Original Article

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Assessment of Familial Predisposition Through Parental Inquiry in Undescended Testis Cases

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Abstract

Aim: Non-syndromic cryptorchidism, also referred to as undescended testis (UDT), represents a developmental abnormality occurring in early childhood, the underlying cause of which remains unclear. It is thought to arise from both hereditary susceptibility and environmental influences. This study aimed to explore parental reports concerning familial predisposition (FP) in order to gain further insight into the origins of this frequently encountered and multifactorial condition.

Methods: Between 2012 and 2023, the phone numbers of 1,024 patients who underwent surgery for UDT were retrieved from electronic medical records. The parents of these 1,024 patients were contacted and asked, "Do you or any of your relatives have a diagnosis of udescended testicles (UDT)?" Parents were contacted again via phone 10 days after the initial contact, and the results were recorded in detail. Data from the parents of 823 patients were ultimately incorporated into the study analysis. The collected data were analyzed for FP in terms of dizygotic and monozygotic twins, fathers, siblings, uncles, cousins, and grandfathers.

Results: For the 162 participants identified with FP, the average age was calculated as 4.08±1.87 years. The mean age of the 661 individuals without FP was 3.27±1.80 years. When the relationship between FP and both the localization and laterality of UDT was analyzed, a significant association was found in cases with proximal localization and bilateral involvement ($p<0.05$). Similarly, a significant relationship was observed between FP and genetic predisposition (dizygotic and monozygotic twins) in UDT cases ($p<0.001$).

Conclusion: Our study provides evidence of a connection between non-syndromic cryptorchidism or UDT and FP through a comprehensive evaluation of a large patient series.

Keywords: Cryptorchidism, children, genetic predisposition to disease, parents

Introduction

Cryptorchidism, commonly referred to as undescended testis (UDT) or incomplete descent of testis, represents a frequent congenital anomaly encountered in pediatric urology. Depending on testicular position, cryptorchidism is categorized into cases with palpable and non-palpable testes. Notably, over 80% of cryptorchidism cases involve palpable testes (1). The etiology of UDT remains largely unclear. However, findings suggest that certain cases of cryptorchidism may result from a multifactorial interaction of genetic, anatomical, hormonal, and environmental factors (2). Cryptorchidism associated with chromosomal or developmental anomalies, often as part of syndromic conditions, represents a minor proportion of cases, whereas the majority manifest as isolated UDT (3,4). Although numerous investigations have thoroughly addressed the general epidemiological aspects of UDT, research specifically examining its familial occurrence remains scarce. Important elements such as prevalence rates, potential hereditary correlations, and clinical features, particularly those involving urogenital system anomalies, have not been comprehensively analyzed. The currently available data are mostly derived from studies involving limited sample sizes, often centered around familial relationships like those between fathers, siblings, and twins. Moreover, evidence concerning how common UDT is within the broader population remains limited (5,6).

Undescended testis affects approximately 3-5% of all newborn males and decreases to about 1% in boys by the age of one (7,8). Studies indicate that the likelihood of

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UDT is significantly increased in certain familial situations: a 10.1-fold higher risk in cases where one male twin is affected, 3.5-fold higher in boys with an affected brother, and 2.3-fold higher when the father has UDT (9).

This study is grounded in the assumption that genetic components have an influence on the development of UDT, potentially leading to higher occurrence rates among first-degree family members. The primary objective was to investigate the frequency and pattern of familial predisposition (FP) reported via parental inquiries about relatives, aiming to enhance understanding of UDT origins by utilizing an extensive patient dataset.

Materials and Methods

Compliance with Ethical Standards

The study was approved by the Tokat Gaziosmanpasa University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 25-MOBAEK-015, date: 27.01.2025), adhering to the principles of the Helsinki Declaration.

Study Design

The present study was conducted at a single institution and designed as a retrospective, cross-sectional investigation. Contact details of 1,024 patients who had undergone surgical treatment for UDT at our clinic between 2012 and 2023 were extracted from digital health records. All participants were made aware that their data would be utilized for research purposes, and informed written consent was collected accordingly.

The diagnosis of UDT was confirmed as documented in the physical examination note within the clinical documents. Undescended testis cases were only indicated by the urology clinic. Ultrasonography was not routinely used as previously recommended in the literature (10). Only UDT cases with completely recorded clinical data were included in the study. Cases with a major birth defect, UDT due to a previous hernia surgery, syndromal UDT, or chromosome abnormalities were excluded from the study. According to these criteria, 201 cases were excluded. A total of 823 parents of patients who were successfully contacted by phone and consented to participate in the survey were included in the study. Parents were asked the following question: "Do you or any of your relatives have a diagnosis of UDT?" To ensure accurate responses, they were given 10 days to consult their family members. After 10 days, parents were contacted again via phone. The responses were evaluated for FP in relation to dizygotic and monozygotic twins, fathers, siblings, uncles, cousins, and grandfathers, and carefully recorded for analysis. The flowchart shows the selection of study participants (Figure 1).

Statistical Analysis

All statistical evaluations were carried out using the MedCalc software (version 20.009; Ostend, Belgium). Descriptive analyses encompassed frequencies, ratios, arithmetic means, and standard deviations. Categorical data were examined via the chi-square method, while the Kolmogorov-Smirnov test was applied to assess the normality of the distribution. Comparative group data were visualized through layered percentage bar graphs. A p-value threshold of <0.05 was adopted to determine statistical significance in all interpretations.

Results

The patients analyzed in this study (n=823) were between 1 and 9 years of age. The cohort included 749 unilateral cases and 74 bilateral cases. There were a total of 331 cases with proximal localization and 492 with distal localization. Scrotal (Bianchi) orchiopexy was performed in 244 patients, while inguinal orchiopexy was performed in 579 patients. The mean age of the 162 individuals with FP was 4.08±1.87 years, whereas the mean age of the 661 individuals without FP was 3.27±1.80 years (Table 1).

Among the 162 individuals with FP, UDT was reported in 33 cases, including dizygotic and monozygotic twins, 38 fathers, 26 siblings, 16 cousins, 46 uncles, and 10 grandfathers. Although rare, FP was identified in more than one relative in some cases (Table 2).

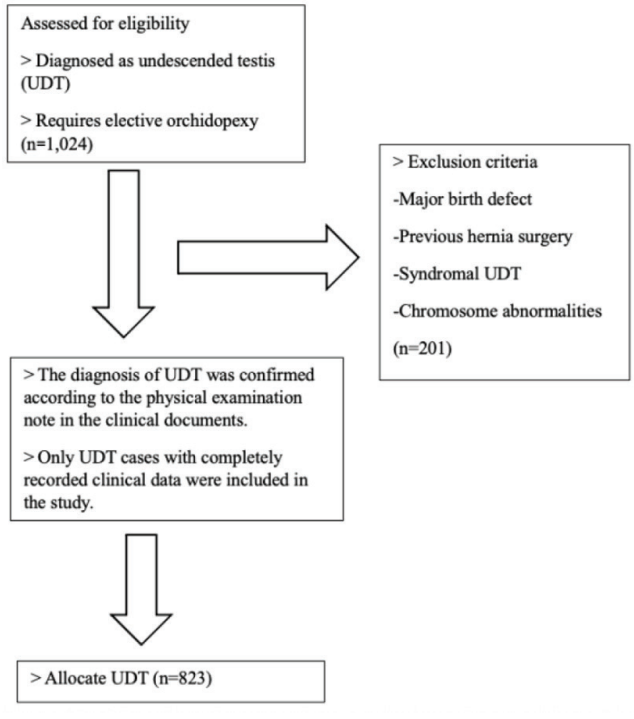

Figure 1. Flowchart shows the selection of study participants
UDT: Undescended testis

When the relationship between FP and UDT localization and laterality was analyzed, a significant association was observed in cases with proximal localization and bilateral involvement ($p<0.05$) (Table 3 and Figures 2, 3). Furthermore, a significant relationship was found between FP and genetic predisposition (dizygotic and monozygotic twins) ($p<0.001$) (Table 3, Figure 4).

Discussion

Familial studies suggest that susceptibility to cryptorchidism is likely influenced by hereditary factors; however, the specific genes responsible for the condition remain unidentified. Some genetic mutations have been associated with syndromic cryptorchidism, although their occurrence in boys with isolated undescended testes is exceptionally rare (11). Research to date, primarily informed by animal model studies, has provided only a limited insight into the etiology of cryptorchidism in humans.

Table 1. Age-related data of individuals with and without familial predisposition

	Familial predisposition					
	Not present			Present		
	n	Mean	SD	n	Mean	SD
Age (year)	661	3.27	1.80	162	4.08	1.87

SD: Standard deviation

Table 2. Distribution of frequencies and percentages in undescended testis cases with familial predisposition

		n	%
Genetic type	**Dizygote**	19	57.6
	Monozygote	14	42.4
Familial proximity	**Father**	38	23.5
	Father&Brother	2	1.2
	Father&Cousins	6	3.7
	Father&Uncle	5	3.1
	Father&Grandfather	2	1.2
	Father&Brother&Uncle	1	0.6
	Father&Cousins&Uncle	1	0.6
	Father&Uncle&Grandfather	2	1.2
	Brother	26	16.0
	Brother&Cousins	1	0.6
	Brother&Uncle	4	2.5
	Brother&Cousins&Uncle	1	0.6
	Cousins	16	9.9
	Uncle	46	28.4
	Uncle&Grandfather	1	0.6
	Grandfather	10	6.2

Most cases of cryptorchidism are non-syndromic, meaning they are not accompanied by other diseases or malformations. Although the underlying causes of non-syndromic cryptorchidism remain largely unknown, numerous medical conditions have been identified in relation to this anomaly (5,11). These include hormonal disorders that impair androgen production or activity, encompassing a wide range of differences in sex development. Such cases may involve impairments in testicular formation or androgen pathways. Both congenital hypogonadotropic and hypergonadotropic hypogonadism have been described, along with syndromes affecting either or both stages of gonadal function. Additionally, alterations in the levels or biological activity of regulatory peptides like INSL3 or AMH have been potentially implicated (12,13). Cryptorchidism has been linked to over 150 comorbid conditions, including

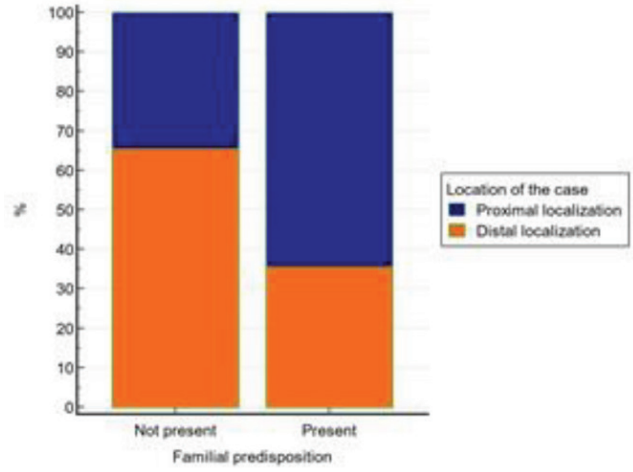

Figure 2. The Relationship between familial predisposition and the localization of undescended testis

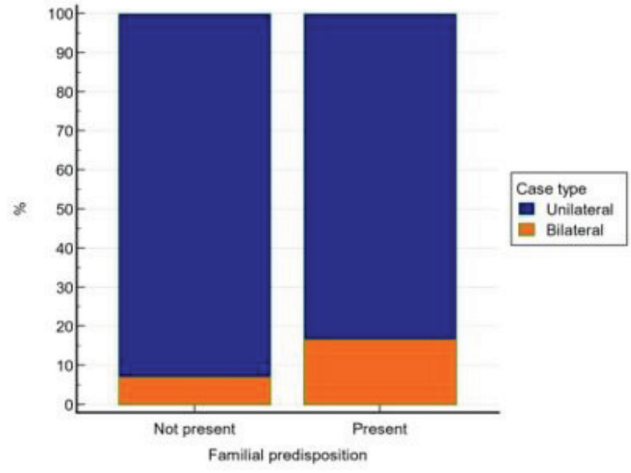

Figure 3. The Relationship between familial predisposition and the laterality of undescended testis

cardiovascular, reproductive, ophthalmologic, mental, dermatologic, and skeletal disorders, as well as hearing loss and cancer (14). The most commonly reported comorbidity of cryptorchidism is hypospadias (5,14). Consequently, several genomic variations have been implicated in the pathogenesis of cryptorchidism. Boys with UDT tend to have a higher prevalence of a positive family history for cryptorchidism compared to healthy controls. Previous research indicates that approximately 7% of their brothers may also be affected (15). Data from Denmark revealed varying concordance rates: 3.2% among unrelated boys, 3.4% in paternal half-siblings, 6.0% in maternal half-siblings, and 8.8% among full siblings. The rate was notably higher-around 25%-in both dizygotic and monozygotic twin pairs. These observations highlight the potential influence of shared intrauterine conditions, particularly in twin pregnancies (16). In a retrospective analysis of 165 children who underwent surgery for UDT, Bjøro K and Dybvik (17) reported that 3.9% of fathers and 6.5% of brothers were also affected by it.

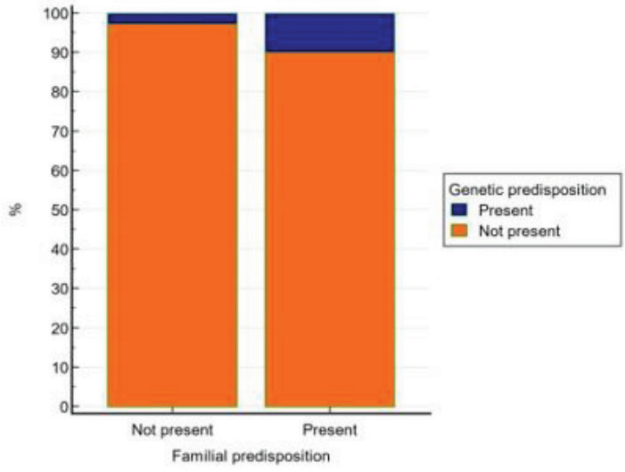

Figure 4. The Relationship between familial predisposition and genetic predisposition

In a separate investigation, Jones and Young (18) analyzed the family histories of 51 children who had undergone similar procedures, identifying UDT in 3.9% of fathers, 9.8% of brothers, and 10.6% of uncles.

Czeizel et al. (19) conducted the only available epidemiological research in this area and noted UDT in 3.98% of fathers and 6.2% of brothers within the affected group. The likelihood of UDT in male infants born into families with known cases was notably higher, up to fivefold when the father is affected and reaching an eightfold increase if a brother is also affected by the condition. Elert et al. (20) demonstrated that while familial clustering was rare, cryptorchidism occurred much more frequently among family members of affected individuals (23%) compared to the control group (7.5%). These findings suggest the presence of genetic risk factors for cryptorchidism.

Similar to other complex diseases, multiple genetic variants are likely to contribute to susceptibility to this condition. Moreover, current research indicates that male offspring and brothers of individuals diagnosed with cryptorchidism are more likely to develop the same condition. Several studies have pointed out that the likelihood of familial transmission tends to decline as genetic relatedness becomes more distant (20-24). For example, Jensen et al. (16) and Schnack et al. (25) identified notably higher concordance rates in maternal half-brothers (6%) when compared to paternal half-brothers (3.4%). Drawing upon these insights, including findings from twin studies, researchers have proposed that future investigations into etiology should prioritize maternal genetic pathways, especially those linked to the X chromosome and factors within the intrauterine environment (25). On the other hand, bilateral cryptorchidism is observed in approximately 10% of all patients with UDT (26). Bilateral undescended testes correlate with an increased risk of infertility and testicular malignancy (27). Prevalence rates exhibit significant regional variations, influenced by environmental, socioeconomic, and genetic factors.

Table 3. The relationship between familial predisposition and localization, laterality, and genetic predisposition of undescended testis

		Familial predisposition				p-value
		Not present		Present		
		n	%	n	%	
Location of the case	**Distal localization**	434	65.7	58	35.8	<0.0001*
	Proximal localization	227	34.3	104	64.2	
Case type	**Bilateral**	47	7.1	27	16.7	0.0001*
	Unilateral	614	92.9	135	83.3	
Genetic predisposition	**Not present**	644	97.4	146	90.1	<0.0001*
	Present	17	2.6	16	9.9	

*Chi-square test results indicate a significant difference at the <0.05 level

However, only a few published studies have focused specifically on the genetic background of undescended testes. According to findings by Czeizel et al. (19), bilateral cases appear to be linked with an elevated risk of recurrence among siblings. The same research also indicated that individuals with bilateral undescended testes had fathers and brothers who were twice as likely to be diagnosed with the condition (19). In another study, 12.2% of patients with bilateral UDT were found to have family relationships with UDT (20). In our study, it was observed that 16.7% of bilateral UDS familial factors were positive. Similarly, in our study, we observed a FP for UDT in proximal localization, which has negative effects on fertility.

We believe that our study contributes valuable insights into the association between UDT and FP. The large sample size enabled the generation of robust statistical data. The analysis of familial relationships was not limited to fathers and siblings but extended to various degrees of relatives. Among the 162 individuals with FP, for instance, UDT was observed in 20% of dizygotic and monozygotic twins, 23.5% of fathers, 16% of siblings, 9.9% of cousins, 28.4% of uncles, and 6.2% of grandfathers. FP was also identified in multiple relatives in some cases, albeit infrequently. The high prevalence observed in our study may be attributed to the large sample size and potential genetic variations. Additionally, our findings demonstrate that FP is more frequently observed when UDT localization is proximal and/or bilateral, and the likelihood increases with a greater prevalence of dizygotic and monozygotic twins. While FP in dizygotic and monozygotic twins is a known factor, the significant increase in FP in bilateral and/or proximally localized cases is a noteworthy finding. We could not determine a clear preference for paternal or maternal inheritance in this study. Therefore, the reasons for the higher prevalence of familial UDT remain uncertain. Potential chromosomal microdeletions, genetic susceptibilities in testosterone-sensitive organs, and/or environmental cofactors should be further explored and discussed.

Study Limitations

The primary limitations of this study include the subjectivity of survey-based data, the unknown impact of genetic and environmental factors on the study's outcomes, and its single-center, regionally focused design. On the other hand, since the data used in a part of our study was obtained by phone calls, we may encounter "recall bias", where respondents may incorrectly remember details when answering. This is another important limitation of our study. Despite these limitations, detailed determination of the pedigrees of cases with UDT is the strength of our study.

Conclusion

A comprehensive analysis of a large family cohort revealed a higher incidence of UDT than previously reported in the literature. Furthermore, our study demonstrated that FP is more frequently observed when UDT localization is proximal and/or bilateral, and its prevalence increases with a higher occurrence of dizygotic and monozygotic twins. It is anticipated that molecular analyses could provide further insights into the genetics of UDT, serving as a focal point for future research.

Ethics

Ethics Committee Approval: The study was approved by Tokat Gaziosmanpasa University Faculty of Medicine Clinical Research Ethics Committee (approvel no.: 25-MOBAEK-015, date: 27.01.2025) adhering to the principles of the Helsinki Declaration.

Informed Consent: Patients were informed that their data would be used for scientific purposes, and written consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.Y., E.K., F.F., Concept: K.Y., E.K., F.F., Design: K.Y., E.K., F.F., Data Collection or Processing: K.Y., E.K., F.F., Analysis or Interpretation: K.Y., E.K., F.F., Literature Search: K.Y., E.K., F.F., Writing K.Y., E.K., F.F.

Conflict of Interest: No conflicts of interest were declared by the authors.

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