Evaluating Chromosomal Microdeletions And Duplications: Ethical Considerations In Life Expectancy For Pediatric Bilateral Cryptorchidism – A Local Community Perspective

Wissam Saleh Hakim[1*], Mohammed Aboud[2], Manal Kadhim[3]

[1]*Pediatric Surgeon, College of Medicine, University of Al Qadisiya, Iraq
[2]MB.CHB. F.I.C.M.S. F.A.C.S. Consultant Pediatric Surgery, The Maternity and Child Teaching Hospital, Al Qadisiya, Iraq
[3]MB.CHB. PhD. Professor of Clinical Immunology, College of Medicine, Al Qadisiya University, Iraq
*Corresponding Authors:
Email: wissam.hakim@qu.edu.iq

Abstract.

Introduction & Objectives: Cryptorchidism is one of the most frequent congenital birth defects in male children and is present in 2–4% of full-term male births. The study aims to validate the associated genomic information to pick up and catalog life expectations with our community's associated syndromes and pathologies. Materials & Methods: The study was carried out between the 1st of June 2014 and the end of December 2018. G-banding of metaphase chromosomes and high-resolution karyotype analysis was performed in all patients using 5 DNA probes, ordered in the deletion intervals, and correlated with the cytogenetic map of the chromosome and sequence tagged size (STS) in the molecular study of microdeletion and microduplication using fluorescence in situ hybridization (FISH). The data were translated to the Statistical Package for Social Science (SPSS) version 22, Excel 2016 . Results: Out of 124 managed and operated on patients, genitourinary anomalies were the most common associated pathologies in 44% of cases, and hypospadias was the most common in 21.77%. Developmental delay and intellectual disabilities with speech disorders are considered the second one 24.19%. Y chromosome microdeletions were observed in 75% of all, the most considered one Y q1.2 D in 45.16%, p-value < 0.05. X p11.2 micro duplications were observed in 8.78% of the cases. Higher ascent of the testis presented with more microdeletion (intra-abdominal 35.48% of the patients) p-value < 0.05. With the STS, sY84 & sy86, and the loci, DYS 273 & 148 the azoospermia factor A region (AZFa) was estimated in 39.51% of the patients. Conclusions: Genomic information and screening are recommended for bilateral cryptorchidism as the chromosomal microdeletions and microduplications have been associated with a spectrum of pathologies, considering this with a catalog of the multidisciplinary team and complete disease network to follow up the clinical pictures after surgery.

Keyword: *Chromosomal Microdeletions; Ethical Considerations and Pediatric Bilateral.*

I. INTRODUCTION

Cryptorchidism, characterized by the absence of one or both testes in the scrotum at birth, is one of the most common congenital birth defects in male children. It affects approximately 2–4% of full-term male births, making it a critical health issue in pediatric urology (1). Cryptorchidism is often diagnosed early in life, and while many cases resolve spontaneously, others may require surgical intervention for correction. In addition to the anatomical abnormalities associated with cryptorchidism, the condition can also be linked to various syndromes and comorbidities that impact the long-term health and life expectancy of affected children (2**).**The condition's complexity is compounded by the genetic and chromosomal abnormalities that may accompany it. Chromosomal deletion syndromes typically involve larger deletions, typically visible on karyotyping. Syndromes involving smaller deletions (and additions) that affect one or more contiguous genes on a chromosome and are not visible on karyotyping are considered microdeletion and duplication syndromes (3). Advancements in molecular genetics have enabled researchers to identify specific chromosomal regions associated with cryptorchidism, providing insight into its complex pathophysiology.

Microdeletions and duplications can disrupt critical genes involved in testicular descent, gonadal development, and hormonal signaling, thus contributing to the condition's manifestation **(4).** Understanding these genetic alterations is vital for early diagnosis, personalized treatment, and counseling, particularly in communities with limited healthcare resources. These genetic factors may play a crucial role in the development of associated conditions, such as developmental delays, intellectual disabilities, and infertility

(5). This research highlights the importance of integrating genetic findings into public health strategies by analyzing the enrollment of chromosomal microdeletion and duplication studies in a local community. It seeks to bridge the gap between genetic research and its practical applications in clinical settings, focusing on improving outcomes for children with bilateral cryptorchidism. Additionally, the study aimed to explore the ethical considerations surrounding the management of cryptorchidism and its associated genetic abnormalities, particularly in a local community context.

II. MATERIALS AND METHODS

Study Design and Duration

The study was a retrospective analysis conducted at a local pediatric hospital between June 1, 2014, and December 31, 2018. 124 pediatric patients diagnosed with bilateral cryptorchidism were enrolled in the study during this period. Inclusion Criteria 1. Male children with a confirmed diagnosis of bilateral cryptorchidism. 2. Availability of parental consent for genetic testing and long-term follow-up. 3. Absence of prior surgical interventions for cryptorchidism. 4. Documentation of associated urological anomalies identified during the diagnostic process or surgery. Exclusion Criteria 1. Children with unilateral cryptorchidism or non-palpable testes of unknown etiology.

2. Cases with syndromic presentations or systemic anomalies unrelated to chromosomal abnormalities. 3. Families who declined genetic testing or follow-up participation.Data collection involved three main domains: clinical evaluation, chromosomal analysis, and ethical/psychosocial assessment. Clinical Evaluation All patients underwent a comprehensive clinical workup, including a physical examination focused on testicular position and palpability, and ultrasound Imaging to confirm anatomical positioning and detect associated urological anomalies. Testicular positions were classified into five categories based on anatomical location: 1. True ectopia 2. Intra-abdominal 3. Canalicular 4. Superficial inguinal pouch 5. Inguinal/pubic (pre-scrotal). Each chromosomal deletion/duplication was cross-analyzed with the testicular position to identify patterns and statistical correlations.

Genetic Testing

All patients underwent comprehensive genetic screening using G-banding of metaphase chromosomes and high-resolution karyotype analysis. Five DNA probes were ordered within the deletion intervals to detect chromosomal microdeletions and duplications. These probes allowed for identifying specific genetic anomalies and were mapped to the corresponding cytogenetic locations. The obtained karyotypes were then correlated with the cytogenetic map of the chromosome and sequence-tagged site (STS) in the molecular study of microdeletion and microduplication. Chromosomal analysis was performed using fluorescence in situ hybridization (FISH) and karyotyping techniques to identify microdeletions and duplications across specific chromosomal regions, including Y chromosome microdeletion analysis, microdeletion analysis of the AZF region was performed by multiplex PCR using 16 sequence-tagged sites. The sequence tagged site primers used were sY14 (SRY); sY84, sY86 (AZFa); sY124, sY127, sY129, sY130, sY134 (AZFb); sY147, sY242, sY254, sY255, SPGY1, sY157, and sY158 (AZFc). Yq12, Yq11.221, Xp11.2, and Yp11.1-q11.1, as well as normal 46XY controls.

Further analysis involved sequence-tagged site (STS) markers in the molecular study of microdeletions and microduplications using fluorescence in situ hybridization (FISH). The ZFX gene on the X chromosome was used as an internal control to confirm PCR amplification. At least 50 metaphases were analyzed for each patient.All chromosomal analyses were conducted in a certified genetic laboratory for quality assurance. Internal quality control measures, including duplicate testing for ambiguous cases, ensured the accuracy of results. Comparisons of anomaly prevalence were conducted using chi-square tests for categorical variables, with statistical significance set at $p < 0.05$. Pairwise comparisons were performed to evaluate the differences in prevalence between anomalies, and the adjusted p-values were reported. Hypospadias, as the most frequently observed anomaly, was used as the reference for statistical comparisons. Additionally, anomalies with rare occurrences, such as Wilms tumor, were analyzed descriptively due to limited sample size.

Data Analysis

The data collected from the genetic tests were processed using the Statistical Package for Social Science (SPSS) version 22 and Excel 2016 for statistical analysis. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Fisher's exact test was applied to assess the significance of associations between chromosomal abnormalities and clinical outcomes. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 124 patients diagnosed with bilateral cryptorchidism were included in the study. The findings highlight variations in the timing of diagnosis and their statistical significance. The mean age at diagnosis was 1–2 years highlighting the majority of cases identified within this age range (33.9%), with the following age distribution, patients diagnosed between 0–3 months 4.8% (6 cases) were the smallest group, with 9 patients (7.3%) identified in the neonatal period, this group was statistically underrepresented compared to all other age categories ($p < 0.001$). , 3–6 months 12.1% (15 cases), 6–9 months 7.3% (9 cases), and above 5 years were 9.7% (12 cases).

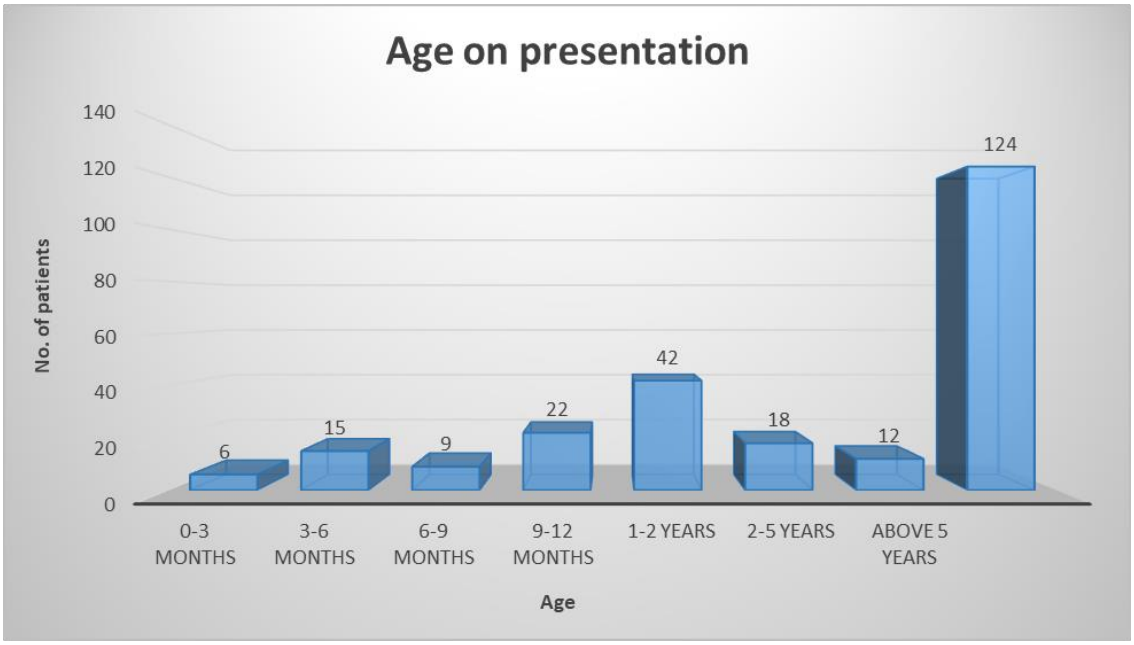

Fig 1. Out of 124 patients who were managed and operated on, the mean age of presentation was 1-2 years.

The study identified various associated anomalies among patients with cryptorchidism. Genitourinary malformations (44%), represented the most common associated anomaly, observed in 66 patients. The prevalence of these malformations was significantly higher than other anomalies ($p < 0.001$).

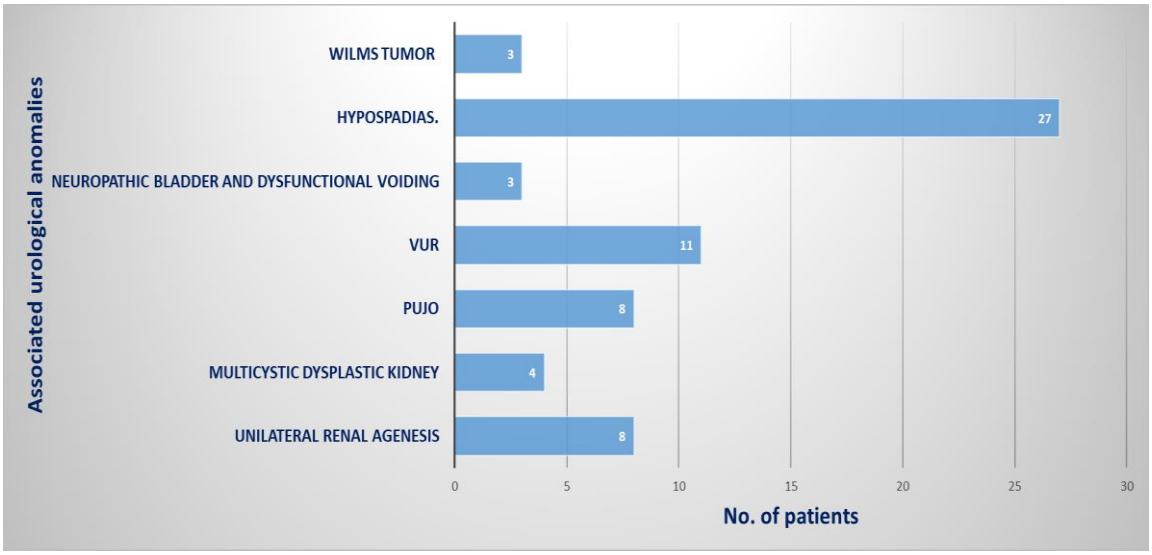

Fig 2. Hypospadias was the most common urological anomaly in 21.77%.

Among these, hypospadias was the most frequently observed condition, affecting 21 (77%) of the patients. Pelviureteric junction obstruction (PUJO) and unilateral renal agenesis were each reported in 8 patients, showing a statistically significant correlation ($p < 0.05$) with the studied cohort. Speech disturbances were noted in 18 patients, ranking as the second most frequent associated anomaly ($p = 0.02$), these disturbances ranged from delayed language acquisition to mild articulation issues.

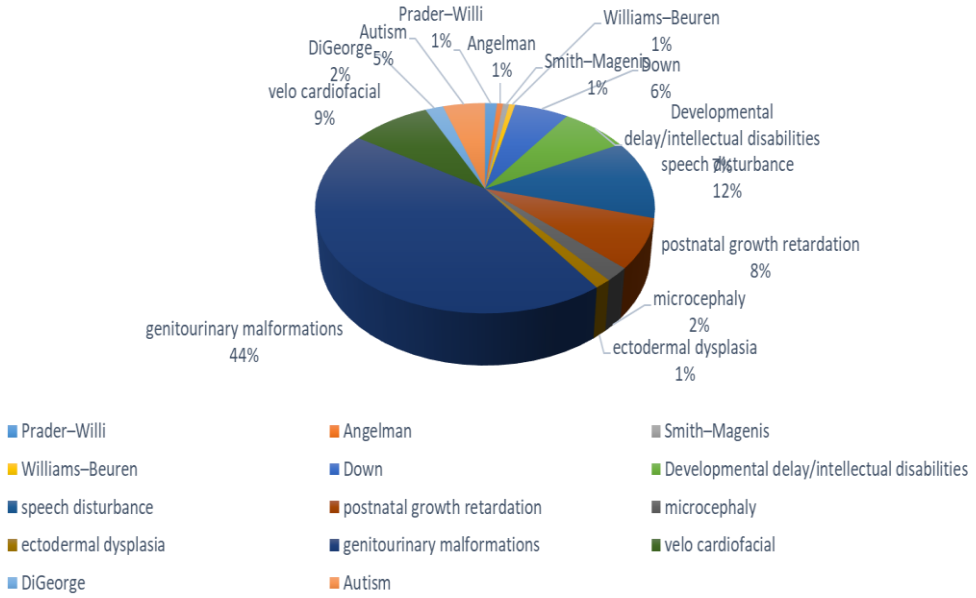

Fig 3. The study revealed that genitourinary anomalies were prevalent in a substantial portion of the patient population, constituting 44% of the cases. Developmental delay and intellectual isabilities with speech disorders were considered the second one in 24.19% of cases.

The distribution of testicular positions in the cohort revealed distinct anatomical variations, Intra-abdominal Testes (35.4%) representing the largest proportion of cases, were identified in over one-third (35.4%) of the cohort. The second most common testicular position, canalicular cases accounted for 28.2% of the cohort. Inguinal or pre-scrotal positions were observed in 16.1% of the cohort, representing a more proximal deviation in descent compared to superficial inguinal cases**.**

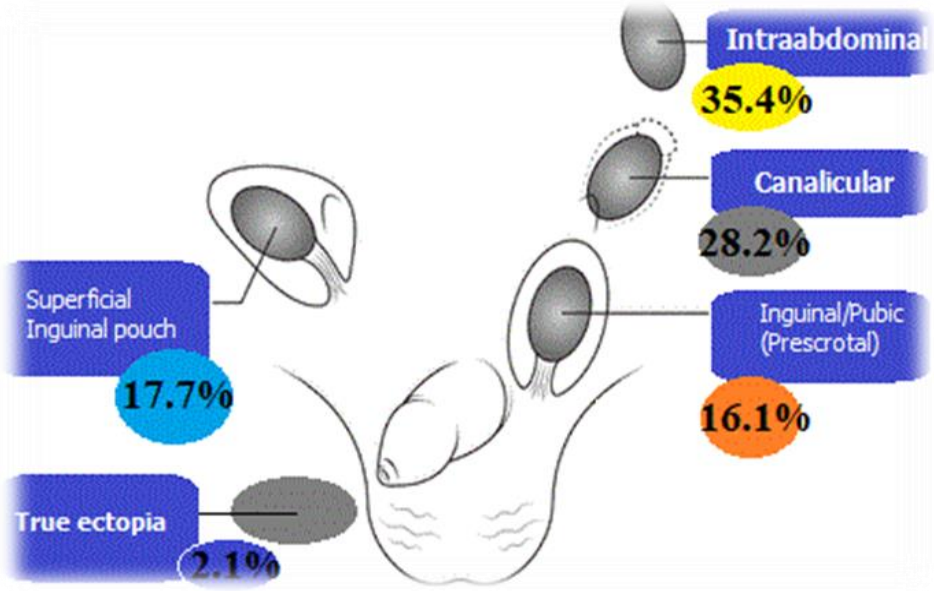

Fig 4. The usual locations of the bilateral undescended

This study analyzed chromosomal deletions focusing on six loci. The distribution of deletions revealed statistically significant differences across loci. Normal 46XY karyotype was identified in 15% of patients (19 out of 124 cases), the absence of chromosomal abnormalities in this group reinforces the contribution of extragenetic factors ($p > 0.1$).

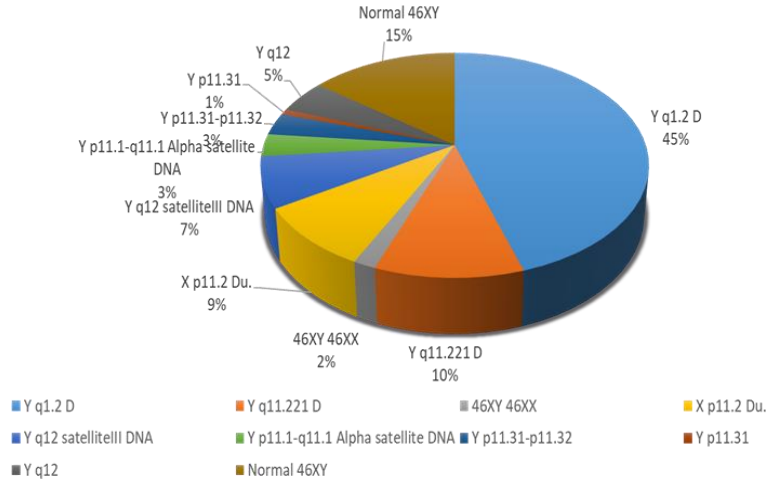

Fig 5. Y chromosome microdeletions were observed in 75% of all, the most considered one Y q1.2 D in 45.16%, p-value < 0.05. X p11.2 micro duplications were observed in 8.78% of the cases.

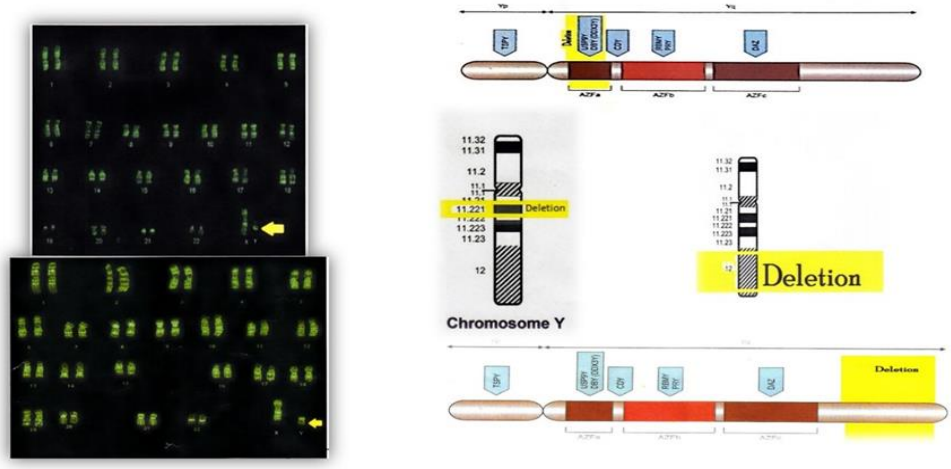

Fig 6. Ideogram of different Y-chromosome deletions in the studied patients.

Yq1.2 deletions were the most common anomaly, observed in 45% of patients (56 out of 124 cases). The high prevalence was statistically significant ($p < 0.001$), marking it the most critical chromosomal abnormality associated with bilateral cryptorchidism. Yq11.221 Deletions (Yq11.221 D) were the second most frequently observed anomaly, this anomaly demonstrated a significant association with cryptorchidism ($p < 0.01$). Yp11.1-q11.1 Alpha Satellite DNA Abnormalities Detected in 3% of patients (4 cases), the association was not statistically significant ($p > 0.1$). X p11.2 micro duplications were observed in 8.78% of the cases.

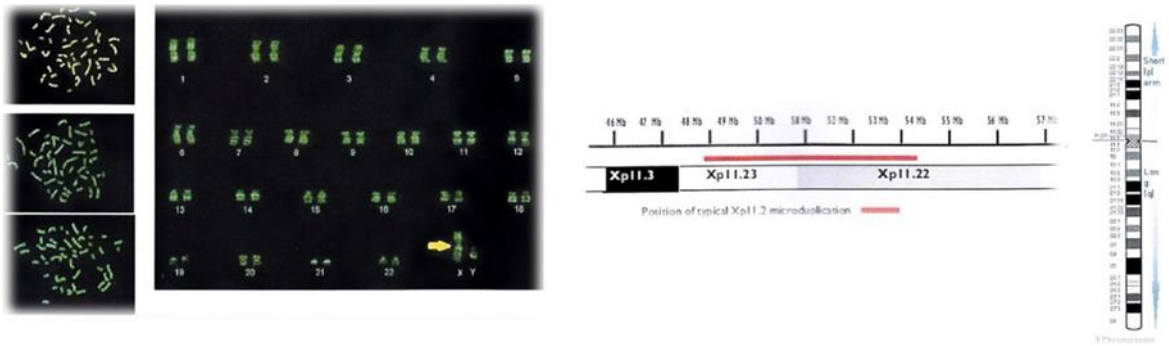

Fig 7. An Xp11. 2 duplication has an extra copy of a small piece of one of the chromosomes.

AZFa, using STS markers sY84 and sY86, along with the loci DYS273 and DYS148, microdeletions in this region were found in 39.51% of patients, the statistical significance of these findings was confirmed, with a p-value < 0.05. AZBc deletions were the least common anomaly, observed in only 5 patients (4%), the low frequency of AZBc deletions did not demonstrate a statistically significant association with cryptorchidism (p > 0.1). Statistical correlations with a chi-square analysis confirmed significant variability in the distribution of chromosomal deletions across the six loci (p < 0.001).

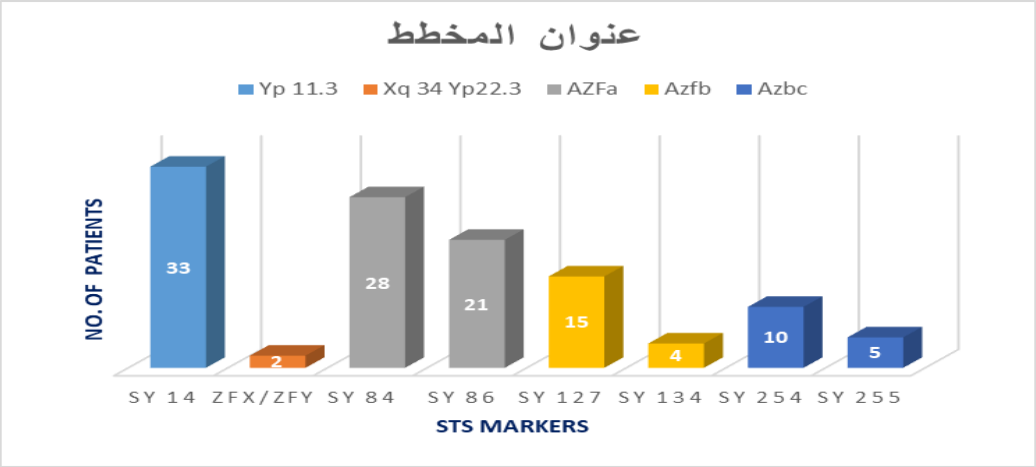

Fig 8. With the STS, sY84 & sy86, and the loci, DYS 273 & 148 the azoospermia factor A region (AZFa) was estimated in 39.51% of the patients in five locus regions.

Our study revealed significant associations between specific chromosomal anomalies and testicular locations. True ectopia, chromosomal abnormalities were rare, with only 3 cases identified (2.4% of the cohort), the anomalies included Yq1.2 deletions in 2 cases and Yq11.221 deletions in 1 case. True ectopia was statistically underrepresented compared to other testicular positions (p < 0.01).

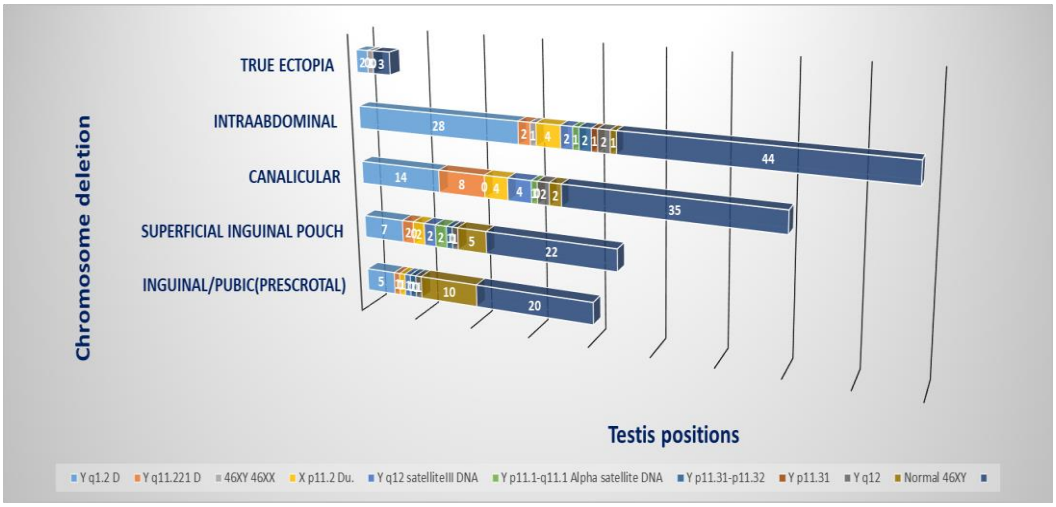

Fig 9. Higher ascent of the testis presented with more microdeletion (intra-abdominal 35.48% of the patients) p-value < 0.05**.**

Intra-abdominal testes, the highest prevalence of chromosomal abnormalities were observed in this group, with 44 cases (35.4% of the cohort), the anomalies included Yq12 deletions in 28 cases (63.6%), Xp11.2 duplications in 8 cases (18.2%), and Yp11.1-q11.1 deletions in 4 cases (9.1%). The strong association between intra-abdominal testes and chromosomal deletions was highly significant (p < 0.001). Inguinal/pubic (pre scrotal) testes, the chromosomal abnormalities were detected in 20 cases (16.1% of the cohort), the anomalies were Yq12 deletions in 11 cases (55%), Xp11.2 duplications in 10 cases (50%), and Yq11.221 deletions in 5 cases (25%). Statistical analysis demonstrated a significant association between these chromosomal abnormalities and this testicular position (p < 0.01), highlighting the genetic complexity in this subgroup. Yp11.1-q11.1 alpha satellite DNA abnormalities, mostly associated with true ectopic testicular positioning, The association was not statistically significant (p > 0.1).

III. RESULT AND DISCUSSION

Cryptorchidism is a multifaceted condition with both genetic and environmental components that affect the clinical outcomes of affected children. The distribution of patient ages at the time of diagnosis in this study highlights significant trends and underscores critical gaps in the timely detection and management of urological anomalies (6). The age distribution reflects the variability in the timing of diagnosis and possibly delayed recognition in some cases. While 42 patients were diagnosed between 1 and 2 years of age, and 26.2% were diagnosed in the first year of life, this suggests heightened clinical vigilance during this period. However, those who were diagnosed after 2 years, including 5 years, raise concerns about missed opportunities for earlier intervention. The delay in diagnosis beyond the recommended 6–12 months treatment window may stem from a lack of awareness, limited access to specialized care, or variations in healthcare-seeking behavior (7). The findings of this study underscore the complex interplay between cryptorchidism and associated anomalies, revealing critical insights into the broader implications of this condition. The results show that 87% of patients in our cohort exhibited associated anomalies, while 13% had no identifiable abnormalities. Among these, genitourinary malformations emerged as the most prevalent anomaly, while speech disturbances, postnatal growth retardation, developmental delays, and other rarer findings further highlighted the systemic nature of cryptorchidism. The diverse spectrum of urological anomalies among the studied cohort, with statistically significant differences in their prevalence, provides valuable insights into these conditions' clinical implications and management. The significant overrepresentation of genitourinary malformations ($p < 0.001$) highlights their strong correlation with cryptorchidism.

Anatomically and developmentally, the genitourinary system and the testes share embryological origins, particularly during the crucial period of organogenesis (8 & 9). Abnormalities in HOX genes, WT1, and androgenic signaling pathways likely contribute to this association (8). Furthermore, the shared embryological basis between the urinary tract and the testicular descent process explains the frequent coexistence of renal anomalies, hypospadias, or other urogenital defects in this cohort. The high prevalence of these malformations reinforces the need for routine evaluation of the genitourinary system in cryptorchid patients, particularly in bilateral cases, to ensure timely diagnosis and treatment of potentially undetected anomalies. Additionally, the diversity of anomalies observed highlights the necessity of a multidisciplinary approach that integrates urology, nephrology, and pediatrics to address the multifaceted needs of affected patients. Speech disturbances were the second most common anomaly in the cohort ($p = 0.02$), ranging from delayed language acquisition to articulation issues. This finding suggests that cryptorchidism may be a marker of broader neurodevelopmental impacts. While the specific mechanisms linking cryptorchidism to speech disturbances remain unclear, genetic syndromes with overlapping features, such as Klinefelter syndrome or microdeletions on the sex chromosomes, may play a role (10). Postnatal growth retardation was observed in 8% of patients ($p = 0.04$), reflecting a moderate but significant association with cryptorchidism. Growth retardation could be linked to genetic syndromes that affect both growth and testicular development, such as Noonan syndrome (11). Furthermore, endocrine dysregulation, including abnormalities in the hypothalamic-pituitary-gonadal axis, may contribute to cryptorchidism and reduced growth velocity.Rarer anomalies, such as velo-cardio-facial features (5%, $p = 0.03$) and microcephaly (2%, $p = 0.07$), indicate the need for syndromic evaluations in cryptorchid patients.

Conditions such as DiGeorge syndrome and ectodermal dysplasia, which are associated with these findings, may present with cryptorchidism as part of a broader phenotype (12). These rare anomalies highlight the necessity of genetic and clinical evaluations, particularly for patients with atypical features or multi-system involvement.In this study, 13% of patients presented with no associated anomalies, serving as a control-like subgroup. These cases emphasize the heterogeneity of cryptorchidism, suggesting that isolated cryptorchidism may stem from localized defects in testicular descent, such as gubernacular dysfunction or environmental influences during fetal development (13). This finding reinforces the multifactorial etiology of cryptorchidism, encompassing both isolated and syndromic forms.The findings from this study provide significant insights into the chromosomal underpinnings of bilateral cryptorchidism. Chromosomal deletions and structural anomalies, particularly on the Y chromosome, were prominently associated with the condition,

underscoring their contribution to testicular maldescent. Yq1.2 deletions emerged as the most significant chromosomal abnormality (4 & 5). These findings suggest a strong genetic influence on testicular descent, possibly linked to critical genes involved in gubernacular development or hormonal signaling pathways. The association between Y chromosome microdeletions and cryptorchidism, particularly at the Yq1.2D locus, aligns with previous studies that have suggested a genetic predisposition for cryptorchidism linked to infertility in adulthood (14).

The identification of these microdeletions at an early age allows for better prognostic counseling regarding fertility outcomes and long-term health risks. The prominence of this deletion points to its potential as a biomarker for cryptorchidism, particularly in cases with bilateral presentation. Yq11.221 deletions were the second most frequently observed anomaly). This region is known to harbor genes essential for cellular migration and androgen signaling, which are vital in the later stages of testicular descent. The statistical significance of this finding underscores its importance in cryptorchidism's pathophysiology. Yq12 Satellite III DNA Abnormalities, found in 7% of patients, these structural anomalies suggest that chromosomal instability or defective gene regulation at Yq12 Satellite III could predispose individuals to cryptorchidism (15). In contrast, anomalies such as Yp11.1-q11.1 alpha satellite DNA abnormalities (3.2%), Yp11.3-p11.32 deletions (3.2%), and Yq12 deletions (4.8%) lacked statistical significance. The statistical significance emphasizes the importance of exploring these microdeletions further in the context of these anomalies or contributing only to specific contexts, such as syndromic or complex phenotypes. A normal 46XY karyotype, underscoring the role of extragenetic factors in the pathogenesis of cryptorchidism. This group likely represents cases influenced by hormonal imbalances, environmental exposures (e.g., endocrine-disrupting chemicals), or epigenetic modifications. Similarly, the 2.4% of patients with a 46XY/46XX karyotype highlights the potential involvement of non-genetic mechanisms, further supporting the multifactorial nature of cryptorchidism (15 & 16). These results are consistent with previous studies that have implicated the Y chromosome in the etiology of cryptorchidism (14, 15 &16). However, the high prevalence of Yq1.2 deletions in this cohort exceeds findings reported in earlier research, suggesting a potentially unique population-specific genetic predisposition or methodological differences in chromosomal analysis.

From the clinical relevance point of view the identification of specific chromosomal anomalies offers potential for diagnostic advancements. Yq1.2 and Yq11.221 deletions, in particular, could serve as genetic markers for early identification of cryptorchidism, enabling timely interventions to prevent associated complications such as infertility or malignancy (17 & 18). Furthermore, understanding the genetic basis of the condition could inform targeted therapies or genetic counseling for affected families. AZFa deletions, while less frequent, may contribute to cases of cryptorchidism with additional phenotypic complexities, including subfertility and spermatogenic failure (19). This supports previous studies suggesting AZFa's role in testicular structure maintenance. As rare contributors AZFb and AZBc deletions were observed in 7% and 3% of patients, respectively, while these loci were not statistically significant, this finding underscores the relevance of AZFa abnormalities in the context of cryptorchidism anomalies and further highlights the importance of genetic assessment in such cases. These loci may be implicated in cases that progress to testicular dysgenesis or azoospermia (20, 21 & 22). Furthermore, the identification of X chromosome microduplications in a subset of patients is noteworthy, as these abnormalities are less well-studied in the context of cryptorchidism. Although less prevalent, these duplications warrant attention and further investigation to understand their potential role in genitourinary anomalies. It may carry speech delay, early puberty, significant weight and height changes, anomalies of the legs and/ or feet, seizures and /or an unusual pattern of electrical activity in the brain in children, and minor facial features in these patients require close monitoring and multidisciplinary care (3 &4).Chromosomal regions such as Yq12, Yq11.221, Xp11.2, and Yp11.1-q11.1 have been implicated in testicular development and descent, and their disruption can result in a spectrum of positional anomalies (5).

These anomalies range from mild forms, such as inguinal or pre-scrotal malposition, to severe cases involving intra-abdominal or ectopic testes. Each positional category represents a unique clinical phenotype with varying degrees of severity and associated risks (22 &23). The genetic anomalies identified in this study likely disrupt critical pathways regulating testicular development, including hormonal signaling,

gubernacular migration, and androgen receptor activation. Y-linked loci such as Yp11.3 and Yp22.3 may interact with downstream effectors in the hypothalamic-pituitary-gonadal axis, leading to arrested testicular descent. X-linked loci such as Xq34 may modulate these processes through transcriptional regulators or epigenetic modifications (10 &11).Early identification of genetic anomalies may guide personalized management strategies, including the timing and type of surgical interventions and the need for long-term surveillance of fertility and hormonal function. Furthermore, the results suggest a potential genotype-phenotype correlation in cryptorchidism, where specific chromosomal regions influence the severity of testicular malposition. Understanding these relationships could pave the way for novel therapeutic targets, such as gene therapy or molecular interventions, to address the underlying causes of cryptorchidism (10, 11 &20).The chromosomal abnormalities identified in this study have varying impacts on life expectancy based on the severity of their effects on health and associated comorbidities, Yq12 deletions are strongly associated with testicular dysgenesis, leading to risks such as infertility, testicular malignancy, and hormonal imbalances (17 &24).

Early detection and intervention can mitigate the risk of testicular cancer, which is curable in most cases when diagnosed early. However, untreated or delayed cases may result in malignancy that significantly reduces life expectancy (24). Patients with Yq12 deletions require lifelong surveillance for malignancies and metabolic disorders to improve long-term outcomes. Yp11.32 and Yq11.221 deletions, these anomalies contribute to impaired testicular descent and function, increasing the risk of infertility and subfertility. However, the associated risks for malignancy are lower compared to Yq12 deletions (22 &23). Patients typically have a normal life expectancy with timely surgical correction and hormonal management. The primary impact lies in reproductive health rather than systemic risks. Rare but significant, these deletions are associated with more severe phenotypes, including syndromic presentations. Syndromic cases may experience systemic complications that reduce life expectancy, particularly if genetic anomalies affect multiple organ systems (25). Comprehensive evaluation and multidisciplinary care are essential to manage associated syndromic features. Structural vulnerabilities in Yq12 predispose individuals to chromosomal instability, potentially exacerbating cryptorchidism and other developmental issues. Life expectancy may not be directly impacted unless associated complications such as malignancy or systemic disorders arise. This study has several limitations that must be acknowledged, although the cohort of 124 patients is substantial, the rarity of some chromosomal anomalies limits the generalizability of these findings. Larger, multi-center studies are needed to validate these results. While the study highlights chromosomal contributions, it does not account for other potential factors, such as hormonal or environmental influences, that may play a significant role in cryptorchidism. The study primarily focused on chromosomal deletions and duplications, potentially overlooking other genetic factors, such as single-nucleotide polymorphisms, epigenetic modifications, or gene-environment interactions.

For broader genomic investigations, whole-genome or array-based analyses should be conducted to identify novel loci and rare variants associated with cryptorchidism. The study does not provide functional evidence linking the identified chromosomal deletions to specific disruptions in testicular descent, necessitating further molecular studies. The study does not include long-term follow-up, which could provide insights into the impact of these chromosomal abnormalities on fertility, malignancy risk, and overall health. Future research should focus on larger, multicenter studies to validate these findings, explore the functional impact of specific genetic abnormalities, and correlate genetic profiles with clinical outcomes. Addressing these gaps will enhance our understanding of cryptorchidism and pave the way for more precise, personalized approaches to diagnosis and treatment.

IV. CONCLUSIONS

This study highlights the significant role of chromosomal microdeletions and duplications in the management of bilateral cryptorchidism. The findings shed light on the hierarchical contribution of specific loci to the condition and highlight the multifactorial nature of its pathogenesis. Genetic screening is recommended for all patients with syndromic cryptorchidism to provide a comprehensive understanding of associated pathologies and to guide future medical and surgical interventions. The integration of genomic

information into clinical practice will improve the long-term outcomes for these patients and provide a more accurate life expectancy prognosis. Furthermore, the ethical implications of genetic screening should be carefully considered, and a multidisciplinary approach is essential in the management of these complex cases.

V. ACKNOWLEDGMENTS

We would like to thank the institutional ethics committee for their approval and all the patients and families who participated in the study. Special thanks to the genetic and medical teams who contributed to the data collection and analysis.

Ethical Considerations

Ethical approval for this study was obtained from the institutional review board. After a detailed explanation of the study objectives, potential risks, and benefits, written informed consent was obtained from parents or guardians. Families were informed about the implications of chromosomal abnormalities, including reproductive outcomes, life expectancy, and potential comorbidities. Parents were offered pre- and post-test genetic counseling to address any psychological, ethical, or social concerns arising from the results. Confidentiality was strictly maintained by de-identifying all patient data and limiting access to the study database.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose regarding this manuscript's content, findings, or publication. This study was conducted independently, without any external financial support, sponsorship, or influence from commercial or non-commercial entities. All aspects of the research, including data collection, analysis, interpretation, and manuscript preparation, were performed objectively and solely to contribute to the scientific understanding of cryptorchidism and its associated anomalies. The authors affirm their commitment to transparency, ethical research practices, and the unbiased reporting of results to ensure the integrity of the study and its findings.

REFERENCES

[1] Virtanen He, toppari J. Epidemiology and pathogenesis of cryptorchidism. Hum Reprod Update 2008; 14:49–58.

[2] Iafrate AJ, Feuk L, Rivera MN, Listewnik ML, Donahoe PK, et al. 2004. Detection of large-scale variation in the human genome. Nat. Genet. 36:949–51

[3] Itsara A, Cooper GM, Baker C, Girirajan S, Li J, et al. 2009. Population analysis of large copy number variants and hotspots of human genetic disease. ***Am. J. Hum. Genet***. 84:148–61

[4] DP, Sharp AJ, McCarroll SA, McGrath SD, Newman TL, et al. 2006. Linkage disequilibrium heritability of copy-number polymorphisms within duplicated regions of the human genome. Am. Genet. 79:275–90

[5] Foresta C, Moro E, Garolla A, Onisto M, Ferlin A. Y Chromosome Microdeletions in Cryptorchidism and Idiopathic Infertility. ***J Clin Endocrinol Metab*** 1999; 84: 3660-65.

[6] Gurney JK, McGlynn KA, Stanley J, et al. Risk factors for cryptorchidism. Nat Rev Urol 2017;14(9):534–48. doi:10.1038/nrurol.2017.90.

[7] Bayne A, Alonzo D, Hsieh M, Roth D. Impact of anatomical and socioeconomic factors on the timing of urological consultation for boys with cryptorchidism. ***J. Urol.*** (2011) 186:1601–5. doi: 10.1016/j.juro.2011.03.102

[8] Acerini CL, Miles HL, Dunger DB, et al. The descriptive epidemiology of congenital and acquired cryptorchidism in a UK infant cohort. Arch Dis Child. 2009

[9] Fantasia J, Aiden J, Lathrop W, Ellsworth P. Undescended testes: a clinical and surgical review. Urol Nurs 2015; 35:117–26.

[10] Gorlov iP, Kamat a, Bogatcheva nV, Jones e, lamb DJ, truong a, Bishop ce, Mcelreavey K, agoulnik ai. Mutations of the great gene cause cryptorchidism. Hum Mol Genet 2002; 11:2309–18.

[11] Yoshiyuki Kojima, Kentaro Mizuno, Kenjiro Kohri, Yutaro Hayashi. Advances in Molecular Genetics of Cryptorchidism. Urology Volume 74, Issue 3, September 2009, Pages 571-578

[12] Heidi P. Elamo, Helena E. Virtanen, Jorma Toppari. Genetics of cryptorchidism and testicular regression. Best Practice & Research Clinical Endocrinology& Metabolism. Volume 36, Issue 1, January 2022, 101619

[13] Mäkelä J-a, Koskenniemi JJ, Virtanen He, toppari J, development t. testis development. Endocr Rev 2018. doi:10.1210/er.2018-00140

[14] Gill B, Kogan S (1997) Cryptorchidism. Current concepts. Pediatr Clin North Am 44:1211–1227

[15] Thorup J, Mclachlan R, Cortes D, Nation TR, Balic A, Southwell BR et al (2010) What is new in cryptorchidism and hypospadias – a critical review on the testicular dysgenesis hypothesis. ***J Pediatr Surg*** 45:2074–2086

[16] Virtanen HE, Bjerknes R, Cortes D, et al. Cryptorchidism: Classification, prevalence, and long-term consequences. ActaPaediatr 2007;96(5):611–16. doi: 10.1111/j.1651

[17] Bani-Hani KE, Matani YS, Bani-Hani IH (2003) Cryptorchidism and testicular neoplasia. ***Saudi Med J 24***:166–169

[18] Agoulnik, A.I., Huang, Z., and Ferguson, L. (2012). Spermatogenesis in cryptorchidism. Methods Mol.Biol. 825, 127–147.

[19] Dada R, Gupta NP, Kucheria K. Cryptorchidism and AZF microdeletion. Asian J. Androl 2002; 4:148.

[20] Hadziselimovic F, Hadziselimovic NO, Demougin P, Oakeley EJ. Testicular gene expression in cryptorchid boys at risk of azoospermia. Sex Dev 2011; 5: 49-59.

[21] Westlander G, Hamberger L, Hanson C, Lundin K, Nilsson L, Söderlund B, et al. Diagnostic epididymal and testicular sperm recovery and genetic aspects in azoospermic men. Hum Reprod 1999; 14:118-22.

[22] Lee PA, Coughlin MT. Fertility after bilateral cryptorchidism. Evaluation by paternity, hormone, and semen data. *Horm Res* 2001; *55:* 29-31.

[23] Goel P, Rawat JD, Wakhlu A, Kureel SN. Undescended testicle: An update on fertility in cryptorchid men. Indian ***J Med Res 2015***;141(2):163–71.

[24] Sonne SB, Almstrup K, Dalgaard M, et al. Analysis of gene expression profiles of micro-dissected cell populations indicates that testicular carcinoma in situ is an arrested gonocyte. Cancer Res. 2009; 69:5241. [PubMed: 19491264]

[25] Kolon TF, Herndon CDA, Baker LA, et al. Evaluation and treatment of cryptorchidism: AUA guideline. ***J Urol. Aug; 2014*** 192(2):337–45. [PubMed: 24857650] [This guideline offers a detailed summary of the natural history and risk factors for cryptorchidism, as well as the current AUA recommendations for both its diagnosis and management.