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Association of DRD2 Gene C957T Polymorphism with Stuttering in Turkish Population

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ABSTRACT: This study aims to evaluate the association of DRD2 gene C957T polymorphism with stuttering within Turkish children who stutter. The sample of the study included 121 children between the ages of 5-16, 44 children with stuttering and 77 typically developing children. The genomic DNA's were extracted from the saliva of the individuals. The genotyping of DRD2 C957T was carried out using polymerase chain reaction-restriction fragment length polymorphism. The relationship between genotypes and stuttering was examined through logistic regression analysis. In the study, it was determined that distributions of allele frequencies and the DRD2 gene C957T polymorphism were not significantly different from the control group (OR 0.762; CI 0.458-1.267, p=0.304). The genotype distributions of the DRD2 gene were estimated for CT (OR 1.103; CI 0.443-2.743, p=0.833) and TT (OR 0.868; CI 0.306-2.461; P=0.791). The genotype distributions of DRD2 C957T polymorphism were not statistically significant for additive, dominant, recessive, and codominant models between study groups. As a result, the polymorphic feature of the alleles and genotypes for the DRD2 gene C957T in Turkish children who stutter were analyzed, and it was detected that the differences between CWS and CWNS groups were not significant.

Keywords: Stuttering, DRD2, rs6277, Turkish population

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INTRODUCTION

Developmental stuttering is a common condition characterized by involuntary sound, syllable, word and phrase repetitions, blocks, and prolongations which disrupt the efficient flow of speech and leads to psychosocial difficulties (Guitar, 2006). It usually begins between the ages of 2-5 and affects more males than females. 5% of people are reported to stutter during part of their lives (Mansson, 2000). Its incidence across all age groups is 0.72% since every 4 out of 5 children recover it spontaneously (Craig et al., 2002).

Although the exact etiology of stuttering has not been yet elucidated, there is substantial research demonstrated by family (Raza et al., 2012, Raza et al., 2013), twin (Howie, 1981; Felsenfeld et al., 2000; Ooki 2005; Dworzynski et al., 2007, Fagnani et al., 2011; Rautakoski et al., 2012) and adoption studies (Felsenfeld and Plomin, 1997) that genetic components have a role in. Although the heritable factors in stuttering are reported to be strong, the exact mode of transmission is unknown yet.

While defining the premotor circuits in the 'dual premotor stuttering hypothesis', Alm (2014) divided circuits into two: the medial system (basal ganglia and complementary motor area) and the lateral system cerebellum and lateral premotor cortex. According to this model, the medical system is responsible for controlling speech initiation signals. In contrast, the lateral system is thought to be involved in motor activation in response to externally cued sensory input, and the movements are performed with attention. Basal ganglia are suggested to help supplementer the motor area by providing internal timing cues to initiate self-initiated speech movements. So, the medial and basal ganglia are thought to be disturbed in people who stutter while the lateral system is intact.

Dopamine is a key neurotransmitter of the basal ganglia and thought to have a major role in fine motor movements (Lan et al., 2009). When the dopamine-excess theory of stuttering is considered, an unusual rise in cerebral dopaminergic activity may be effecting stuttering. PET scanning studies (Wu et al., 1997) reveal that dopaminergic activity in people who stutter is 50-200% higher than controls. It is anticipated that the most intense dopamine innervation in the brain is taken by basal ganglia's striatum and in the pharmacological studies and it has been seen that the medications, which inhibit type D2 dopamine receptors (D2Rs), impair stuttering systems (Brady, 1991; Stager et al., 2005; Tran et al., 2008).

A molecular case-control study by Lan et al. (2009) explored the role of dopaminergic polymorphisms in Han Chinese people who stutter. Results of the research revealed that the C allele of the *dopamine D2 receptor* (DRD2) C957T polymorphism (rs6277) on chromosome 11q23 may exemplify the enhanced susceptibility for developmental stuttering. In a larger sample, Kang et al. (2012) studied the association between stuttering and SNPs that reside in (*DRD2*) gene in Brazilian and western European people who stutter and their sex-matched controls. However, their data did not support the previous findings of Lan et al., claiming that the C allele of rs6277 is associated with stuttering. In a later study, Montag et al. (2012) investigated the association between personality trait neuroticism and the DRD2 C957T (rs6277) in Caucasian people who stutter. Consistent with Kang et al.'s findings, no connection was discovered among stuttering and polymorphism on the DRD2 gene by the authors. However, carriers of the CC and the CT genotype in their sample are reported to have significantly higher neuroticism scores (Montag et al., 2012).

There is not any study exploring the role of stuttering candidate genes in Turkish people who stutter. Thus, this initial study aims to explore the potential associations of dopaminergic gene DRD2 and stuttering within Turkish-speaking children who stutter.

MATERIALS AND METHODS

Participants

Participants were 44 Turkish children who stuttered (CWS) who had clinical diagnoses from the Kocaeli University Hospital, Child and Adolescent Psychiatry Unit, Speech and Language Therapy Clinic. All participants were diagnosed by experienced speech and language therapists based on a detailed clinical interview and Stuttering Severity Instrument IV (SSI-4) at the first session. The experimental group included 44 CWS (34 boys, 10 girls) aged between 5.00 and 16 (8.65±2.54). The participants had no any other speech or language problem nor had any history of neurological, psychiatric, or hearing disorder had received any therapy for stuttering or had any learning problem. 75% of the children had a positive family history of stuttering.

The control group of the sample included a total of 77 children aged 5-14 years and were accessed by contacting the schools in the same city. Inclusion criteria for the control group participating in the study were not having the diagnosis of an accompanying psychiatric or neurological condition, not having speech and language problems and not using drugs likely to affect cognitive processes (Pellowski and Conture, 2002), which was obtained through a demographic data form.

Ethical approval for the study was obtained from the Kocaeli University Ethical Board of Noninterventional Research (KÜ GOKAEK 2019/174). The study was designed and conducted in accordance with Helsinki Declaration. Informed consent was obtained from the parents of the children accepting to participate in the study.

Instruments

Stuttering Severity Instrument Version 4: The Turkish version of Stuttering Severity Instrument (SSI-4) (Mutlu, 2015) was administered to all of the participants by a speech and language therapist to determine the severity of stuttering.

Isolation of DNA

DNA isolation was performed from the saliva using the EURx GeneMATRIX Tissue&Bacterial DNA Purification Kit following the procedures recommended by the company. DNA concentrations of the samples were measured using the Qubit 2.0 Fluorometer kit (Invitrogen, America).

Polymerase Chain Reaction and RFLP

PCR amplified the DRD2 gene C957T genotypes with the primers 5'-ACCACGGTCTCCACAGCACTCT-3’ (forward 1), 5’- ACCATGGTCTCCACAGCACTCT-3’ (forward 2), and 5'-ATGGCGAGCATCTGAGTGGCT-3' (reverse) (Mohammadi et al., 2018). PCR steps were involved: 5 minutes at 95 ℃ (predenaturation), 40 cycles at 95 ℃ for 30 s (denaturation), 30 s at 62 ℃ (annealing), 30 s at 72 ℃ (extension), and 7 min at 72 ℃ (final extension). PCR product size was predicted as 196 bp. The PCR products were digested with Taq 1 (ER0671, Thermo Fisher Scientific Inc), PCR products were digested at 65 ℃ for an hour, followed by electrophoresis on 3% high-resolution agarose gel (100 V for 75 minutes) and visualized with a UV transilluminator by using Safe-T staining (ethidium bromide alternative) with the purpose of detecting the DNA bands. The wild-type allele “C” encapsuled two particles, 174 bp and 22 bp. When the 196 bp particle subsisted uncut, the polymorphic variant T was discovered (Figure 1).

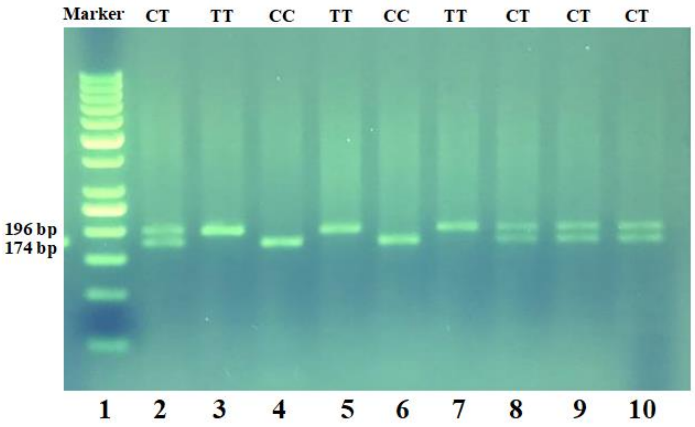

Figure 1. High-resolution agarose gel electrophoresis model of the RFLP outputs of DRD2 C957T polymorphism. While column 1 demonstrates a 50-bp DNA molecular marker, column 2,8,9 and 10 illustrates the CT genotype, columns 3, 5, and 7 demonstrate the TT genotype, and columns 4 and 6 indicate the CC genotype, columns 2-5 pertain to the CWS and columns 6-10 pertain to the CWNS.

RFLP refers to Restriction particle length polymorphism; while CWS, refers to Children who stuttered; and finally CWNS, as Children who did not stutter.

Data Analysis

The genotype and allele frequencies of the DRD2 C957T polymorphism were examined for Hardy-Weinberg Equilibrium (HWE) via a chi-square test. Deviations from HWE were investigated by means of Michael H. Court's (2005-2008) online calculator. Statistical analysis of demographic features was performed via chi-square test and Man Whitney U test by using SPSS version 20. For the DRD2 gene C957T polymorphism, unconditional logistic regression was used to calculate odds ratios (OR) in 95% confidence intervals (95% CI) for CWS. $P<0.05$ value was considered statistically significant.

RESULTS AND DISCUSSION

In this study, we examined 44 CWS patients and 77 CWNS well-person controls. Table 1 shows the allele and the genotype frequencies of the DRD2 gene C957T polymorphism in CWS and CWNS. No aberration was beheld from the Hardy-Weinberg equilibrium for both CWS and CWNS, when the genotype frequencies of this polymorphism were evaluated ($p>0.05$). For the C957T polymorphism of the DRD2 gene according to the additive model, in the CWS group, 11 patients (25%) were CC genotype, 21 patients (48%) were TC genotype, and 12 patients (27%) were TT genotype; in the CWNS group, 19 healthy individuals (25%) were CC genotype, 40 individuals (52%) were CT genotype, and 18 individuals (23%) were TT genotype. For the DRD2 SNP, we detected that CT genotype versus CC genotype resulted in the odds ratio of 1.103 fold, but the ratio was not statistically significant ($p=0.833$). The dominant model, which compares the combined the genotypes of CT+TT with the CC genotype, was not statistically different between the CWS and CWNS groups ($p>0.05$). At the same time, the recessive model (CC+CT genotype combination versus TT genotype) and the codominant model (CC+TT genotype combination versus CT genotype) were not statistically significant (respectively, $p=0.633$ and $p=0.655$) between both groups. When the allelic frequencies of the DRD2 rs6277 are considered, there were no discrepancy between the CWS and CWNS groups in the Turkish population ($p>0.05$) (Table 2).

Table 1. Descriptive Statistics Regarding Demographic Features of participants

Groups	Female n (%)	Male n (%)	p value	Age (y) mean ± SD	p value
CWS	10 (23)	34 (77)	1.000	8.65±2.54	0.703
CWNS	18 (23)	59 (77)		8.68±2.23	

CWS: Children with stuttering, CWNS: Children with nonstuttering, n: Number of participants

Table 2. Distribution of the genotype and allele frequencies of DRD2 C957T polymorphism in CWS and CWNS subjects.

DRD2 C957T		CWS (n= 44) *n (%)*	CWNS (n=77) *n (%)*	*p* value	OR CI (95%)
Additive	CC	11 (25)	19 (25)	-	-
	CT	21 (48)	40 (52)	0.833	1.103 (0.443-2.743)
	TT	12 (27)	18 (23)	0.791	0.868 (0.306-2.461)
Dominant	CC	11 (25)	19 (25)		
	CT+TT	33 (75)	58 (75)	0.968	1.018 (0.432-2.397)
Recessive	CC+CT	32 (73)	59 (77)		
	TT	12 (27)	18 (23)	0.633	0.814 (0.349-1.899)
Codominant	CC+TT	23 (52)	37 (48)		
	CT	21 (48)	40 (52)	0.655	1.184 (0.564-2.485)
Alleles	C	43 (44)	78 (51)		
	T	55 (56)	76 (49)	0.304	0,762 (0.458-1.267)

CWS: Children with stuttering, CWNS: Children with nonstuttering, n: Number of participants

The first genetic studies on stuttering are carried between 1924-1939 and mainly focused on family incidence. Scientists for over 80 years have used family pedigrees and twin studies to investigate the inheritance of stuttering and determined that it tends to cluster in families (Kraft, 2010). In the early 2000s, with the advancement of technology, specific genes in stuttering disease began to be investigated using blood samples (Kraft, 2010).

Studies on the stuttering estimate that it is compatible with the family history of stuttering. Twin studies confirm these findings. Also, male relatives actually have a higher risk than female relatives (Kraft, 2010; Perez and Stoeckle, 2016). Linkage analysis has shown that the disease may be associated with changes in some regions on chromosomes 9, 10, 12, 13, 15, and 18. (Shugart et al., 2004; Riaz et al., 2005; Suresh et al. 2006; Wittke-Thomps et al., 2007, Domingues et al., 2014).

DRD2 polymorphism has been found to be associated with a severe risk of alcoholism (Noble, 1998). The A1 variation of the DRD2 gene has also been found with a higher rate in alcoholics, drug abusers, smokers, and other addictive, compulsive or impulsive diseases. (Kraft, 2010). This gene affects dopamine receptors and reinforces repetitive behaviours in an individual. Genetic examination of the DRD2 gene, a prevalent dopamine receptor in the brain, has shown that the frequency of a specific allele in adults who stutter (AWS) is increased (Lan et al., 2009). However, this finding could not be obtained in later studies.

Stuttering affecting fluency is a neurobiological disease that is predicted to be inherited, and its prevalence among adults is around 1% (Dworzynski et al., 2007; Kang et al., 2011). Pharmacological and neurobiological findings show that the neurotransmitter dopamine and the basal ganglia may play an important role in stuttering, whose etiology is not understood yet and the pathogenesis is still unknown. (Wu et al., 1995; Maguire et al., 2004; Alm, 2004). The first genetic study in this area was conducted by Lan et al. (2009) in the Han Chinese people who stutter. They reported that the C allele of

the DRD2 C957T polymorphism found in 11q23 could be a possible element in the development of a speech disorder such as stuttering in their research (Lan et al., 2009). Human DRD2 C957T polymorphism regulates DRD2 availability in the striatum. Individuals with the CC genotype show the lowest D2 receptor affinity (Hirvonen et al., 2004). Montag et al. (2012) investigated the role of the DRD2 gene C957Tpolymorphism in neuroticism in stutterer. They found that personality traits such as neuroticism and biomarkers such as rs6277 SNPs on the DRD2 gene would deeply understand stuttering (Montag et al., 2012).

Investigating the connection between developmental stuttering in children and the levels of serum homovanillic acid (HVA), DRD2 rs6277, and solute carrier family with 6 members 3 (SLC6A3) human dopamine transporter (hDAT) rs28364997 polymorphisms in a study on the Iranian Kurdish population, Mohammadi et al. (2018) detected that the difference of the allele frequencies of DRD2 C957T between the CW and the CWNS was tenuous. On the contrary, the TT genotype frequency was statistically higher among the CWS ($p=0.02$, OR=2.25, 95% CI=1.03-4.90). They indicated that DRD2 C957T polymorphism might be a risk factor for the development of stuttering there among their inhabitant (Mohammadi et al., 2018).

In the investigations on the association of the DRD2 gene C957T polymorphism and stuttering in different populations, while the C allele in Han Chinese population and TT genotype in the Iran population is statistically significant (Lan et al., 2009; Mohammadi et al., 2018), it was stated that no relation was found in Brazilian, Western European (Kang et al., 2012), Caucasian (Montag et al., 2012) and Iranian populations (Mohammadi et al., 2018).

Consistent with the results of studies conducted in Brazil, Western Europe, and Caucasian populations, we could not find any statistically significant findings between Turkish people who stutter and the DRD2 gene rs6277 polymorphism in both genotype and allele frequencies.

Indeed, Kraft (2010) stated that the role of the DRD2 gene in individuals who stutter would below. In Kraft's (2010) study, Fatty acid desaturase 2 (FADS2, rs7119667, 11q12-q13.1) gene, located on the same chromosome with the DRD2 gene, was found to be important, and in addition to the FADS2 gene, 8 more genes associated with stuttering were detected.

CONCLUSION

Stuttering is a developmental speech disorder that usually starts between the ages of 2-5, and it is known that more than one factor plays a role in its onset and course. The familial pedigrees, twin studies, and GWAS studies reveal that stuttering may have a genetic basis. However, there are very few studies to shed light on the genetic basis of this disease. Due to the Covid 19 pandemic, we had to suspend the DNA isolations we obtained from the saliva sample in stuttering individuals. This situation constituted the limitation of our study, and therefore it remained a pilot study. We still wanted to publish and share the data we have obtained up to this stage.

In conclusion, in our study, we investigated the relationship between stutterers and the DRD2 gene C957T polymorphism in the Turkish population. We could not obtain a statistically significant result between the DRD2 gene rs6277 polymorphism and CWS. The relationship between the DRD2 gene and stuttering, with different results in different populations, should be reassessed with a larger population sample, along with other genes suggested in the literature. This study is the first genetic polymorphism study on stuttering in Turkish society. There are no genetic studies on speech and language disorders in Turkish society. In addition to the DRD2 gene, the extraction of FOXP2, GNPTAB, SPCH1, CNTNAP2, ATP2C2, CMIP genetic profiles, which are thought to be related to these diseases, will contribute to the literature of our country.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Authors' Contribution: All authors have contributed in experimental study and writing of the manuscript equally.

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