

Genetic Variants Associated with Hypospadias: Insights from the Eastern Anatolia Region

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ABSTRACT

Objective: This study investigates genetic factors contributing to hypospadias in patients from Eastern Anatolia, aiming to identify pathogenic variants and enhance diagnosis and personalised treatment strategies.

Methods: An extensive evaluation was performed on 124 patients diagnosed with hypospadias, incorporating clinical examinations and family history reviews. Next-generation sequencing (NGS) was utilised to evaluate DNA samples, with a focus on 26 genes associated with 46,XY sexual development abnormalities. The genetic variations identified were then categorised according to the standards established by the American College of Medical Genetics (ACMG). This process involved a comparison with 124 healthy individuals who served as a control group.

Results: It is notable that the investigation yielded several significant genetic discoveries, comprising probable deleterious mutations in genes such as SRD5A2, MAP3K1, and LHCGR. It is notable that 51 subjects exhibited the homozygous c.265C>G (p.Leu89Val) mutation in the SRD5A2 gene, while 19 patients presented with the heterozygous form. The investigation revealed that neither variant was present in the control group. The variant was thus categorised as a variant of unknown significance (VUS), on the basis of its possible pathogenicity. Furthermore, other VUSs were identified in the SOX9, DYNC2H1, and GATA4 genes.

Conclusion: The development of hypospadias is significantly influenced by genetic factors. The present study identified SRD5A2 c.265C>G as a candidate for further functional research, emphasising the significance of genetic analysis in the diagnosis of sexual development abnormalities. Advances in genomic technologies, such as NGS, hold considerable potential in identifying therapeutic targets, thereby enhancing our understanding, diagnosis and treatment of hypospadias.

INTRODUCTION

Hypospadias is caused by inadequate virilization of the genital tubercle, resulting in the urethral orifice being abnormally positioned from the ventral side of the glans penis to the perineum, often accompanied by ventral curvature (chordee) and abnormal prepuce formation.^[1] Severe forms, such as penoscrotal hypospadias, are associated with other congenital anomalies and are usually detected between 29 and 34 weeks of gestation, while isolated glanular hypospadias can be diagnosed earlier at 20 weeks.^[2,3]

Hypospadias is a condition influenced by various genetic and environmental factors, with many genes identified as

critical to its etiology. These genes play vital roles in urogenital development, steroid metabolism, and sex differentiation. Notably, genes such as GLI3, CYP11A1, CYP17A1, EGF, TGFBR3, FGFR2, RYR1, INSL3, ADAT3, ARNT2, SNAP29, CYP11A2, and DGKK have been associated with the condition.^[4] Genetic mutations in NR5A1, SRD5A2, and AR have been identified as mutational hotspots in severe cases of hypospadias. Studies have shown that genetic causes account for approximately 30% of all cases and 28% of severe cases.^[5] Moreover, altered methylation statuses of candidate genes like WTI, SFI, BMP4, BMP7, HOXA4, HOXB6, AR, FGF8, FGFR2, HSD3B2, SRD5A2, ATF3, MAMLD1, MID1, BNC2, ESRI, ESR2, DGKK, CYP11A1, GSTM1, GSTT1, CTGF, CYR61, and EGF have been ob-

served in hypospadias patients.^[6] Specific mutations in SRD5A2, AR, and MID1 have been correlated with abnormal male genital development and hypospadias, with a reported genetic abnormality rate of 22.2% in affected patients.^[7] Genetic polymorphisms in the RYR1 gene are linked to the severity of the condition, while environmental factors such as pregnancy complications, maternal drug use, and low birth weight have been identified as significant risk contributors.^[8] Genome-wide association studies (GWAS) have revealed novel risk loci, including the 12q13.13 region, and demonstrated that disruption of SPI and SP7 transcription factor activity is associated with multiple hypospadias-related genes.^[9] Additionally, severity-specific genetic associations have been noted, with SNPs in STS and STARD3 linked to severe hypospadias and an AR gene SNP associated with Type III hypospadias.^[10] Furthermore, novel genetic variants in genes like HSD3B2 have been implicated in familial cases of hypospadias.^[11]

Cases of glandular hypospadias generally have normal karyotypes. However, abnormal karyotypes are more common in severe hypospadias with conditions such as undescended testis.^[12] This is explained by the fact that chromosomal changes tend to be familial in origin and that de novo cases are more rare.^[13] Undescended testis in the setting of hypospadias may be a reason for further assessment for intersex. Studies show that about 8% of boys with hypospadias have undescended testicles.^[14] There is also a known link between hypospadias and undescended testicles, and studies show that these conditions can occur together.^[15] There was a positive correlation between the severity of hypospadias and the presence of intersex, suggesting that the two conditions may be linked.^[16] The presence of undescended testes in the context of hypospadias has been associated with other abnormalities such as epididymal abnormalities and testicular tumors.^[17] Furthermore, between 9% and 16% have been reported to have hypospadias associated with inguinal hernias and/or hydrocele.^[18]

Hypospadias is often associated with other findings and cryptorchidism. There are at least 49 known syndromes in which hypospadias is associated. The presence of a micropenis, an undescended testis and/or scrotal anomalies in 38 (78%) of these 49 syndromes seems to point to an endocrinopathy in the etiology of hypospadias.^[19] Hypospadias can be associated with several intersex conditions. These include adrenogenital syndrome, mixed gonadal dysgenesis, male pseudohermaphroditism, and true hermaphroditism. Although hypospadias and intersex represent different points on a spectrum, sexual identity dilemma is rarely seen in boys with an isolated urethral orifice in the shaft of a normal-sized penis, but the likelihood of intersex increases when hypospadias is associated with other signs such as a urethral orifice in the scrotum or perineum. In particular, hypospadias in association with cryptorchidism has the potential to be an indication of intersex conditions. If the undescended testis cannot be palpated, the risk of intersex may be as high as 50%.^[16]

Steroid 5 α -reductase (SRD5A2) is located on chromosome 2 and is the enzyme that converts testosterone into the more potent hormone dihydrotestosterone.^[20] SRD5A2 consists of 5 exons and is predominantly expressed in the external genitalia and prostate.^[21] Mutations in the SRD5A2 gene can lead to malfunctioning of the 5 α -reductase type 2 enzyme, resulting in conditions such as 46,XY disorders of sexual development.^[22] The SRD5A2 gene has been shown to affect semen quality, and changes in this gene can affect semen quality.^[23]

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital (No: BAEK 2020/23-220, Date: 21/12/2020) and conducted according to the Declaration of Helsinki.

Our patients consisted of 124 people living in the East Anatolian region of Turkey between December 2020 and December 2024. They applied to or consulted Erzurum Regional Hospital with the complaint of hypospadias. All patients were assessed for family history, consanguinity status and clinical findings. This is a retrospective study conducted in the genetic outpatient clinic. According to the results of the SRD5A2 test, a control group of 124 people was subsequently tested.

Genetic Analysis

Patient samples were analyzed using an NGS panel containing AKRIC2, AMH, AMHR2, AR, ARX, ATRX, CYB5A, CYP11A1, CYP17A1, DHCR7, DHH, DYNC2H1, GATA4, HSD17B3, HS6ST1, HCCS, LHCGR, MAMLD1, MAP3K1, NR5A1, OPHN1, SOX9, SRD5A2, SRY, WT1, ZFPM2 genes (Table 1).

The selection of these genes reflects the genetic diversity and clinical features of 46 XY sex disorders. Blood samples from the patients were used for DNA isolation. DNA isolation was carried out using standard methods. Genetic analysis Genomic DNA was isolated from peripheral blood samples (200 μ L) using the QiagenQIAamp DNA Blood Mini QIAcube Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The DNA samples obtained were prepared and sequenced for the NGS panel. Sequencing was carried out on the Illumina platform. The raw sequencing data obtained were analyzed after primer and quality checks. Genetic variants were evaluated by comparison with relevant databases and literature. For the specific study of the SRD5A2 gene, genomic DNA was isolated from 200 μ L peripheral blood samples using the QIAamp DNA Blood Mini QIAcube Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. PCR-amplified DNA sequences were sequenced using the Illumina MiSeq platform (Illumina, Inc., San Diego, CA, USA).

The potential adverse health effects of the genetic variations were analyzed using the ClinVar and HGMD Professional databases. Additionally, we employed tools

Table 1. Genes and Their Functions Identified in the 46,XY Panel

GENE	FUNCTION/RELATION
AKR1C2	Involved in testosterone metabolism; mutations can lead to hormonal imbalances.
AMH/AMHR2	Critical for male urogenital development; regulates anti-Müllerian hormone and its receptor.
AR	Essential for androgen effects; mutations increase risk of hypospadias.
ARX and ATRX	Roles in male urogenital and brain development; loss of function can lead to hypospadias and other anomalies.
CYB5A and CYP11A1	Involved in steroidogenesis; mutations linked to hormonal disorders.
CYP17A1	Crucial for testosterone synthesis; deficiencies associated with hypospadias.
DHCR7	Affects steroid metabolism; mutations disrupt urogenital development.
DHH	Associated with testis development and urethral differentiation.
DYNC2H1	Plays a role in cellular transport; linked to urogenital anomalies.
GATA4	Regulates gonadal development and gene expression.
HSD17B3	Critical for testosterone production; mutations affect sexual differentiation.
HCCS	Linked to mitochondrial functions; may indirectly influence hypospadias risk.
LHCGR	Luteinizing hormone receptor; deficiencies reduce testosterone production.
MAMLD1	Commonly associated with hypospadias.
MAP3KI	Involved in signal transduction for sexual differentiation.
NR5A1	Affects gonadal development and steroidogenesis.
OPHN1	Plays a role in cytoskeletal organization and signal transduction.
SOX9	Essential for gonadal development; mutations linked to hypospadias.
SRD5A2	Catalyzes conversion of testosterone to dihydrotestosterone; deficiencies cause hypospadias.
SRY	Key regulator of male sex differentiation.
WT1	Important for urogenital system development.
ZFPM2 (FOG2)	Transcription factor involved in sex differentiation.

such as Revel, AlphaMissense, Eve, MUT Assessor, SIFT, Polyphen2, FATHMM, DANN, MetaLR, PrimateAI, and BayesDel. Variants were deemed pathogenic or possibly pathogenic if they were associated with known pathogenic mechanisms, observed in the patient cohort, rare among controls, involved conserved amino acid changes, and/or predicted to be deleterious. Confirmation of all variants was performed through Sanger sequencing. The SRD5A2 gene analysis of healthy individuals in the control group was performed using an AB 3130 XL 16-capillary Sanger sequencer. The start (forward) primer used in this analysis was “5'-CGGAATTCAACACGGCGCGATGCAGGT TTCA-3'” and the end (reverse) primer was “5'-GGTC TAGAGGATAGGGTCCCTGGAAGGGTAGG-3'”. These primers ensured efficient copying and sequencing of the relevant region of DNA. All variants were confirmed by Sanger sequencing. Patient phenotypes were reviewed with their physicians. Statistical analysis was performed using SPSS 25.0, assessing the prevalence of the polymorphism and its correlation with hypospadias risk factors through tests and logistic regression.

RESULTS

Among 124 hypospadias patients, almost all of whom were

neonates or 1-month-old infants from the Eastern Anatolian region, 13% (16 patients) had a history of hypospadias in first-degree relatives, and 8% (10 patients) had a distant degree of consanguinity (cousin marriage) between the parents. According to the clinical findings, distal hypospadias (including glanular, coronal, and penile types) was observed in 48.9% (61 patients), whereas proximal hypospadias (including penoscrotal and perineal types) was found in 17% (21 patients). Additionally, 9.6% (12 patients) had undescended testis, 12.8% (16 patients) had penile curvature (chordee), 4.3% (5 patients) had associated urinary anomalies, and 7.4% (9 patients) had scrotal anomalies (Fig. 1). Most patients were diagnosed at birth (77.4%, 96 patients) or within 1 month (22.6%, 28 patients).

The patients were referred to the pediatric urology and pediatric surgery departments and then to the medical genetics outpatient clinic. Firstly, chromosome analysis was performed in all patients, and the chromosome analysis result was 46,XY. Then, the 46,XY Disorders of Sexual Development/Complete Gonadal Dysgenesis NGS panel was analyzed, revealing several significant genetic findings that highlight the complex genetic basis of these conditions.

Among the detected mutations, the variants in LHCGR

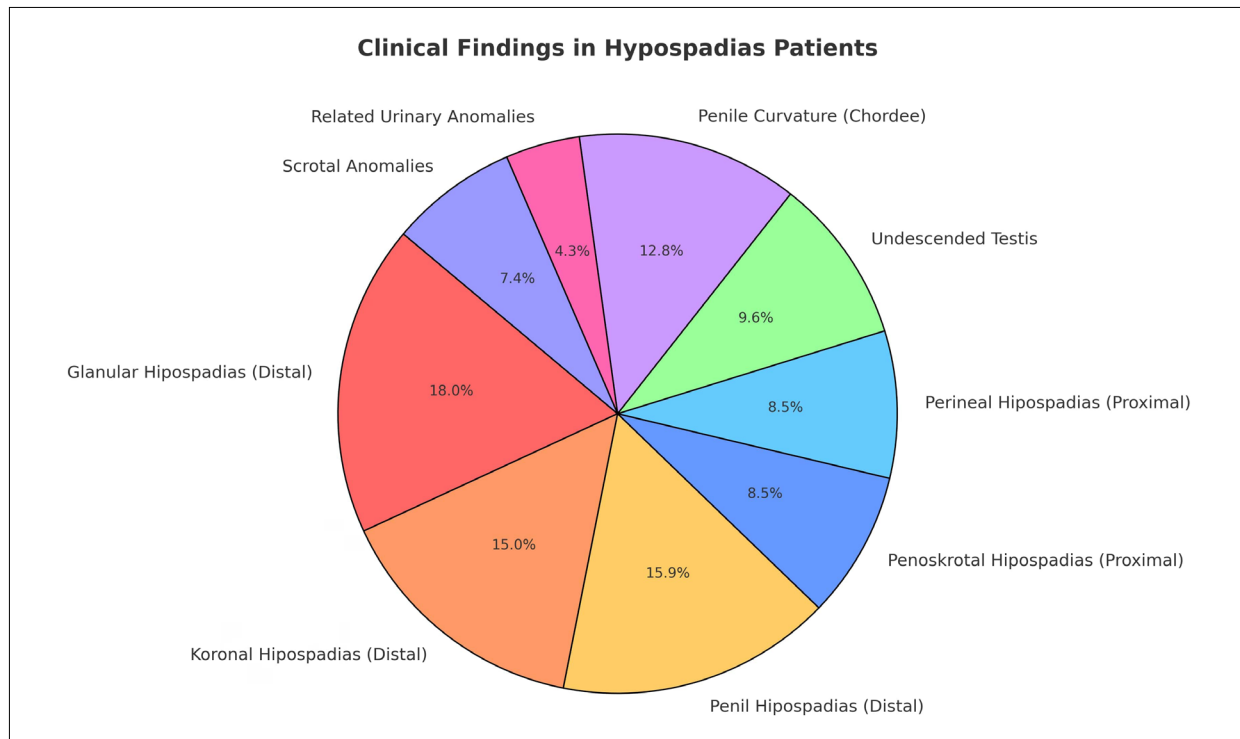


Figure 1. Clinical findings in hypospadias patients.

Table 2. Results of the NGS panel test

GENE	HYOSPADIAS TYPE	INHERITANCE TYPE	LOCATION	CLINICAL IMPORTANCE (ACCORDING TO ACMG CRITERIA)
LHCGR:c.1331T>G p.Phe444Cys	Proximal (Penoskrotal)	Heterozygous	A.D.	L.PATHOGENIC
MAP3K1:c.602G>A p.Trp201*	Proximal (Perineal)	Heterozygous	A.D.	L.PATHOGENIC
SRD5A2:c.589G>A p.Glu197Lys	Proximal (Penoskrotal)	Heterozygous	A.R.	L.PATHOGENIC
GATA4:c.1000+56 C>A	Distal (Coronal)	Homozygous	A.D.	VUS
DYNC2H1:c.3181C>G p.Leu1061Val	Distal (Penile)	Heterozygous	A.D., A.R.	VUS
DYNC2H1: c.11308 G>A p.Ala3763Thr	Distal (Penile)	Heterozygous	A.D., A.R.	VUS
SOX9:c.200A>G p.Asp67Gly	Distal (Coronal)	Heterozygous	A.D.	VUS
HS6ST1:c.226G>C p.Glu76Gln	Distal (Glanular)	Heterozygous	A.D.	VUS
AMHR2:c.71G>A p.Cys24Tyr	Proximal (Penoskrotal)	Heterozygous	A.R.	VUS
AR:c.2450T>C p.Ile817Thr	Proximal (Perineal)	Hemizygous	X.L.R.	VUS
ARX:c.82_84del p.Cys28del	Proximal (Perineal)	Hemizygous	X.L.R.	VUS
ATRX:c.7462C>T p.Gln2488*	Proximal (Penoskrotal)	Hemizygous	X.L.R.	VUS
CYP11A1:c.1236+5G>A	Proximal (Penoskrotal)	Heterozygous	A.R or A.R	VUS
DHCR7:c.1249G>A p.Ala417Thr	Distal (Penile)	Heterozygous	A.R.	VUS
DYNC2H1:c.12007G>A p.Ala4003Thr	Distal (Penile)	Heterozygous	A.D., A.R.	VUS
GATA4:c.825C>T p.Cys275=	Distal (Coronal)	Heterozygous	A.D.	VUS
MAMLD1:c.602G>A p.Gly201Glu	Distal (Penile)	Hemizygous	X.L.R.	VUS
MAMLD1:c.1234A>T p.Ser412Cys	Distal (Penile)	Hemizygous	X.L.R.	VUS
NR5A1:c.987G>T p.Gln329His	Proximal (Penoskrotal)	Heterozygous	A.D.	VUS
SOX9:c.1065_1082del p.Pro359_Ala364del	Distal (Coronal)	Heterozygous	A.D.	VUS
SOX9:c.1330G>A p.Asp444Asn	Distal (Coronal)	Heterozygous	A.D.	VUS
WT1:c.859G>A p.Ala287Thr	Proximal (Penoskrotal)	Heterozygous	A.D.	VUS
ZFPM2:c.617T>C p.Leu206Pro	Proximal (Perineal)	Heterozygous	A.D.	VUS

Table 3. Results for SRD5A2 gene

GENE	INHERITANCE TYPE	CLINICAL IMPORTANCE (ACCORDING TO ACMG CRITERIA)	NUMBER OF RESULTS
SRD5A2 c.265C>G p.Leu89Val	Homozygous	VUS	51
SRD5A2 c.265C>G p.Leu89Val	Heterozygous	VUS	19
SRD5A2 c.265C>T	Heterozygous	VUS	2
Normal			52

(c.1331T>G, p.Phe444Cys), MAP3K1 (c.602G>A, p.Trp201*), and SRD5A2 (c.589G>A, p.Glu197Lys) were classified as likely pathogenic and were predominantly associated with proximal (penoscrotal) hypospadias, suggesting a strong genetic contribution to these phenotypes. In addition, numerous variants of uncertain significance (VUS) were identified in a wide range of genes, including GATA4 (c.1000+56 C>A), DYNC2H1 (c.3181C>G, p.Leu1061Val; c.11308 G>A, p.Ala3763Thr), and SOX9 (c.200A>G, p.Asp67Gly), among others. These VUS mutations were more frequently observed in distal hypospadias subtypes, including coronal, penile, and glanular presentations, emphasizing the need for further functional and clinical studies to determine their pathogenic roles. Of particular note, hemizygous variants in AR (c.2450T>C, p.Ile817Thr), ARX (c.82_84del, p.Cys28del), and ATRX (c.7462C>T, p.Gln2488*) suggest a possible X-linked contribution to the etiology of these disorders*. These X-linked variants were primarily found in proximal hypospadias cases (penoscrotal or perineal subtypes), indicating a possible role of androgen receptor signaling in the etiology of these phenotypes. The recurrence of VUS in genes such as SOX9 and MAMLD1 suggests their potential relevance in the phenotypic spectrum of these disorders, particularly in distal hypospadias phenotypes. These findings further underscore the genetic heterogeneity and complexity of 46,XY DSD-associated hypospadias (Table 2).

However, the SRD5A2 homozygous c.265C>G p.Leu89Val variant (classified as a VUS) was identified in 51 patients, while the heterozygous form was detected in 19 patients. Considering that the c.265C>G p.Leu89Val variant may not be a VUS but may be potentially pathogenic, the SRD5A2 gene was analysed in a control group of 124 individuals. No homozygous or heterozygous forms of the c.265C>G p.Leu89Val variant were detected in this control group (Table 3).

DISCUSSION

The results of this study highlight the importance of genetic factors in 46,XY disorders of sex development and hypospadias. Variants in the GATA4, DYNC2H1 and SOX9 genes support the critical role of these genes in sex development and gonadal differentiation. In particular, VUS variants identified in the GATA4 and SOX9 genes further emphasize the role of these genes in regulating important

pathways in sex development, while the presence of variants in the DYNC2H1 gene indicates their potential impact on sex development.^[24]

Studies have shown that the rate of genetic diagnosis in 46,XY DSD patients is approximately 43%, suggesting that a significant proportion of cases remain undiagnosed at the genetic level.^[24] Despite advances in understanding the genetic basis of sex determination, most cases of 46,XY gonadal dysgenesis remain without a definitive genetic diagnosis.^[25] In addition, studies have shown whether GATA4 variants are associated with heart defects in people with 46,XY DSD in the context of additional knock-outs in other DSD genes.^[26]

SOX9 is essential for male sex development. This is particularly evident in conditions such as 46,XY DSD, where patients show sex reversal when SOX9 is lost.^[27] In addition, DYNC2H1 variants have been linked to limb development abnormalities such as polydactyly, highlighting its role in skeletal development.^[28] The importance of these genes in the complex processes of sex determination and gonadal development in humans is highlighted by the combination of genetic findings in these genes. In this case, interaction of genetic variants in GATA4, DYNC2H1 and SOX9 sheds light on the complex mechanisms of sex development and gonadal differentiation in individuals with 46,XY DSD and related conditions. These genes play a critical role in controlling key pathways for proper sex development. Variations in these genes can have profound effects on the phenotypic outcomes observed in affected individuals.

The SRD5A2-V89L polymorphism shows a significant association in studies of hypospadias patients in different populations, based on the findings in the literature.^[29-31] In addition, SRD5A2-V89L and SRD5A2-A49T polymorphisms have been shown to be associated with hypospadias in a study of the Iranian population.^[32] The V89L polymorphism in the SRD5A2 gene has been extensively studied in prostate cancer in different populations and the results have been conflicting.^[33,34] The presence of a leucine (L89) at codon 89 has been shown to cause a 30% reduction in the activity of the enzyme, resulting in lower levels of testosterone metabolites.^[35,36] The difference in the functional potential of these two gene products makes this polymorphism of particular interest in the pathogenesis of hypospadias. In another study, the V89 allele of the SRD5A2 gene, when homozygous, was reported to reduce the risk of hypospadias in Turkish patients with a

higher leucine frequency than in Swedish patients.^[30]

The analysis revealed a remarkable prevalence of the c.265C>G (p.Leu89Val) variant in the SRD5A2 gene in patients, with 51 homozygous and 19 heterozygous cases identified. Although currently classified as a variant of uncertain significance (VUS), its potential pathogenicity is suggested. To investigate further, the SRD5A2 gene was analysed in a control group of 124 individuals in whom the variant was absent. These results suggest that the c.265C>G (p.Leu89Val) variant is more common in hypospadias patients and may contribute to the development of the disease. However, further studies and functional analysis are needed to confirm its pathogenic role.

Given these findings, the importance of genetic analysis in diagnosing and treating sexual development disorders such as hypospadias becomes even more apparent. In identifying genetic variants that may provide potential pathogenic and therapeutic targets, the use of advanced technologies such as NGS plays an important role. In addition, a better understanding of the pathogenicity and clinical significance of specific mutations in the SRD5A2 gene may be achieved by further investigation of their association with hypospadias risk.

CONCLUSION

This study highlights the potential importance of genetic analysis in understanding the genetic basis of hypospadias and similar disorders of sexual development and in the management of these conditions. The functional impact of these genetic variants and potential therapeutic targets on the development of hypospadias should be further clarified in future studies.

Ethics Committee Approval

The study was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital (Date: 21.12.2020, Decision No: BAEK 2020/23-220).

Informed Consent

The requirement for informed consent was waived due to the retrospective nature of the study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: O.Y., M.D., H.D., M.C.G.; Design: O.Y., M.D., H.D., M.C.G.; Supervision: O.Y.; Fundings: M.D., H.D.; Materials: O.Y., M.D., H.D., M.C.G.; Data collection &/or processing: M.C.G.; Analysis and/or interpretation: O.Y.; Literature search: M.C.G.; Writing: O.Y.; Critical review: O.Y., M.D., H.D., M.C.G.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Hipospadias ile İlişkili Genetik Varyantlar: Doğu Anadolu Bölgesi'ne İlişkin Bulgular

Amaç: Bu çalışma, Doğu Anadolu'daki hastalarda hipospadias katkıda bulunan genetik faktörleri araştırmakta, patojenik varyantları tanımlamayı ve tanı ve kişiselleştirilmiş tedavi stratejilerini geliştirmeyi amaçlamaktadır.

Gereç ve Yöntem: Hipospadias tanısı konulan 124 hasta üzerinde klinik muayene ve aile öyküsü incelemelerini içeren kapsamlı bir değerlendirme yapılmıştır. DNA örneklerini değerlendirmek için yeni nesil dizileme (NGS) kullanılmış ve 46,XY cinsel gelişim anormallikleri ile ilişkili 26 gene odaklanılmıştır. Tanımlanan genetik varyasyonlar daha sonra American College of Medical Genetics (ACMG) tarafından belirlenen standartlara göre kategorize edilmiştir. Bu süreç, kontrol grubu olarak görev yapan 124 sağlıklı bireyle bir karşılaştırmayı içeriyordu.

Bulgular: Araştırmanın SRD5A2, MAP3K1 ve LHCGR gibi genlerde olası zararlı mutasyonları içeren birkaç önemli genetik keşif ortaya çıkarması dikkate değerdir. SRD5A2 geninde homozigot c.265C>G (p.Leu89Val) mutasyonu 51 kişide görülürken, 19 hastada heterozigot formun görülmesi dikkat çekicidir. Araştırma, kontrol grubunda her iki varyantın da bulunmadığını ortaya koymuştur. Bu nedenle varyant, olası patojenitesi temelinde önemi bilinmeyen varyant (VUS) olarak kategorize edilmiştir. Ayrıca, SOX9, DYNC2H1 ve GATA4 genlerinde başka VUS'lar da tespit edilmiştir.

Sonuç: Hipospadias gelişimi genetik faktörlerden önemli ölçüde etkilenmektedir. Bu çalışma, SRD5A2 c.265C>G'yi daha ileri fonksiyonel araştırmalar için bir aday olarak tanımlamış ve cinsel gelişim anormalliklerinin tanısında genetik analizin önemini vurgulamıştır. NGS gibi genomik teknolojilerdeki gelişmeler, terapötik hedeflerin belirlenmesinde önemli bir potansiyele sahiptir, böylece hipospadias anlayışımızı, teşhisimizi ve tedavimizi geliştirir.

Anahtar Sözcükler: Hipospadiyas; polimorfizm; steroid 5-alfa redüktaz tip 2.