the groups for STRAIN variables

Based on STRAIN, the total count of stressors was not significantly different between groups ($p > 0.05$). Only the total count of financial ($p=0.024$) and treatment/health ($p=0.004$) stressors were significantly different between groups. While patients reported significantly higher treatment/health stressors, controls reported significantly higher financial stressors (Figure 3.1.). The results of the analysis of group differences for the total count of stressors were listed in Table 3.8.

Table 3.8. Total count of stressors in Primary Life Domain in patients with 22q11.2DS and controls

	GROUPS				
	22q11.2DS (n=17)		**Controls (n=15)**		**p**
	Mean ± S.D.	**Min-Max**	**Mean ± S.D.**	**Min-Max**	
Housing	2.41 ± 3.34	0-11	1.4 ± 1.88	0-6	0.354
Education	0.35 ± 0.61	0-2	0.13 ± 0.35	0-1	0.259
Work	0.76 ± 1.15	0-4	0.93 ± 1.03	0-4	0.352
Treatment/Health	4.35 ± 3.28	0-12	1.2 ± 1.15	0-4	0.004
Marital/Partner	0.76 ± 1.03	0-3	1.87 ± 2.1	0-8	0.068
Reproduction	0.06 ± 0.24	0-1	0.07 ± 0.26	0-1	0.928
Financial	0.18 ± 0.39	0-1	1.13 ± 1.68	0-5	0.024
Legal/Crime	0.41 ± 1.06	0-4	0 ± 0	0	0.093
Other Relationships	0.88 ± 1.17	0-4	1.47 ± 1.25	0-4	0.142

Death	1.29 ± 1.1	0-3	2 ± 1.6	0-5	0.251
Life-Threatening Situations	0.94 ± 1.09	0-3	1.4 ± 1.8	0-6	0.617
Possessions	0.53 ± 0.72	0-2	0.2 ± 0.41	0-1	0.163

Note. Mann-Whitney U test was applied to data. Abbreviations: M, Mean; S.D., Standard Deviation (n=17 for patients with 22q11.2DS, n=15 for controls).

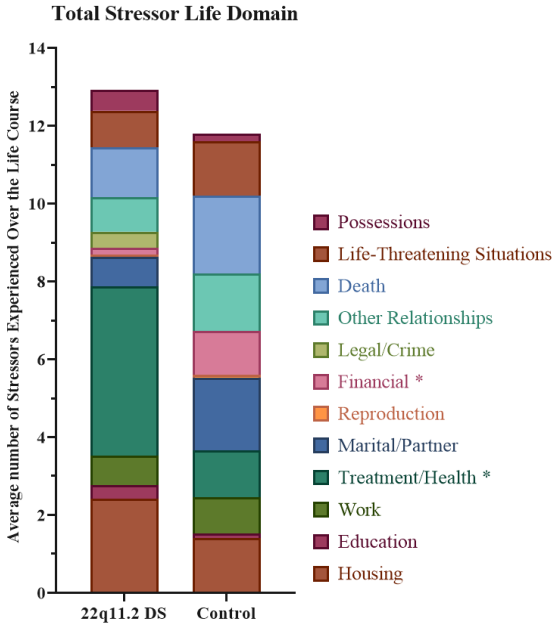

Figure 3.1. Lifetime stressors exposure by stressor category for patients with 22q11.2DS and controls. *p<0.05

Based on STRAIN, with respect to core-social psychological characteristics, there was significantly differences between groups. Patient with 22q11.2DS experienced less interpersonal loss (p=0.021) and entrapment (p=0.001) stressors, and higher physical danger stressors (p=0.010). The results of the analysis of group difference for total count of stressors were listed in Table 3.9.

Table 3.9. Total count of stressors in Core Social-Psychological Characteristics in patients with 22q11.2DS and controls

	GROUPS				
	22q11.2DS (n=17)		Controls (n=15)		p
	Mean ± S.D.	Min-Max	Mean ± S.D.	Min-Max	
Interpersonal Loss	2.24 ± 1.44	0-4	3.87 ± 2.07	1-8	0.021
Physical Danger	4.82 ± 3.17	0-9	1.87 ± 2.1	0-7	0.010
Humiliation	1.24 ± 1.35	0-4	0.87 ± 0.92	0-3	0.577
Entrapment	0.76 ± 1.3	0-5	2 ± 1.07	1-4	0.001
Role Change/Reversal	4.12 ± 4.54	0-17	3.6 ± 3.6	0-12	0.744

Note. Mann-Whitney U test was applied to data. Abbreviations: M, Mean; S.D., Standard Deviation

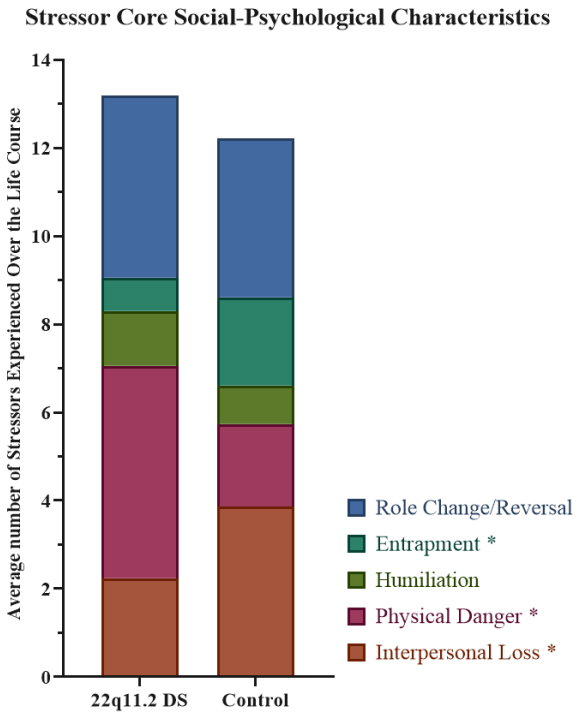

Figure 3.2. Lifetime stressors exposure by stressor category for patients with 22q11.2DS and controls. *p<0.05

Based on STRAIN, 22q11.2DS patients reported significantly higher acute life stressors in treatment/health (p=0.000) and physical danger (p=0.009) domains than controls. The results of the analysis of group difference for total acute life stressors were listed in Table 3.10 and visualized depending on domain or characteristics in Figure 3.3.

Table 3.10. Total count of acute life events in patients with 22q11.2DS and controls

Count of Acute Life Events	22q11.2DS patients (n=17)	Controls (n=15)	p
	Mean ± S.D.	Mean ± S.D.	
Housing	2.06 ± 3.07	1 ± 1.77	0.178
Education	0.35 ± 0.61	0.13 ± 0.35	0.259
Work	0.29 ± 0.77	0.07 ± 0.26	0.34
Treatment/Health	2.88 ± 1.87	0.47 ± 0.64	**0.000**
Marital/Partner	0.24 ± 0.56	0.93 ± 1.67	0.139
Reproduction	0 ± 0	0.07 ± 0.26	0.287
Financial	0.06 ± 0.24	0.8 ± 1.61	0.094
Legal/Crime	0.35 ± 1	0 ± 0	0.093
Other Relationships	0.06 ± 0.24	0.13 ± 0.35	0.478
Death	1.29 ± 1.1	2 ± 1.6	0.251
Life-Threatening Situations	0.88 ± 0.99	1.27 ± 1.49	0.589
Possessions	0.53 ± 0.72	0.2 ± 0.41	0.163
Interpersonal Loss	1.53 ± 1.28	2.67 ± 1.84	0.078
Physical Danger	4.12 ± 2.6	1.6 ± 1.88	**0.01**
Humiliation	0.76 ± 1.09	0.4 ± 0.51	0.561
Entrapment	0	0	1.000
Role Change/Reversal	2.65 ± 3.6	2.53 ± 3.54	0.784

Note. Mann-Whitney U test was applied to data. Abbreviations: S.D., Standard Deviation (n=17 for patients with 22q11.2DS, n=15 for controls).

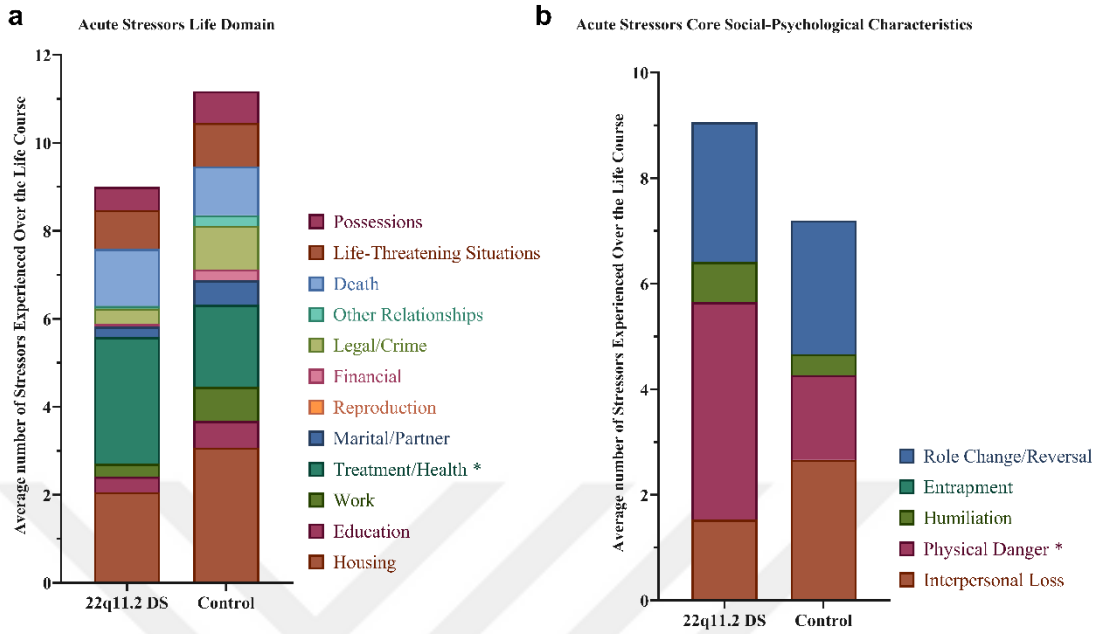

Figure 3.3. Acute life event stressors exposure by stressor category for patients with 22q11.2DS and controls. *p<0.05

Based on STRAIN, 22q11.2DS patients reported significantly lower chronic life stressors in entrapment (p=0.001) characteristics than controls. The results of the analysis of group difference for total chronic life stressors were listed in Table 3.11 and visualized depending on domain or characteristics in Figure 3.4.

Table 3.11. Total count of chronic life events in patients with 22q11.2DS and controls

Count of Chronic Difficulties	GROUPS		p
	22q11.2DS patients (n=17)	Controls (n=15)	
	Mean ± S.D.	Mean ± S.D.	
Housing	0.35 ± 0.61	0.4 ± 0.51	0.633
Education	0	0	1.000
Work	0.47 ± 0.63	0.87 ± 0.84	0.143
Treatment/Health	1.47 ± 1.78	0.73 ± 0.8	0.225
Marital/Partner	0.53 ± 0.72	0.93 ± 0.71	0.096
Reproduction	0.06 ± 0.25	0 ± 0	0.348
Financial	0.12 ± 0.34	0.33 ± 0.49	0.147
Legal/Crime	0.06 ± 0.25	0 ± 0	0.348
Other Relationships	0.82 ± 1.14	1.33 ± 1.05	0.121
Death	0	0	1.000
Life-Threatening Situations	0.06 ± 0.25	0.13 ± 0.52	0.893
Possessions	0	0	1.000
Interpersonal Loss	0.71 ± 0.92	1.2 ± 0.95	0.114
Physical Danger	0.71 ± 0.85	0.27 ± 0.8	0.059
Humiliation	0.47 ± 0.8	0.47 ± 0.75	1.000
Entrapment	0.76 ± 1.31	2 ± 1.07	**0.001**
Role Change/Reversal	1.47 ± 1.42	1.07 ± 0.89	0.468

Note. Mann-Whitney U test was applied to data. Abbreviations: S.D., Standard Deviation (n=17 for patients with 22q11.2DS, n=15 for controls).

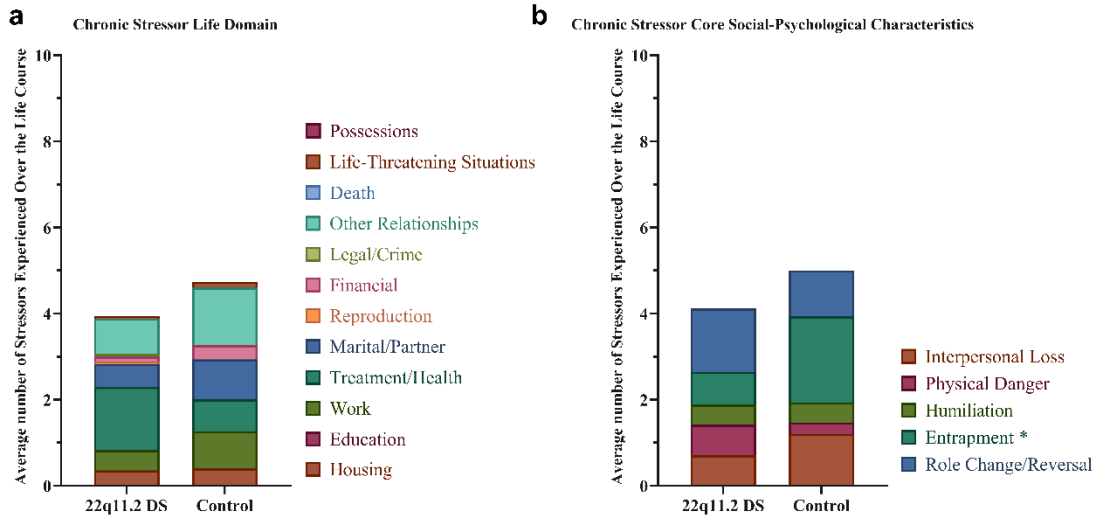

Figure 3.4. Chronic life event stressors exposure by stressor category for patients with 22q11.2DS and controls. *p<0.05

3.3. Comparison of the groups for cognitive assessments

Overall summary score for neurocognitive test battery, "g factor", was calculated. Based on statistical analysis of g factor, patients have significantly lower scores than controls (p = 0.007). The result of the analysis can be found in Table 3.12.

Table 3.12. "g factor" scores in patients with 22q11.2DS and controls

		GROUPS		
		22q11.2DS patients (n=16)	**Controls (n=15)**	**p**
g factor	**Mean**	-0.47	0.51	**0.007**
	S.D.	0.88	0.88	

Note. Mann-Whitney U test was applied to data. Abbreviations: S.D., Standard Deviation. (n=16 for patients with 22q11.2DS, n=15 for controls).

The false positive, true negative and total correct scores for CPF and delayed version were significantly different between two groups (p < 0.05), patients had lower scores for TN and CR than controls (Table 3.13).

Table 3.13. Facial Memory and Delayed Version in patients with 22q11.2DS and controls

	GROUPS		
	22q11.2DS patients (n=16)	**Controls (n=15)**	**p**
	Mean ± S.D.	**Mean ± S.D.**	
CPF_TP	13.44 ± 5.72	15.47 ± 3.91	0.312
CPF_FP	9.75 ± 5.73	3.53 ± 3.34	**0.002**
CPF_TN	10.25 ± 5.73	16.47 ± 3.34	**0.002**
CPF_FN	6.56 ± 5.72	4.53 ± 3.91	0.312
CPF_CR	23.69 ± 4.47	31.93 ± 4.23	**0.000**
CPFD_TP	13.44 ± 6.19	15.33 ± 3.33	0.691
CPFD_FP	9.63 ± 6.43	3.27 ± 3.08	**0.004**
CPFD_TN	10.38 ± 6.43	16.73 ± 3.08	**0.004**
CPFD_FN	6.56 ± 6.19	4.67 ± 3.33	0.691
CPFD_CR	23.81 ± 4.46	32.07 ± 2.81	**0.000**

Note. Mann-Whitney U test was applied to data. Abbreviations: S.D., Standard Deviation. (n=16 for patients with 22q11.2DS, n=15 for controls).

22q11.2DS patients had significantly higher false positive score, whereas they had higher true negative and total correct scores for SVOLT and delayed version ($p < 0.05$) than control group. The result of statistical analysis is represented in Table 3.14.

Table 3.14. Visual Object Learning Task (SVOLT) and Delayed Version Scores in patients with 22q11.2DS and controls

	GROUPS		
	22q11.2DS patients (n=16)	**Controls (n=15)**	**p**
	Mean ± S.D.	**Mean ± S.D.**	
SVOLT_TP	6.75 ± 2.89	6.93 ± 1.94	0.905
SVOLT_FP	6.31 ± 3.24	2.6 ± 1.64	**0.001**
SVOLT_TN	3.69 ± 3.24	7.4 ± 1.64	**0.001**
SVOLT_FN	3.25 ± 2.89	3.07 ± 1.94	0.905
SVOLT_CR	10.44 ± 2.61	14.33 ± 2.32	**0.000**
SVOLTD_TP	6.81 ± 2.81	7.27 ± 2.02	0.643
SVOLTD_FP	6.44 ± 3.1	3.93 ± 1.98	**0.016**
SVOLTD_TN	3.56 ± 3.1	6.07 ± 1.98	**0.016**

SVOLTD_FN	3.19 ± 2.81	2.73 ± 2.02	0.643
SVOLTD_CR	10.38 ± 1.82	13.33 ± 2.5	**0.001**

Note. Mann-Whitney U test was applied to data. Abbreviations: S.D., Standard Deviation. (n=16 for patients with 22q11.2DS, n=15 for controls).

The true positive, false positive, true negative, false negative and total scores for CPN, CPL and CPT were not significantly different between the groups except the false negative score of CPN ($p = 0.042$). All the results of the analysis can be found in Table 3.15.

Table 3.15. Continuous Performance Test (Number and Letter) Scores patients with 22q11.2DS and controls

	GROUPS		
	22q11.2DS patients (n=16)	**Controls (n=15)**	**p**
	Mean ± S.D.	**Mean ± S.D.**	
CPN_TP	42.06 ± 14.4	39.8 ± 17.27	0.936
CPN_FP	28.56 ± 34.46	5.8 ± 3.78	0.077
CPN_TN	80.19 ± 38.98	86.2 ± 30.44	0.843
CPN_FN	12.31 ± 11.18	6.2 ± 8.28	**0.042**
CPL_TP	42.31 ± 14.39	38.4 ± 14.5	0.417
CPL_FP	37.13 ± 39.45	10.13 ± 7.59	0.078
CPL_TN	71.63 ± 43.2	81.87 ± 29.97	0.621
CPL_FN	12.06 ± 12.56	7.6 ± 8.09	0.416
CPT_TP	84.38 ± 26.64	78.2 ± 31.32	0.635
CPT_FP	65.69 ± 71	15.93 ± 10.98	0.068
CPT_TN	151.81 ± 79.53	168.07 ± 60.21	0.953
CPT_FN	24.38 ± 21.11	13.8 ± 15.23	0.143

Note. Mann-Whitney U test was applied to data. Abbreviations: S.D., Standard Deviation. (n=16 for patients with 22q11.2DS, n=15 for controls).

Only the correct response for PCET was significantly lower in-patient group than control group ($p < 0.05$). All the results of the analysis can be found in Table 3.16.

Table 3.16. Conditional Exclusion Test Scores in patients with 22q11.2DS and controls

	GROUPS		
	22q11.2DS patients (n=16)	**Controls (n=15)**	**p**
	Mean ± S.D.	**Mean ± S.D.**	
PCET_CR	22.13 ± 11.02	34.07 ± 10.94	**0.012**
PCET_ER	37.06 ± 14.34	40.93 ± 19.47	0.198
PER_ER	18.5 ± 12.44	26.67 ± 15.59	0.063
PER_RES	19.81 ± 13.29	29.4 ± 16.98	0.055

Note. Mann-Whitney U test was applied to data. Abbreviations: S.D., Standard Deviation. (n=16 for patients with 22q11.2DS, n=15 for controls).

The correct responses for fear, happy, neutral, sad facial expressions and total scores for the ER-40 task were significantly different between two groups ($p < 0.05$) except the correct response for angry facial expression ($p = 0.076$). All the results of the analysis can be found in Table 3.17.

Table 3.17. Emotion recognition task in patients with 22q11.2DS and controls

	GROUPS		
	22q11.2DS patients (n=16)	**Controls (n=15)**	**p**
	Mean ± S.D.	**Mean ± S.D.**	
ER40_ANG	4.06 ± 2.05	5.2 ± 1.26	0.076
ER40_FEAR	4.25 ± 2.41	6.8 ± 1.47	**0.003**
ER40_HAP	6.56 ± 1.59	7.87 ± 0.35	**0.001**
ER40_NOE	5.31 ± 2.36	7.47 ± 1.06	**0.003**
ER40_SAD	4.19 ± 2.23	7 ± 1.31	**0.000**
ER40_CR	24.38 ± 6.77	34.33 ± 3.92	**0.000**

Note. Mann-Whitney U test was applied to data. Abbreviations: S.D., Standard Deviation. (n=16 for patients with 22q11.2DS, n=15 for controls).

The false positive scores for 0-back, 1-back, 2-back trials and also total false positive score for LNB test were significantly different between two groups ($p < 0.05$) while none of true positive score was different between two groups ($p > 0.05$). All the details is represented in Table 3.18.

Table 3.18. Letter-N-Back Scores in patients with 22q11.2DS and controls

	GROUPS		
	22q11.2DS patients (n=16)	**Controls (n=15)**	**p**
	Mean ± S.D.	**Mean ± S.D.**	
LNB2_TP0	13.38 ± 2.09	12.47 ± 2.45	0.411
LNB2_FP0	3.5 ± 5.01	0.73 ± 1.22	**0.025**
LNB2_TP1	11.5 ± 2.83	11.13 ± 2	0.560
LNB2_FP1	6.06 ± 7.05	0.8 ± 1.26	**0.022**
LNB2_TP2	11 ± 3.39	10.4 ± 2.53	0.520
LNB2_FP2	8.38 ± 10.29	0.33 ± 0.49	**0.018**
LNB2_TP	35.88 ± 7.14	34 ± 5.33	0.275
LNB2_FP	17.94 ± 19.41	1.87 ± 2.56	**0.009**

Note. Mann-Whitney U test was applied to data. Abbreviations: S.D., Standard Deviation. (n=16 for patients with 22q11.2DS, n=15 for controls).

Only discriminability score was significantly different between groups (Table 3.19.)

Table 3.19. PRT results in patients with 22q11.2DS and controls

	GROUPS		
	22q11.2DS (n=11)	**Controls (n=11)**	**p**
	Mean ± S.D.	**Mean ± S.D.**	
Response Bias	0.15±0.1	0.14±0.16	0.974
Discriminability	0.05±0.08	0.32±0.13	0.000

Note. Data were analyzed by Mann-Whitney U test. Abbreviations: M, Mean; S.D., Standard Deviation. (n=17 for patients with 22q11.2DS, n=15 for controls).

Since cognitive differences between groups is significantly different from each other, response bias score difference could be affected by this difference. In PRT, discriminability score represents the cognitive performance. To correct the response bias scores depending on the cognitive performance, discriminability score was used in the regression model. The regression model was created with response bias score as a dependent variable and discriminability score and group were used as independent variables. Based on regression model, $F(2,19)=0.218$, $p=0.806$, $R^2=0.022$, neither group nor discriminability score could predict response bias score.

Table 3.20. Linear regression model to assess predictors of response bias

	Response Bias		
	B	**p**	**95% Confidence Interval**
Discriminability	-0.219	0.562	-0.742 to 0.416
Group	0.107	0.777	-0.172 to 0.226

3.4. Comparison of the groups for blood biomarkers

Patients with 22q11.2DS had significantly higher CRP levels (p=0.001); whereas controls had significantly higher lymphocytes (p=0.023) and methylation level on promoter region (p=0.003). The results of the analysis of group difference for blood measurements were listed in Table 3.7. The scatterplot of group difference for methylation level at cg00130530 region was represented in Figure 3.21.

Table 3.21. Blood biomarkers measurement in patients with 22q11.2DS and controls

	GROUPS		
	22q11.2DS patients (n=16)	**Controls (n=15)**	**p**
	Mean ± S.D.	**Mean ± S.D.**	
CRP	4.9 ± 3.59	1.66 ± 1.64	**0.001**
	22q11.2DS patients (n=17)	**Controls (n=15)**	**p**
	Mean ± S.D.	**Mean ± S.D.**	
WBC Count (K/µL)	6.49 ± 1.74	7.25 ± 1.61	0.299
Neutrophil Ratio (%)	58.41 ± 8.2	55.8 ± 7.49	0.344
Neutrophil Count (K/µL)	3.79 ± 1.17	4.07 ± 1.11	0.484
Lymphocyte Ratio (%)	28.71 ± 7.54	33.53 ± 6.5	0.104
Lymphocyte Count (K/µL)	1.86 ± 0.78	2.43 ± 0.64	**0.023**
NLR	2.65 ± 2.82	1.77 ± 0.62	0.131
Methylation level at cg00130530	60.96 ± 8.27	66.31 ± 3.44	**0.003**

Note. Mann-Whitney U test was applied to data. Abbreviations: S.D., Standard Deviation, NLR, Neutrophil-Lymphocyte Ratio. (n=16 for patients with 22q11.2DS, n=15 for controls).

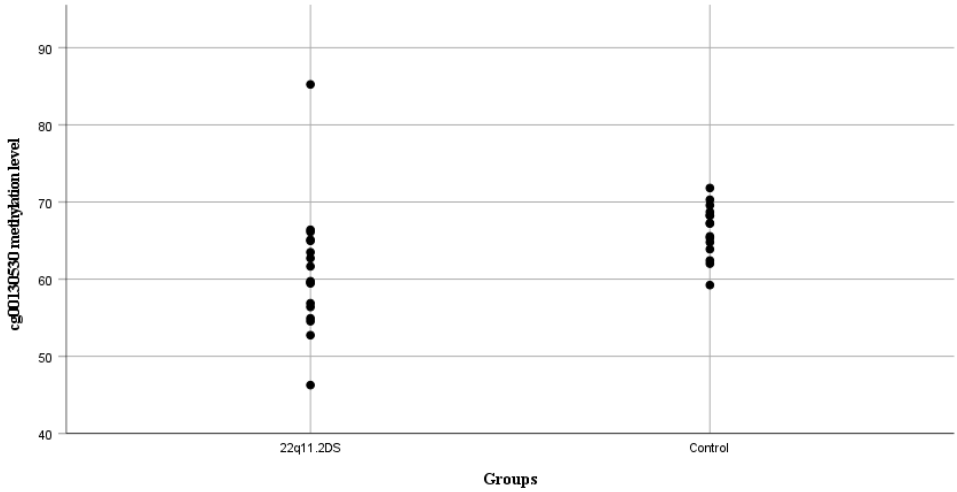

Figure 3.5. The scatterplot of cg00130530 methylation level depending on the groups.

3.5. Correlations between FKBP5 methylation level and Stressors and Scales for Psychopathology

According to bivariate correlation analysis in patient with 22q11.2DS group, cg00130530 methylation level is strongly correlated with stressors of legal/crime (acute life events), other relationships (acute life events and its severity), SCL90_INT, SCL90_PAR and SAPS ($p< 0.01$). In addition, it is correlated with stressors of legal/crime (total count of stressors), other relationships (total severity), possessions (acute life events and total count of stressors), interpersonal loss (severity of acute life events), humiliation (severity of chronic difficulties) and SCL90_FOB ($p < 0.05$).

Table 3.22. Correlation between methylation level and variables in only 22q11.2DS population

Variables	Methylation level at cg00130530
Legal/Crime - Count of Acute Life Events	.705**
Legal/Crime - Total Count	.602*
Other Relationships - Count of Acute Life Events	.757**
Other Relationships - Severity of Acute Life Events	.757**
Other Relationships - Total Severity	.567*
Possessions - Count of Acute Life Events	.584*
Possessions - Total Count	.584*
Interpersonal Loss - Severity of Acute Life Events	.505*
Humiliation - Severity of Chronic Difficulties	.500*
SCL90_INT	.687**
SCL90_PAR	.679**
SCL90_FOB	.581*
SAPS	.764**
**. Correlation is significant at the 0.01 level (2-tailed).	
*. Correlation is significant at the 0.05 level (2-tailed).	

Note. Bivariate correlation was applied. Abbreviations: r, Pearson correlation; SCL90_INT, Interpersonal Sensitivity; SCL90_PAR, Paranoid Ideation; SCL90_FOB, Phobic Anxiety (n=17 for patients with 22q11.2DS).

Based on bivariate correlation analysis in controls, cg00130530 methylation level is strongly negatively correlated with perceived social support ($p < 0.01$). Moreover, it is negatively correlated with age, financial stressors (chronic life events) and NLR ($p < 0.01$). On the other hand, financial stressors (severity of acute life events), other relationships (chronic life events and its severity and total count of stressors), BDI, ASRS-A ($p < 0.05$).

Table 3.23. Correlation between methylation level and variables in only control population

Variables	Methylation level at cg00130530
Age	-.592*
Financial - Count of Chronic Difficulties	-.519*
Financial - Severity of Acute Life Events	.559*
Other Relationships - Count of Chronic Difficulties	.608*
Other Relationships - Total Count	.580*
Other Relationships - Severity of Chronic Difficulties	.541*
Beck Depression Score	.524*
ASRS-A	.519*
Perceived Social Support	-.691**
NLR	-.636*
*. Correlation is significant at the 0.05 level (2-tailed).	
**. Correlation is significant at the 0.01 level (2-tailed).	

Note. Bivariate correlation was applied. Abbreviations: r, Pearson correlation; ASRS-A, Adult Attention Deficit Hyperactivity Disorder Rating Scale (n=15 for control group).

After the bivariate correlation analysis, there is no relation between the lifetime or current psychiatric disorders and cg0013530 methylation level, therefore, the mediation analysis related to stressors and psychiatric disorders as a mediator cg0013530 methylation was not applied.

3.6. Predictors of Methylation level at cg00130530

In a multiple linear regression model, socioeconomic status, age, gender, group, NLR and total stressors were used as predictor variables, cg00130530 methylation as dependent variable. It was found that only group ($p=0.010$, $\beta=7.245$) significantly predicted cg0013530 methylation level. The overall regression model was not statistically significant ($R^2=.31$, $F(6,25) = 1.858$, $p= 0.128$).

In a multiple linear regression model, socioeconomic status, age, gender, group, NLR and acute life events stressors were used as predictor variables, cg00130530 methylation as dependent variable. It was found that group ($p=0.004$, $\beta=8.104$), and the

acute life events stressors (p= 0.043, β=0.503) significantly predicted cg0013530 methylation level. The overall regression model was not statistically significant (R^2=.35, F (6,25) = 2.269, p= 0.069).

In a multiple linear regression model, socioeconomic status, age, gender, group, NLR and acute life was used as predictor variables, cg00130530 methylation as dependent variable. It was found that only group (p=0.027, β= 8.104) significantly predicted cg0013530 methylation level. The overall regression model was not statistically significant (R^2=.245, F (6,25) = 1.308, p= 0.29).

To predict cg00130530 methylation level, total stressor (acute and chronic life events) was investigated with cofounding variables. The overall regression model was not significant. This model was applied for acute life events and chronic life events, separately. Neither for acute life stressor nor chronic life stressor, total regression models were not significant. Although regression model was not significant (R^2=.43, F (6,25) = 3.106, p<0.05), acute life stressor (p = 0.043, β= 0.684) and group (p= 0.004, β= 8.846) could predict the methylation level significantly in the model.

In the specific manner for stressors, stressors of legal/crime and stressors of other relationship were investigated in a regression model. In a multiple linear regression model, socioeconomic status, age, gender, group, NLR and other relationships acute life event stressors were used as predictor variables, cg00130530 methylation as dependent variable. It was found that stressors (other relationships-acute life) (p=0.008), and group (p=0.020) significantly predicted cg0013530 methylation level. The overall regression model was statistically significant (R=.43, F (6,25) = 3.106, p < 0.05).

Table 3.24. Linear regression model for other relationships stressor in sample to predict methylation level at cg00130530

Model	B	Coefficients Std.Error	p
(Constant)	57.279	6.667	0.000
Group/Control	5.667	2.283	**0.020**
Age	-0.196	0.129	0.140
Gender/Male	-0.238	2.348	0.920
SES	0.751	1.054	0.482
NLR	0.235	0.515	0.652
Other Relationships - Count of Acute Life Events	10.686	3.692	**0.008**

Note. Linear regression model was applied to data. Abbreviations: SES, socioeconomic status; NLR, Neutrophil Lymphocyte ratio (n=17 for patients with obesity, n=15 for controls).

In another regression model, SES, age, gender, group, NLR and legal/crime total stressors were used as predictor variables, cg00130530 methylation was dependent variable. It was found that stressors (legal/crime total stressors) ($p<0.001$), group ($p<0.001$), positively, and age ($p=0.002$), negatively predicted cg0013530 methylation level in a significant level. The overall regression model was statistically significant ($R^2=.62$, $F(6,25) = 6.722$, $p<0.001$).

Table 3.25. Linear regression model for legal/crime stressor in sample to predict methylation level at cg00130530

Model	B	Coefficients Std. Error	p
(Constant)	56.942	5.416	0.000
Group/Control	8.960	1.942	**0.000**
Age	-0.379	0.112	**0.002**
Gender/Male	0.650	1.930	0.739
SES	0.218	0.862	0.803
NLR	0.284	0.421	0.506
Domain: Legal/Crime - Total Count	6.154	1.231	**0.000**

Note. Multiple linear regression model was applied to data. Abbreviations: SES, socioeconomic status; NLR, Neutrophil Lymphocyte ratio (n=32 (17 patients with obesity, 15 controls).

3.7. The relationship between stressors, cognitive functions, immune factors, and epigenetic mechanisms changes depending on the psychiatric diagnosis in 22q11.2 DS population

22q11.2DS population was grouped according to having current GAD, current SAD, current depression, and lifetime suicidal ideation. In 17 patients with 22q11.2DS, 7 patients have GAD, 4 patients have SAD, 4 patients have depression, 7 patients have lifetime suicidal ideation.

Level of the stressors were compared in 22q11.2DS population depending on these types of groups. Between patients with GAD and without GAD, there is no significant difference. Patients with SAD had reported significantly more stressors about education domain (acute life events, p=0.019; total stressors, p=0.019). Between patients with depression and without depression, there is no significant difference. Between patients with lifetime suicidal ideation had reported significantly more stressors about housing domain (acute life events, p=0.019; total stressors, p=0.045) and role change/ reversal characteristics (acute life events, p=0.010; total stressors, p=0.010). All differences of total stressors could be found in Figure 3.6., detailed comparison for acute and chronic life events could be found Appendix D (Figure 5.2. & Figure 5.3.).

Cognitive performances were also compared between these groups, g factor was not different between groups. In detail, between patients with GAD and without GAD, only correct response for happy faces was significantly different (p=0.033). Between patients with lifetime suicidal ideation and without ideation, there is significant difference about total correct response of emotion recognition (p= 0.008), correct response for happy faces (p=0.002) and correct response for neutral faces (p=0.031).

Immune factors and cg00130530 methylation level were also compared between these groups. Patients without SAD had significantly more lymphocyte cell count than

patients with SAD (p = 0.009). There is no cg00130530 methylation difference within groups for SAD, GAD, depression, and lifetime suicidal ideation.

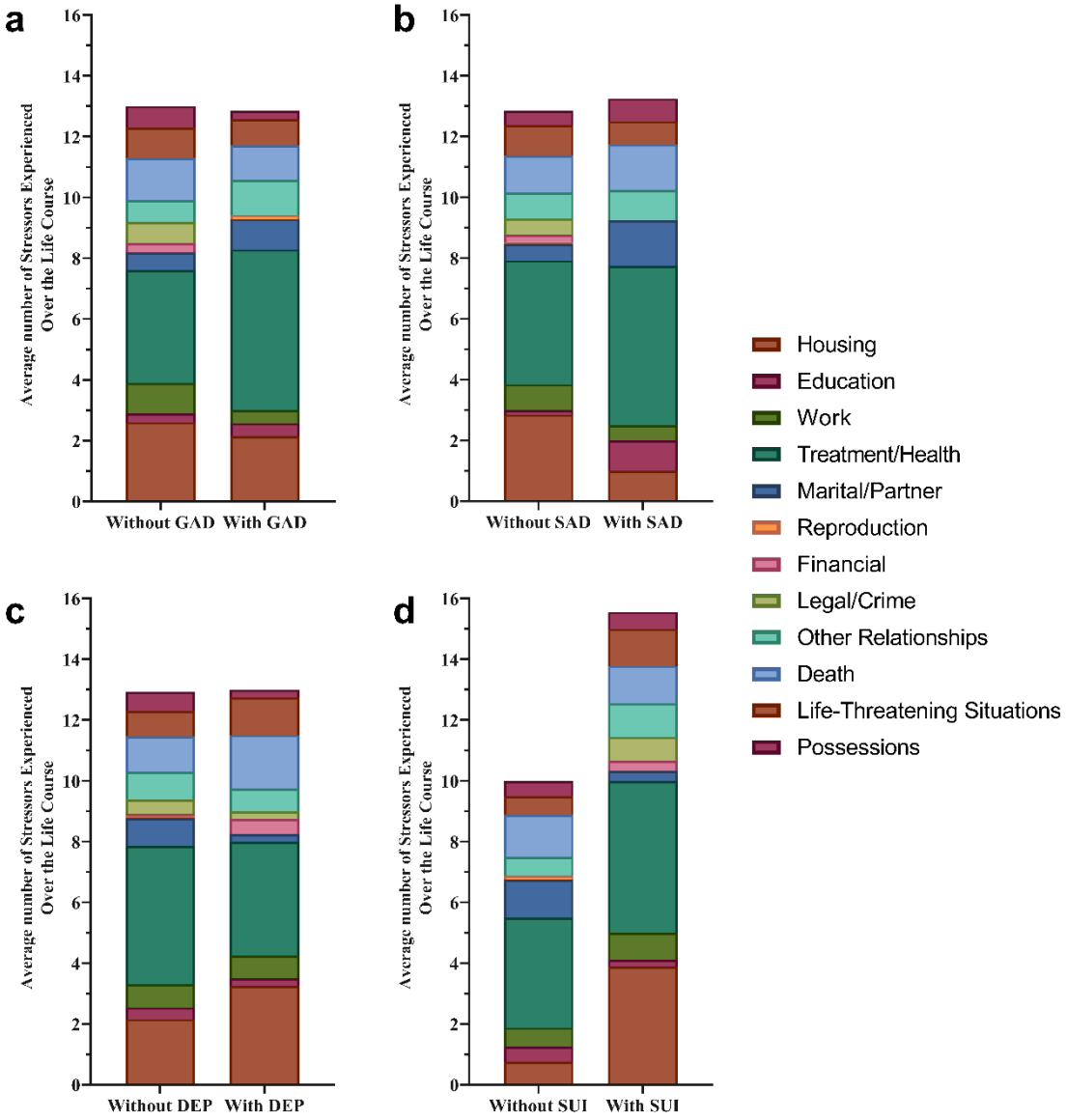

Figure 3.6. Lifetime stressors exposure by stressor category for psychiatric conditions in 22q11.2DS population *p<0.05

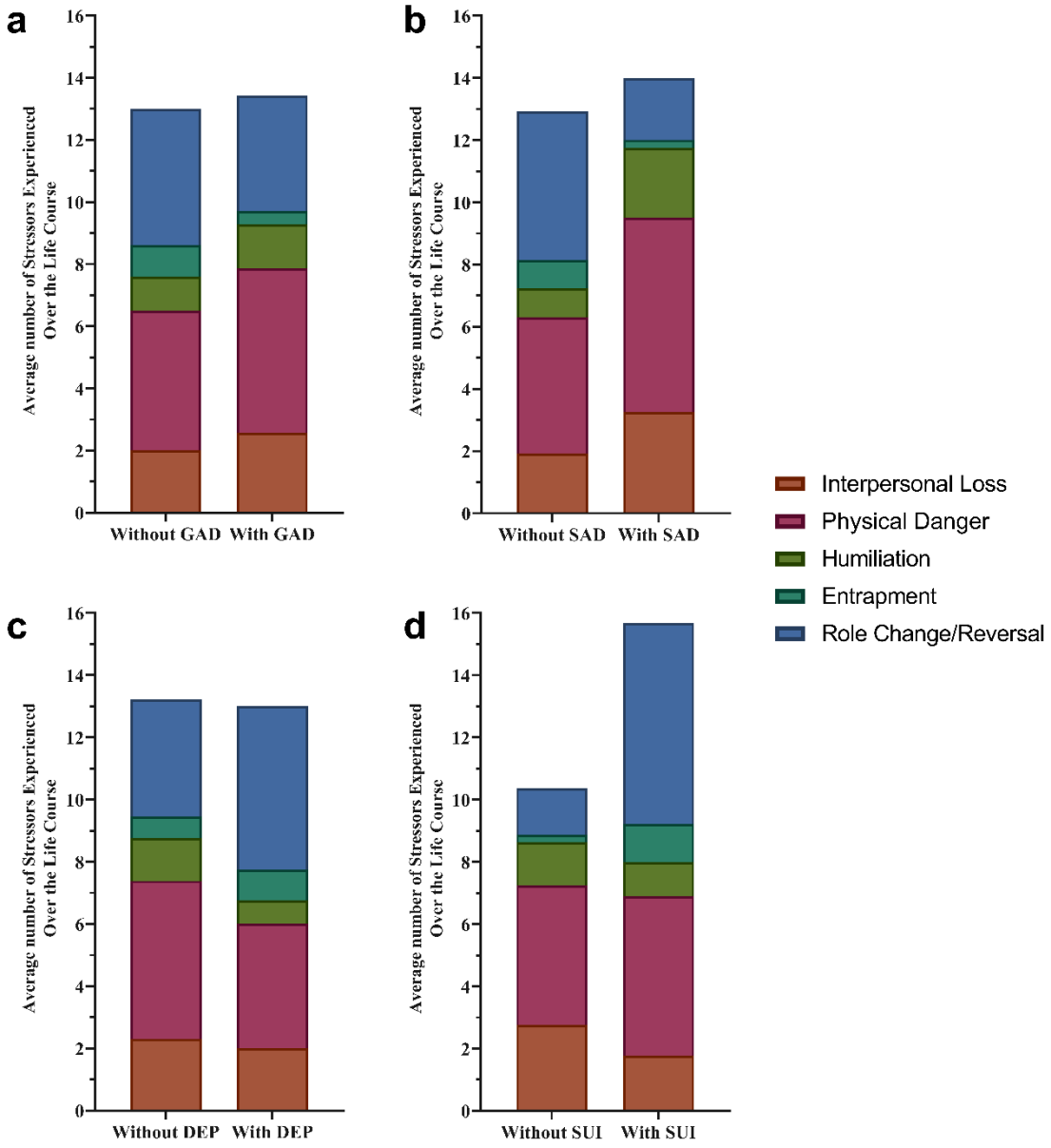

Figure 3.7. Lifetime stressors exposure by stressor category for psychiatric conditions in 22q11.2DS population *p<0.05

Chapter 4

DISCUSSION

In our study, we observed that patients with 22q11.2DS had higher psychiatric diagnoses; general anxiety disorder, social anxiety disorder, and obsessive-compulsive disorder (OCD) compared to controls in a lifetime. Consistent with this finding anxiety subscale score of BPRS was found to be significantly higher in 22q11.2DS. Based on the literature, the prevalence of psychiatric disorder diagnosis was seen more frequently in the 22q11.2DS population (Green et al., 2009; D. M. McDonald-McGinn et al., 2015), and psychotic disorders and schizophrenia were more frequently reported (M. Armando et al., 2017; Monks et al., 2014; M. Schneider et al., 2014). Based on a meta-analysis, in which 74 studies and 7041 individuals were analyzed, Provenzani et al. (2022) reported that psychotic disorder incidence was 11.5%, which is about four times higher than the general population and three times higher than the population with mental retardation. Although the literature represented a high prevalence of the psychotic disorder, our results showed that lifetime any anxiety disorder (76.47%) and mood disorder (41.18%) were most frequently observed in the 22q11.2DS population. One of the reasons we could not find a high prevalence for psychosis as in the literature that the clinical symptoms of ASD and psychosis symptoms could not be easily differentiated in the previous studies. Since not all studies were longitudinal, misinformation during the childhood period could make diagnosis step harder (Lai & Baron-Cohen, 2015). Similar symptoms (catatonic behavior and extreme reaction or overwhelmed (Wing & Shah, 2000)), psychotic belief and paranoid ideation (Van Schalkwyk et al., 2015), social isolation and negative symptoms (Fitzgerald & Corvin, 2001), idiosyncratic speech and thought, and disorganized speech and formal thought disorder (Tebartz van Elst et al., 2013; Wing, 1981) could cause the misdiagnosis, and this situation could also cause underdiagnosis of ASD in the 22q11.2DS population. The difference in the prevalence could have emerged from the diagnosis tool and scales used in the studies, for example our study did not cover ASD, ADHD, PTSD psychiatric disorders in SCID interview, whereas Patel et al. (2022) did not include ASD.

On the other hand, Karayiorgou et al. (2010) suggested that the 22q11.2 locus mutations could be specific to schizophrenia but not autism, depending on the common disease-common allele hypothesis. This study also pointed out that studies looking into the risk factors for psychosis in people with 22q11.2 CNVs have identified some potential relationships to explore, but more research is needed in this area. In this manner, our study tried to understand the relationship between adverse life events and psychiatric disorders and symptoms in the 22q11.2DS population. Still, unfortunately, we could not analyze the adverse life events as a risk factor for psychosis in the 22q11.2DS population since only one patient with 22q11.2DS had a psychotic disorder. Based on a prospective study with children, a predictor of developing psychosis was found as lower verbal IQ at baseline but not having attention-deficit disorder (Gothelf et al., 2007). All patients in our sample were older than 18 years of age, and those with IQ lower than 70 were not included in the study. Maybe for these reasons, we could not observe psychotic disorder or schizophrenia in this population, depending on our clinical evaluations. We will not be able to compare verbal IQ findings (Gothelf et al., 2007) with our study since the lack of a verbal measure, such as vocabulary or verbal reasoning, in our cognitive measurements.

Our findings suggested anxiety disorders had the highest prevalence in the adult population with 22q11.2DS, in accordance with that Fung et al. (2010) found a similar result in their study. They recruited 40 patients with 22q11.2DS (median age: 30 years old, min-max:20-57) only from the cardiac clinic and highlighted their recruitment step was only one non-psychiatric source. Fung et al. also pointed out that one of the reasons behind their finding related to the lower incidence of psychotic disorder could be using a diverse population (large range for age in a sample, generally related to psychiatric departments) in previous studies.

In this manner, our recruitment step was similar to Fung et al. (2010) for the recruitment of patients from a nonpsychiatric clinic. In our study, we recruited patients from various departments of the hospitals (genetics, pediatric cardiology, and immunology). This could be one explanation for similar findings for general anxiety disorder prevalence.

Our result of the high incidence of anxiety may not completely contradict the previous findings related to psychotic diseases. According to literature, the possibility of developing psychotic disorders in the general population with anxiety disorders is quite high, and anxiety and psychotic disorders are comorbid (Huppert & Smith, 2005; Tien & Eaton, 1992). This finding could be supported in the 22q11.2DS population by Zoller et al. (2019) study. They studied 78 patients (17.19 ± 5.37, min-max= 8.1-29.7) with 22q11.2DS and 85 HCs (16.73 ± 5.37, min-max= 8.1-30.0) to determine indicators to find the risk factors for the 22q11.2DS population in developing psychosis. They found that the abnormal functioning of the amygdala/hippocampus and its modulation by the prefrontal cortex may be a characteristic feature of anxiety and could make individuals with 22q11DS more susceptible to psychosis.

In our study, we used PennCNB to measure different cognitive functions. Based on the "g" factor analysis, which is the composite score for executive control (PCET, CPT, LNB) and episodic memory (CPF, SVOLT), the general cognitive score was significantly lower in patients with 22q11.2DS than controls. This finding is supported by the results of Sanders et al. (2022) study, which investigated the difference between typically developing (TD) children and the 22q11.2DS population. Sanders et al found that TD children had higher IQ scores than the children with 22q11.2DS. In this study, WISC-IV Full Scale Intelligence Quotient (FSIQ) was used to evaluate general intellectual functioning, which was compared to PennCNB scores in the study of R. C. Gur et al. (2021). This study showed that PennCNB could be used rather than IQ scores to evaluate the relationship between the brain and behavior beyond intelligence (R. C. Gur et al., 2021).

In the present study, there were significant differences between groups; patients had lower TN and CR scores and higher FP scores in these tasks, CPF and delayed version, and SVOLT and delayed version. This difference could show us episodic memory deficits were observed in our 22q11.2DS population.

In the LNB task, there were significant differences between groups; patients had higher FP scores in LNB tasks in 0-back, 1-back, 2-back and total trials. In the PCET task, patients with 22q11.2DS have a lower correct response. In addition, their PER_RES

scores were not significant but lower than the control group (p= 0.055). Only FN scores of CPN were significantly different between the groups in CPT. These tests were included in the executive functions. Depending on our results, we did not find a dramatic difference between correct response scores except PCET. These findings did not directly show that there were no deficits in executive functions in our 22q11.2DS population. Since this task was quite difficult for these participants, it could be interpreted as they had difficulty in being cooperative.

These tests were used in another study with two different cohorts with 22q11.2DS from Tel Aviv (n=59, mean age: 21.4 ± 6.3) and Philadelphia (n=155, mean age: 19.7 ± 6.3) (Yi et al., 2016). In our population, the mean correct response of CPF was 23.69 ± 4.47, whereas the same score of Tel Aviv and Philadelphia populations was 24.31 ± 3.57 and 24.85 ± 3.48, respectively. In the SVOLT task, the mean of correct response was 10.44 ± 2.61, whereas the same score of Tel Aviv and Philadelphia populations was 12.67 ± 2.70 and 13.47 ± 2.54, respectively. One of the explanations for a higher correct response for episodic memory could be age; other populations were younger than our population (mean age: 28.07 ± 8.9, 18-48). This finding was consistent with the literature; PennCNB scores (specifically memory and executive functions) were negatively correlated with age (Gur et al., 2001; Gur et al., 2010).

Based on the findings of our previous study with the normative population (n=58, mean age: 29.67 ± 11.50), the mean of correct response for CPF and SVOLT tasks were 31.59 ± 3.63 and 16.32 ± 2.30 (Izgi et al., 2022). In line with that, our present study results showed that the CPF and SVOLT task scores of the control group were 31.93 ± 4.23 and 14.33 ± 2.32. This slight difference could be explained by age and education factors. The sample of Izgi et al. (2022) was slightly older than ours, but at the same time, an education level (13.29 ± 3.0) was higher (12.13 ± 3.48).

R. E. Gur et al. (2021) pointed out that there is a connection between schizophrenia and certain cognitive traits, such as intelligence quotient (IQ), and researchers should consider using polygenic risk scores (PRSs) to better understand the variation in the risk and progression of psychosis. Our study, PRS, was not included in our study, but cognitive performance scores could be used for understanding the risk for

and progression of psychosis. In our sample, there was dramatically different between groups in emotion recognition, episodic memory, and partially working memory.

Our findings suggested that the 22q11.2DS population had significantly lower emotion recognition ability than their matched controls. This finding is also supported by previous studies since social cognition was highlighted in the literature with deficits in 22q11.2DS, and it was also related to psychosis (Kimoto et al., 2019; Zaharia et al., 2018). In Yi et al. (2016) study, the mean correct response of ER40 of Tel Aviv and Philadelphia populations were 25.75 ± 5.66 and 28.63 ± 4.36, respectively. Moreover, in one of our studies (in progress), in which PennCNB was used, individuals with ultra-high risk for psychosis (UHR) and patients with schizophrenia disorder were included. Based on the results, the mean of CPF_CR scores were 26.93 ± 3.77 (SCZ) and 28.86 ± 5.1(UHR), and the mean of ER40_CR scores were 27 ± 5,84 (SCZ) and 32,83 ± 2,79 (UHR), whereas; our present study finding showed that of the mean of CPF_CR score was 23.69 ± 4.47 and mean of ER40_CR score was 24.3 ± 6.77. As we have mentioned earlier, age and education factors could cause a difference in cognitive functions. Therefore, there was a slight difference between our results and the previous study of Yi et al. (2016) and our previous study (in progress).

Weinberger et al. (2016) also mentioned that individuals with 22q11DS who have psychosis features have more severe cognitive impairments than those without psychosis features, and they can be distinguished from other 22q11DS individuals by their greater deficits in executive function, complex cognition, and social cognition.

In light of these growing pieces of evidence, we could suggest a neurocognitive phenotype of psychosis in our sample. This could explain the reason for the low incidence of psychotic disorder in the population and lower scores of episodic memory, social cognition, working memory, and general cognitive decline. Based on (Maes, 2022), machine learning algorithms that were not guided by human supervision were able to identify a new subtype of schizophrenia called major neurocognitive psychosis (MNP), which is characterized by negative symptoms, a slowing of motor function, and general cognitive decline. This subtype is distinct from other forms of schizophrenia and cannot be accurately studied without taking it into account. In line with that, in our study, patients

with 22q11.2DS had significantly higher negative symptoms, lower g factor scores, social cognition, and episodic memory. We also found that scores of SANS and each of its subscales were higher in 22q11.2DS.

Our study also showed that patients with 22q11.2DS differed from the control group on discriminability but not response bias in the PRT task. Similar findings were reported in the study with SCZ, Bipolar Disorder (BD), and HC participants by Lewandowski et al. (2016). Depending on this study, researchers suggested that reward learning was associated with symptoms of psychosis, particularly negative symptoms, and it was predictive of deficits in social cognition. However, the study did not find any association between reward learning and neurocognitive performance. This suggested that, across SCZ and BD patient groups, social cognition may share common pathways with this aspect of reinforcement learning, but neurocognition does not (Lewandowski et al., 2016).

If we discuss our findings in terms of negative life events, the total count of stressors did not significantly differ between groups, but some specific types of stressors were found to be significantly different between groups. In this manner, as we expected, stressors about treatment/health count were found to be higher in the patient group. But unexpectedly, the count of financial stressors was found to be higher in the control group than in the 22q11.2DS patient. From the social-psychological perspective, patients had significantly higher physical danger stressors, whereas controls had higher interpersonal loss and entrapment stressors. These stressors were categorized as acute and chronic difficulties; treatment/ health and physical danger as acute difficulties and entrapment as chronic difficulty were significantly different between groups.

Moreover, there was no significant difference between groups for self-report measurements; PSS, MSPSS, CTQ, and subscales. These results were seemingly contradictory to our clinical evaluation and patients ’story. Based on their family sayings, these patients have been bullied by peers, had educational struggles, and were vulnerable to abuse. Only the minimization score was seen as significantly different and higher in the 22q11.2DS population. A significantly high minimization score of CTQ could be evidence to patients with 22q11.2DS who had no proper insights about how people

behave them. In addition, a high minimization score could show us there could be a response bias in which the magnitude of childhood trauma suffered is minimized. Our findings on adverse life events showed us that the patient group is not exposed to more adverse life events than the population, except for the medical stress due to CNV, and we even observed that the population is more exposed to some types of stressors of life events. At this point, it can be argued that the control group in our study had a lifetime diagnosis of psychiatric disease and was more exposed to negative life events at some points than the patients. In the clinical interviews we conducted, we can say that our control group survived these events and illness periods without medical help, although they had some events and diseases in the past, so we can say that they are a resilient group. Apart from this, we may not have been able to obtain an accurate result, especially regarding non-objective stresses (exclusion, humiliation, etc.) due to the "self-report bias" we observed in patients. Another finding supporting this situation is that although the ASRS scores of the patients were not different from the control group, the FP scores in CPT, which is an objective measure, were quite high.

On the other hand, in our sample, there was a difference between groups in one subscale of SCL-90, a self-report scale for psychopathology. This subscale consists of these items“ Trouble falling asleep?”, “Sleep that is restless or disturbed?”, “Awakening in the early morning?”, “Poor appetite?”, “Thoughts of death or dying?”, “Overeating,” Feeling of guilt.” According to the literature, the population with 22q11.2 CNV carriers had higher sleep disturbances with nondependent psychiatric conditions, but at the same time, sleep problems could affect the psychiatric symptoms. There were some studies about the relation between sleep and the LZTR1 gene; in the 22q11.2 locus, literature suggested that with affecting GABAergic signaling, the LZTR1 gene had a role in sleep (Benes et al., 1992; Hoftman et al., 2015; Horder et al., 2018; Marsman et al., 2014; Schür et al., 2016). Therefore, we could suggest that the genetic condition of the 22q11.2DS population probably caused this SCL-90 additional scale differences.

In our study, the CRP level was significantly higher in the patient group, whereas the lymphocyte count was significantly lower. One of the recent studies by Mekori-Domachevsky et al. (2017), in which 49 22q11.2DS patients and 30 HC participated,

found that 22q11.2DS patients had significantly higher levels of certain inflammatory markers; CRP, IL-6, TNFα, and IL-10. Another recent study H.-H. Yu et al. (2022) represented that lymphopenia was seen in 93% of the population with 22q11.2DS population. These findings supported our study in terms of higher CRP levels and lymphopenia in the 22q11.2DS group.

From the epigenetic perspective, we found that patients with 22q11.2DS had significantly lower methylation levels at the cg00130530 region. In further examination, we observed that methylation level was correlated with different stressors in different groups. In the control group, cg00130530 methylation level negatively correlated with social support and count of financial stressors. In the 22q11.2DS population group, it was found to be positively correlated with legal/crime and other related stressors.

To understand the role of FKBP5 methylation level in 22q11.2DS, we looked at the literature about the relationship between stressors, psychiatric disorders, and cg00130530 methylation. Growing evidence about the relationship between FKBP5 gene methylation and childhood adversities, Marzi et al. (2018) tried to understand the victimization and methylation relation with children and adolescents (1669 blood samples were used) by using the CTQ scale, but they did not find the methylation level change at the cg00130530 region. They pointed out that victimization could cause methylation change in adulthood. Weder et al. (2014) also investigated the methylation level between traumatized and non-traumatized children; they did not find any significant results at this point. Our study could not see any relation between CTQ scores and methylation level at cg00130530. With 1231 participants (mean age= 69.55 ± 9.35), Needham et al. (2015) studied the effect of childhood SES on methylation level; they did not find any relation between cg00130530 and childhood SES. With the same cohort, Smith et al. (2017) also tried to understand neighborhood characteristics and methylation level of genes, but they could not find any significant relationship between these dimensions: education, occupation, income and wealth, poverty, employment, and housing. In line with that, we could not find any relationship between the methylation level and housing stressors in our population.

S. R. H. Beach et al. (2022) studied young African-American adults (n= 449, mean age= 28.67± 0.79) who experienced threatening events during childhood. The study investigated danger, family conflict, discrimination, and family SES relation between methylation. They found a relationship between danger and cg00130530 methylation. The "danger" was measured with these questions in their study: if there was a fight in the neighborhood with weapons, any sexual assault, and rubber in the last six months. In addition, Steven R. H. Beach et al. (2022) studied with the same cohort and found a change in methylation levels at cg20813374 and cg00130530 regions with "danger." This change in methylation was strongly linked to aging. We could say that our study was similar to these two studies with this finding; a significant correlation between legal/crime acute and total stressors with methylation level at the cg00130530 region in the 22q11.2DS population. From social discrimination perspective, our sample looked similar to the sample of Beach's studies (Steven R. H. Beach et al., 2022; S. R. H. Beach et al., 2022).

Zannas et al. (2019) tried to understand how methylation and stress play a role in immunological factors in different population with cardiovascular disease (n >3000, mean age= 55.79, min:18 max:87). They found that aging and stress-related change in FKBP5 methylation could play a role in inflammation, which could predict cardiovascular disease. We also investigated whether cg00130530 methylation level and stressors relation had a role in developing a psychiatric disorder, but the mediation analysis could not be applied. Acute life stressors and cg0013530 methylation level were found related, but the psychiatric disorder (e.g., Acute Stress Disorder, PTSD) relation could not be analyzed since our clinical interview does not cover PTSD symptoms. Therefore, the relationship between psychiatric disorders and stressors and the role of cg0013530 methylation level (as a mediator) could not be investigated.

Depending on the regression analysis using all our samples, cg00130530 methylation level was predicted separately with legal/crime total stressors and other relationships acute stressors. Moreover, research has shown that aging could lead to increased demethylation of FKBP5 in several brain regions, including the intron 7 and promoter region of the gene (Blair et al., 2013). In accordance with the literature, age

negatively and significantly predicted cg00130530 methylation level in a regression model with legal/crime total stressors.

Considering growing evidence about the FKBP5 gene methylation and stress. We could explain our results that the higher vulnerability of psychiatric disorders could be explained by the lower methylation level of the FKBP5 gene. This site is promoter associated region, and the decreasing methylation level could mean that the gene expression increases. Therefore, FKBP5 gene expression and, theoretically, protein level would be high, and it could cause the inhibition of GR signaling, which causes the deficit in the negative feedback loop in the HPA axis (stress-induced HPA axis). In addition, we could observe that stressors positively predict the methylation level at this CpG, so maybe this methylation site in the promotor-associated region could behave differently depending on the SNP and transcription binding site and factors near this region. Unfortunately, we could not analyze genetic variations and any factors related to chromatin structure change and affect the transcription mechanism until now. On the other hand, after considering the analysis in only 22q11.2DS depending on their psychiatric symptoms, we could say that this population's genetic vulnerability could be the most important predictor for their psychiatric condition rather than their adverse life events. In addition, cumulative effect of the intensities of different stressors should be taken into account. According to Stephanie H. Parade et al. (2021), there are many different factors that can affect how adversity impacts a person, such as the type and timing of the adversity, the availability and effectiveness of resources to help cope with the adversity, and any new events or the amount of time that has passed since the early adversity. To be clear about the relation between stress and psychiatric disorders in 22q11.2DS population with a mediation of FKBP5 methylation; we should consider count, type, severity, time and the duration of the stressors. Here we used the domains of stressors but we need to apply further analysis with the stressors in trajectory analysis like in used by Slavich and Shields (2018).

This study has several strengths. Firstly, patients were recruited from different centers (genetics, immunology, and cardiology) and not specifically from the psychiatry outpatient clinic. Therefore, our sample was more representative rather than the studies

recruiting samples from one specific clinic. There is no recruitment bias in our study. Secondly, the psychiatrist used structured clinical interviews for psychiatric evaluations to apply standardized measurement in the study. Besides, we used the STRAIN battery and valid stress scales to obtain a 3D stress universe. In addition, epigenetic mechanisms related to stress and the relation with psychiatric disorders were considered in this study. To the best of our knowledge, this is the first study to evaluate various stressors and psychiatric disorders related to FKBP5 methylation in the 22q11.2DS population. Methylation changes with gene x environment interaction (stress universe) and as a potential biomarker of risk for developing psychiatric disease would be an essential next step.

This study has some limitations. Our research had a small sample size for patients and controls. There were some reasons; patients were not motivated to come hospital, COVID-19 issues, and many struggles while finding controls matched to education level and age. Our control group had different lifetime psychiatric disorder diagnoses; this could be criticized. As we have explained before, they did not need any medical support and recovered; we could say that this group was resilient. As we have already mentioned, we could have a self-report bias in the 22q11.2DS population since their minimization score was high. Also, some stressors, like bullying, were reported by family members more than our data.

On the other hand, to obtain every detail of the stress universe of the participants, different questionnaires that try to measure their stress levels and the STRAIN battery, which evaluates the traumas they have experienced throughout their lives, were used. Still, we may have yet to cover some of the stress conditions of the participants completely. Although this is inevitable in human studies, it should be mentioned. Besides the group, we could not apply any quality criteria to PennCNB since FP scores of the 22q11.2DS population were represented to us; this task was too hard to handle by this population. This situation was also seen in PRT; many patients could not pass the quality criteria step. At last, the literature suggested that there could be a relationship between smoking status and methylation change, but we did not take this information from our participants.

For future perspectives, this procedure would be applied to more control samples, and the sample size would be larger. We would like to create composite biological and stressor scores and apply trajectory analysis to get a more accurate stressor analysis. To understand the relationship between childhood adversities and FKBP5 methylation level change in 22q11.2DS, we would like to use methylation analysis cg25114611 site in the promoter region, intron 2, intron 5 and intron 7 region in FKBP5 gene. In addition to a more comprehensive understanding of the population, SNP analysis would be applied, and cortisol, IL-1, IL-6, and TNF-α levels would be measured. In the present study, we could not show the relation between cg00130530 methylation level and stressors, but this could be merged by using only the type of stressors, not composite scores. According to S. H. Parade et al. (2021), it is essential to continue to recognize the complexity of the interplay between biological and environmental factors and individual differences and to keep this in mind when considering the findings of different studies, as apparent discrepancies may indicate areas for further research and more nuanced theoretical understandings.

For further analysis, structural and resting functional magnetic resonance (fMRI) images will be obtained from the participants, and the relationship between the changes in brain cortical thickness and gray matter volume changes and clinical measurements in 22q11DS individuals according to the controls will be examined. On the resting state fMRI images, the differences between the amygdala and prefrontal cortex areas in participants with 22q11.2DS and controls and the effects of stressful life events on this connectivity would also be examined. Moreover, the Virtual Trier Social Stress Test (VR-TSST) would treat participants with acute stress. Heart rate, cortisol, IL-1, IL-6, and TNF-α levels would be measured as stress biomarkers, and self-report questionnaires would determine affective changes. This way, the differences in stress responses of individuals with 22q11DS would be investigated.

In summary, the present study showed that individuals diagnosed with 22q11DS have higher psychiatric diagnoses and cg00130530 methylation levels than the general population. According to our preliminary analysis, we could say that the relation behind the high prevalence of psychiatric disorders (specifically anxiety) could be explained by

their chromosomal abnormalities. Effects of the stressors and FKBP5 methylation would be decided after applying future perspectives.

CHAPTER 5

APPENDIX

APPENDIX A – INFECTION CHECKLIST

Enfeksiyon Kontrol Listesi

Son 1 hafta içinde aşağıdaki belirtilerden hangilerini yaşadığınızı belirtiniz.

1. Ateş
2. Halsizlik
3. Öksürük
4. Boğaz ağrısı
5. Kulak ağrısı veya kulaktan akıntı
6. Burun akıntısı veya burunda tıkanıklık
7. Geniz akıntısı
8. Koku alamama
9. Nefes almada güçlük
10. Göğüs ağrısı
11. İshal
12. Karın ağrısı
13. İdrar yaparken yanma
14. Sık idrara çıkma
15. İdrar renginde değişiklik
16. Genital bölgede akıntı, kaşınma ya da kızarıklık
17. Kas ya da eklem ağrısı
18. Baş ağrısı
19. Üzerinde kızarıklık, ağrı ve ısı artışı olan cilt yarası

Bilinen kronik bir rahatsızlığınız var mı?

Düzenli kullandığınız bir ilaç var mı? (doğum kontrol hapı, kortizon, antidepresan)

Son 1 hafta içinde hiç ilaç kullandınız mı?

APPENDIX B - VALIDATION OF FKBP5 PYROSEQUENCING PRIMER

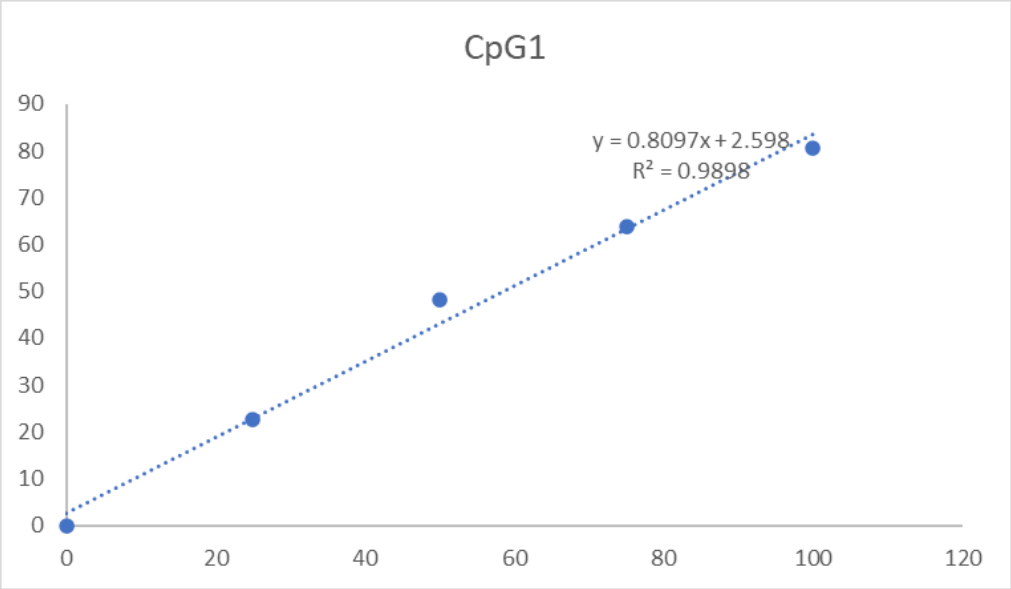

Figure 5.1. Validation results of FKBP5 pyrosequencing primer

APPENDIX C – REPORT OF cg00130530 PYROSEQUENCING PRIMER

Table 5.1. Details about cg00130530 pyrosequencing primer

Pyrosequencing Assay Design Analysis Report

Assay Name	Assay1	**Created by**	KUH\mzeybel
Assay Type	Methylation Analysis (CpG)	**Created Date**	15.07.2022 09:43
Direction	Forward	**Changed Date**	15.07.2022 09:43
Description			
Notes			

Primer Set 1			**Score: 84 Quality: Medium**		
Primer	**Id**	**Sequence**	**Nt**	**Tm, ºC**	**%GC**
PCR	F1	GATGTTTAGTAGGGATTGGGGAAATT	26	59.7	38.5
PCR	R1	AACTCAACCCTAAAACCTCTTCCTATT	27	57.6	37.0
Sequencing	S1	GGATTGGGGAAATTTTATT	19	44.7	31.6

Target Polymorphisms	Position4
Sequence to Analyze	TYGAGAATTA ATTTAGTAGA TATTATT

Analysis Steps

Name: **Biotinylated PCR Primer Hairpin Analysis**
Description: Evaluates hairpin structures on the biotinylated PCR primer.
Penalty: 0

Name: **Duplex Formation Analysis**
Description: Identifies possible annealing between the sequencing primer and the biotinylated PCR primer.
Penalty: 0

Name: **Mispriming Analysis**
Description: Identifies alternate annealing sites for the sequencing primer on the amplicon.
Mispriming 1

```
                                  5'- GGATTGGGGAAATTTTATT -3'
                                       |||||    | ||| ||||
3'-
...TAAAAAAAAACCTATAAATCACTAACATTTCTAATATAAAAAAAAACC
AAACA... -5'

   Mispriming 3' Position: 262
   Penalty:                34
```

	Misprimin g 2 5'- GGATTGGGGAAATTTTATT -3' ||| | | || ||||| 3'- ...CCTTTAAAATAAAGCTCTTAATTAAATCATCTATAATAAAAAAAAACC TATAA... -5' Mispriming 3' Position: 226 Penalty: 33 Misprimin g 3 5'- GGATTGGGGAAATTTTATT -3' | | ||||| || 3'- ...AAAATAAAGCTCTTAATTAAATCATCTATAATAAAAAAAAACCTATAA ATCAC... -5' Mispriming 3' Position: 231 Penalty: 14 Penalty: 34
	Name: **Template Loop Analysis** Descripti on: Identifies possible template loops on the amplicon. Template loop 01 AA...TTCCCCAATCCCTACTAAACATCA -3' A |||| || | TC...CTATAAATCACTAACATTTCTAATATAAAAAAAAACCAAACAATAA AAAATTCATCC... -Biotin-5' Added A at 3' end of template Loop size: 73 Penalty: 7 Penalty: 7

Primer Pair		
Amplicon length	167	
Score	87	
Amplicon %GC	24.0	
Analysis Steps	Name:	**Amplicon Length Analysis**
	Description:	Checks the deviation of the amplicon length from the optimum length.
	Penalty:	22
	Name:	**Duplex Formation Analysis**
	Description:	Identifies possible PCR primer cross-annealing.
	Penalty:	0
	Name:	**GC Content Analysis**
	Description:	Calculates the deviation of GC content between PCR primers and amplicon.

	Penalty: 11
	Name: **Melting Temperature Difference** Description: Identifies melting temperature differences between the PCR primers. Penalty: 1

PCR Primer	
Sequence	GATGTTTAGTAGGGATTGGGGAAATT (26 nt)
Score	93
Position, 5'-3'	169 - 194
%GC	38.5
Tm, ºC	59.7
Analysis Steps	Name: **Complementarity Analysis** Description: Identifies low complementarity for the PCR primer. Penalty: 24
	Name: **Duplex Formation Analysis** Description: Identifies possible PCR primer self-annealing. Penalty: 0
	Name: **Hairpin Loop Analysis** Description: Investigates possible hairpin structures on the PCR primer. Penalty: 0
	Name: **Melting Temperature Analysis** Description: Calculates the melting temperature of the PCR primer and compares it with the optimum. Algorithm NearestNeighbor_MisMatch Tm, °C 59.7 Penalty: 0
	Name: **Mispriming Analysis** Description: Identifies alternate annealing sites for the PCR primer on the DNA template. Penalty: 0
	Name: **Primer End Stability Analysis** Description: Compares the stability between the 3'-end and the 5'-end on the PCR primer. Stability `5' end delta G: -11.16 kcal/mol` `Mean 3' end delta G: -7.59 kcal/mol` Penalty: 0

	Name: **Primer Length Analysis** Description: Show warnings for short primers Penalty: 0 *Note: This penalty will not affect the final score*

PCR Primer		
Sequence	AACTCAACCCTAAAACCTCTTCCTATT (27 nt)	
Score	93	
Position, 5'-3'	335 - 309	
%GC	37.0	
Tm, ºC	57.6	
Analysis Steps	Name: **Complementarity Analysis** Description: Identifies low complementarity for the PCR primer. Penalty: 24	
	Name: **Duplex Formation Analysis** Description: Identifies possible PCR primer self-annealing. Penalty: 0	
	Name: **Hairpin Loop Analysis** Description: Investigates possible hairpin structures on the PCR primer. Penalty: 0	
	Name: **Melting Temperature Analysis** Description: Calculates the melting temperature of the PCR primer and compares it with the optimum. Algorithm NearestNeighbor_MisMatch Tm, °C 57.6 Penalty: 5	
	Name: **Mispriming Analysis** Description: Identifies alternate annealing sites for the PCR primer on the DNA template. Penalty: 0	
	Name: **Primer End Stability Analysis** Description: Compares the stability between the 3'-end and the 5'-end on the PCR primer. Stability `5' end delta G: -9.42 kcal/mol` `Mean 3' end delta G: -6.76 kcal/mol` Penalty: 0	

	Name: **Primer Length Analysis** Description: Show warnings for short primers Penalty: 0 *Note: This penalty will not affect the final score*	

➞ Sequencing Primer		
Sequence	GGATTGGGGAAATTTTATT (19 nt)	
Score	100	
Position, 5'-3'	181 - 199	
%GC	31.6	
Tm, ºC	44.7	
Analysis Steps	Name: **Complementarity Analysis** Description: Identifies low complementarity for the sequencing primer. Penalty: 0	
	Name: **Duplex Formation Analysis** Description: Identifies possible sequencing primer self-annealing. Penalty: 0	
	Name: **Hairpin Loop Analysis** Description: Investigates possible hairpin structures on the sequencing primer. Penalty: 0	
	Name: **Melting Temperature Analysis** Description: Calculates the melting temperature of the sequencing primer and compares it with the optimum. Algorithm NearestNeighbor_MisMatch Tm, °C 44.7 Penalty: 0	
	Name: **Primer Length Analysis** Description: Show warnings for short primers Penalty: 0 *Note: This penalty will not affect the final score*	
	Name: **Target Distance Analysis** Description: Show warnings if sequencing primer is located outside the target distance settings. Penalty: 0 *Note: This penalty will not affect the final score*	
	Name: **Homopolymer Analysis**	

Description:	Checks homopolymer sequence adjacent to target polymorphism.
Penalty:	0
Name:	**A-nucleotide Analysis**
Description:	Checks for A in target polymorphism.
Penalty:	0

Assay Design Settings

PCR Primer

Min Primer Length [nt]	18
Max Primer Length [nt]	30
Optimal Amplicon Length From [nt]	50
Optimal Amplicon Length To [nt]	100
Max Amplicon Length [nt]	400
Allow Primer Over Variable Position	Yes
Melting Temp Algorithm	NN Mismatch
Primer Concentration [µM]	0.2
Min Melting Temperature [°C]	50.0
Max Melting Temperature [°C]	72.0
Max Allowed Tm Difference [°C]	10.0
Max GC Difference [%]	50

Sequencing Primer

Min Primer Length [nt]	15
Max Primer Length [nt]	25
Min Distance From Target [nt]	0
Max Distance From Target [nt]	10
Allow Primer Over Variable Position	Yes
Generate Forward Primers	Yes
Generate Reverse Primers	Yes
Melting Temp Algorithm	NN Mismatch
Min Melting Temperature [°C]	29.0
Max Melting Temperature [°C]	59.0

Primer Set

Primer Set #	100

Sequence with marked primers

```
     GATGTTTAGT AGGGATTGGG GAAATT
     ||||||||||  ||||||||| ||||||
                 GGATTGGG GAAATTTTAT T
                 |||||||| |||||||||| |
 169 GATGTTTAGT AGGGATTGGG GAAATTTTAT TTYGAGAATT AATTTAGTAG
ATATTATTTT TTTTTGGATA TTTAGTGATT GTAAAGATTA


 259 TATTTTTTTT TGGTTTGTTA TTTTTTAAGT AGGAGATTTT AGGAGATTAA
AATAGGAAGA GGTTTTAGGG TTGAGTT 336

|||||||||| ||||||| || |||||||

TTATCCTTCT CCAAAATCCC AACTCAA
```

APPENDIX D - ACUTE AND CHRONIC LIFE EVENT STRESSORS DIFFERENCES BETWEEN GROUPS (BASED ON PSYHIATRIC CONDITIONS)

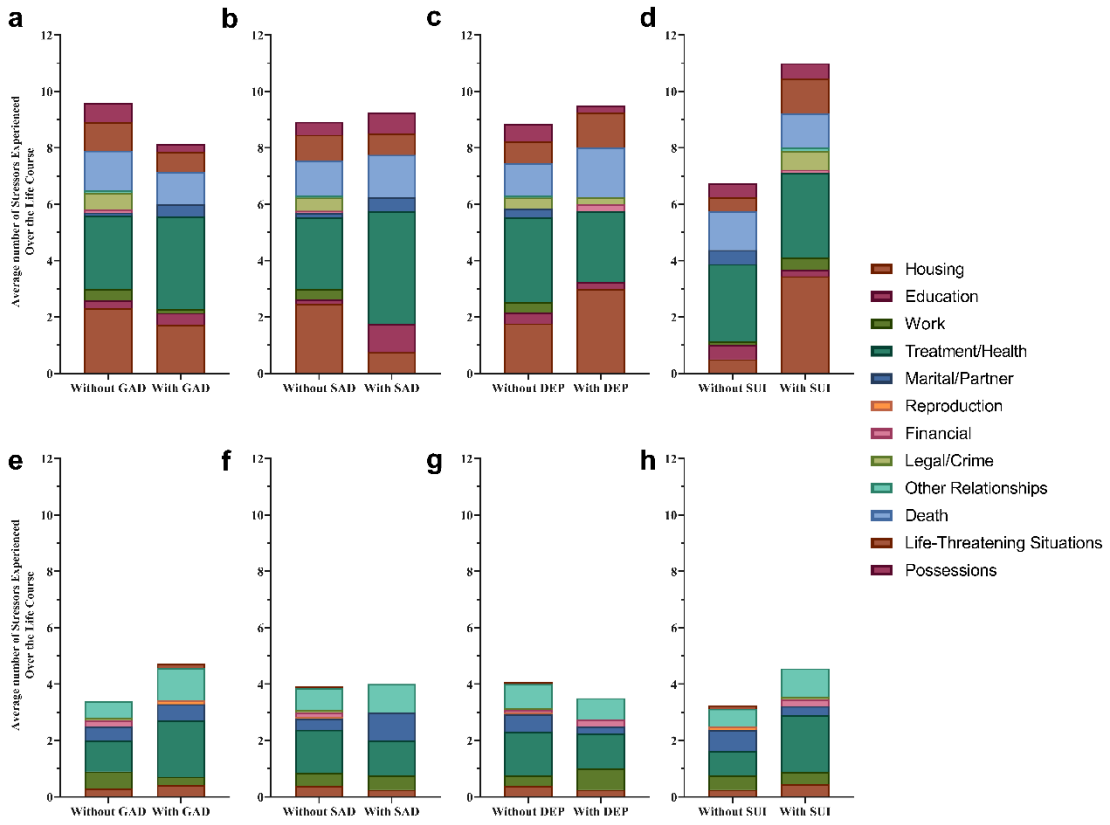

Figure 5.2. Lifetime stressors exposure by stressor category for psychiatric conditions in 22q11.2DS population , * $p<0.05$

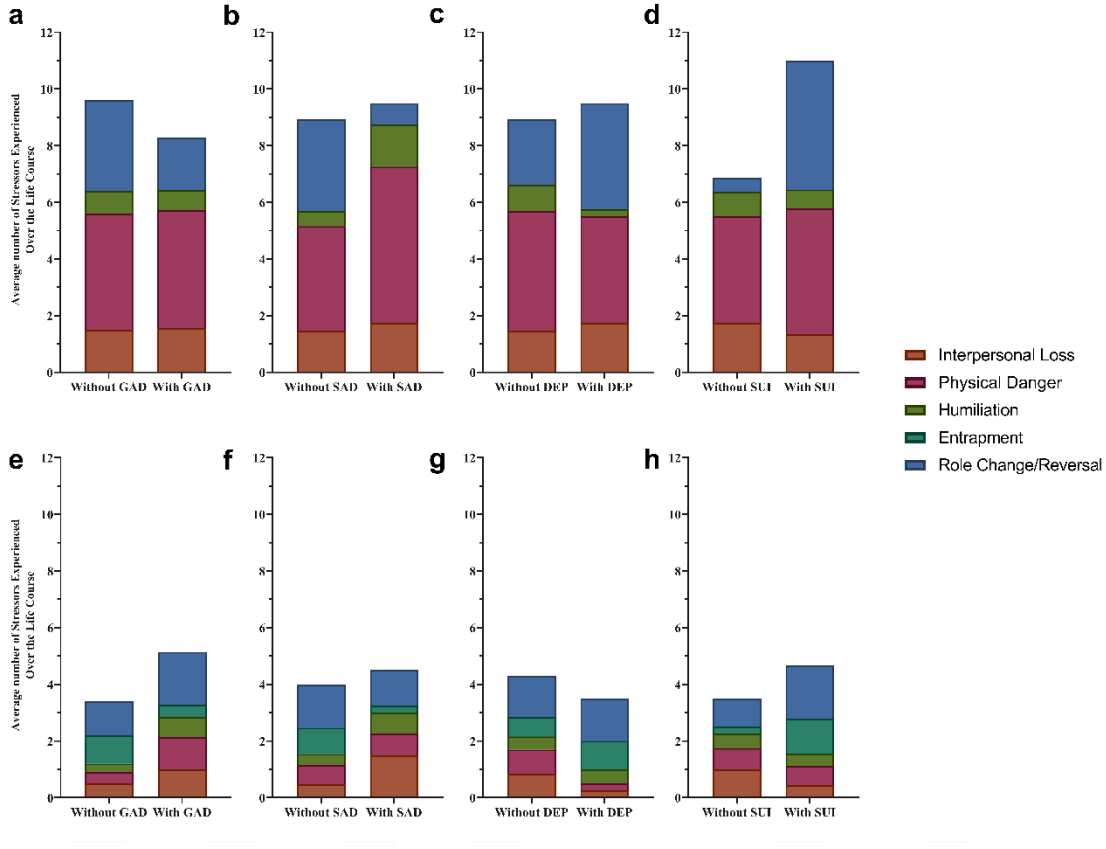

Figure 5.3. Lifetime stressors exposure by stressor category for psychiatric conditions in 22q11.2DS population , * $p<0.05$

CHAPTER 6

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