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The Potential Role of Chromosomal Polymorphic Variations Attributed to Male Infertility: A Retrospective Cohort Study

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Abstract

Background: Infertility is a complex condition that can originate from either male or female factors, or both. Genetic factors, such as damage to the Y chromosome, gene defects, and chromosomal anomalies significantly contribute to infertility. Consequently, cytogenetic analysis is a critical component of the systematic clinical evaluation for diagnosing, managing, and monitoring infertility. The purpose of the present study was to assess the prevalence, types, and significance of chromosomal polymorphisms in the East Indian population with a clinical history of male infertility.

Methods: An investigation was conducted on 650 infertile men and 150 fertile men from general population, following the Helsinki Declaration guidelines. A cytogenetic investigation was conducted using G-banding, Ag-NOR banding, and centromeric heterochromatin staining. A Chi-square test was performed to compare the prevalence of chromosomal polymorphic variants.

Results: The results of this study revealed significant chromosomal anomalies among the study population. Specifically, 2.61% of these individuals exhibited numerical chromosomal anomalies, while 1.53% showed structural chromosomal anomalies. Notably, there was a statistically significant ($p<0.05$) increase in the occurrence of total chromosomal polymorphic variations, with 24% of the infertile males found to have total chromosomal polymorphisms. Furthermore, the prevalence of the Yqh+ variant was statistically significant among infertile males ($p=0.010$), while the 9qh+ variant also showed a significant prevalence ($p=0.0.35$).

Conclusion: The increased prevalence of chromosomal polymorphic variants underscores the need to evaluate their potential role in the etiology of male infertility.

Keywords: Ag-NOR banding, Cytogenetic analysis, Centromeric heterochromatin staining, Chromosomal polymorphic variants, Male infertility, Y chromosome deletion.
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Introduction

Infertility is a worldwide health concern, with prevalence increasing rapidly, affecting one in six individuals of reproductive age. According to the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO), infertility is defined as the inability of an individual to conceive after 12 months of unprotected intercourse (1-3). It can be caused by multiple factors in both males and females, including age, endocrine disorders, infections, genetic abnormalities, and environmental influences (4).

Male infertility accounts for 50% of infertility cases in couples. Approximately 70% of infertility cases have an identifiable cause. In comparison, the remaining 30% are unknown, often linked to chromosomal abnormalities such as numerical or structural chromosome anomalies and quantitative or positional alterations of constitutive heterochromatin (5-7). Heterochromatin consists of highly repetitive satellite DNA sequences present on 1, 9, and 16 chromosomes (specifically in the centromeric region), on the terminal end of the q arm (long arm) of the Y chromosome, and on the short arms of acrocentric chromosomes (the D/G group) which do not affect an individual's phenotype (8). However, recent reports show that these variations are more common in infertile and subfertile individuals than in the general population, primarily based on cytogenetic data from newborn screening surveys (9). Heteromorphic regions of chromosomes contain repetitive satellite DNA sequences that do not encode proteins. When these repetitive sequences are found on the same chromosome, they can increase the likelihood of homologous unequal recombination. This process can lead to micro-rearrangements, such as deletions, duplications, and inversions, which may have a significant impact on clinical conditions like infertility and recurrent miscarriage (10). There are limited available studies regarding the significant association of variations in chromosomal polymorphism and male infertility. Therefore, the purpose of the current investigation was to evaluate the prevalence, type, and significance of chromosomal polymorphisms in the East Indian population who had a history of male infertility.

Methods

Subject preparation: A multicentric retrospective cohort study was designed and performed as per the Helsinki guidelines (2013) for human research to assess the association of chromosomal polymorphic variants (CPVs) in infertile men. The investigation was carried out between September 2022 and December 2024 at the inDNA Center for Research and Innovation in Molecular Diagnostics, in collaboration with the School of Biotechnology, KIIT deemed to be University, Odisha, India. The study was reviewed, and ethical clearance was obtained from an Independent Ethics Committee at inDNA Life Sciences Pvt. Ltd. (REF: EC/IND/CYT/09/22/02), located in Odisha on September 02, 2022. In compliance with ethical guidelines, prior informed consent was obtained from all participants. Clinical information, including familial history, baseline data, endocrine disorders, and relevant surgical and diagnostic assessments related to reproductive health, was recorded for clinical correlation.

Participants: The investigation was focused on 800 men, consisting of 650 males experiencing infertility issues and 150 fertile males from the general population, aged 24 to 55, who sought treatment at an infertility clinic. These men, undergoing fertility treatment, were referred for cytogenetic analysis as part of standard clinical evaluation following failure to achieve pregnancy after ≥12 months of unprotected intercourse. Individuals with incomplete clinical records were excluded from the study. The fertile individuals were retrospectively identified in the laboratory repository as those who had achieved at least one natural pregnancy which had resulted in a live birth or an ongoing clinically documented pregnancy without assisted reproductive methods. Individuals with uncertain fertility history or incomplete records were excluded from the study. The fertile individuals were taken as a reference population to determine the baseline frequency of chromosomal polymorphic variants. Given the retrospective nature of the study, the sample size was established based on the availability of suitable cytogenetic records throughout the study duration. No formal a priori calculation was conducted for sample size comparisons between groups. The prevalence-based formula, n=(Z^2*P*(1-P))/ d^2, was applied only to ensure adequate overall sample size for estimating the prevalence of CPVs with acceptable precision.

Sample collection: Initially, 2 to 3 *ml* of heparinized peripheral whole blood was collected from each patient, and each sample was labeled with a unique laboratory identification number.

A standard T-cell specific culture was initiated in a T-25 flask using complete RPMI-1640 medium (Gibco-11875-093; Thermo Fisher Scientific, USA) supplemented with 12-15% fetal bovine serum (Gibco-10270-106; Thermo Fisher Scientific, USA), 1% L-glutamine, 1% penicillin-streptomycin (A007-100ML; HiMedia, India), and phytohemagglutinin-M (PHA-M) (Gibco-10576-015; Thermo Fisher Scientific, USA). Each sample was uniquely marked and then incubated in a 37°*C* incubator with 5% CO_2 for 72 *hr*. Between the 69th and 71st *hr*, 10 *mg/ml* of colcemid (Gibco-15210-040; Thermo Fisher Scientific, USA)

was added to each T-25 flask and kept at 37°*C* for an additional *hr*. After incubation, the cell suspensions were spun at 400×*g* for 15 *min* and treated with a 0.075 *M* potassium chloride solution (Catalog/CAS No :7447-40-7; Merk, Germany). The tubes were then placed in a water bath at 37°*C* for 30-35 *min*, followed by another centrifugation at 400×*g* for 15 *min*. The cells were fixed by adding pre-chilled Carnoy's fixative (Merck, Germany) to the cell pellet and placed at 4°*C* for 12-14 *hr*. Subsequently, 3-4 washes with pre-chilled Carnoy's fixative were performed. Mitotic cells were collected, and chromosomal slides were prepared.

The slides were stained using the G-banding technique with Giemsa (-S011-100ML; HiMedia, India) and trypsin (Gibco-27250018; Thermo Fisher Scientific, USA), following the procedures outlined in the Association of Genetic Technologists (AGT) Cytogenetics Laboratory Manual (4^{th} edition). Silver staining was performed following the Association of Genetic Technologists (AGT) Cytogenetics Laboratory Manual, 4th edition, to confirm the presence of heterochromatin regions containing tandem repeat sequences.

C-banding using barium hydroxide (Cat. No: 85499; Sisco Research Laboratories, India) and DAPI staining was performed as described by Sumner et al. (1977) with minor modifications, in order to visualize constitutive heterochromatin at centromeric and secondary constriction regions (11). The Olympus BX43 microscope, paired with a Leica DFC365 FX monochrome digital camera, was used to examine the G-banded slides. A total of twenty elongated and well-spread metaphases were documented, and the location of each metaphase spread was recorded using the Slide Finder tool. Metaphase chromosome karyotyping was performed at approximately 400–500 band resolution using CytoVision 4.0 software (Leica Biosystems, USA). All karyotypes were documented according to the International System for Human Cytogenomic Nomenclature 2024 (ISCN-2024).

Statistical analysis: The frequencies of different categories of chromosomal polymorphisms were expressed as percentages. The Pearson Chi-square test was conducted to evaluate the differences in the frequency of chromosomal polymorphisms between group I (infertile males) and group II (fertile males). For sample sizes below three, counts and percentages were utilized, but they were not included in the hypothesis testing process. For these uncommon variations, neither p-values nor confidence intervals were computed. Statistical significance was defined as $p<0.05$. All statistical analyses were performed using SPSS software, version 29.0.2.0 (IBM, USA).

Results

Association of chromosomal anomalies in infertile males: Conventional cytogenetic study was conducted on 650 male individuals with a clinical history of infertility, alongside 150 fertile for comparison. Out of 650 infertile males, 467 were found to have a normal chromosomal constitution while 183 exhibited alternations in their chromosomal constitution. Table 1 encapsulates the comprehensive findings of the study, highlighting the different types of structural and numerical chromosomal anomalies observed.

Out of 650 infertile males, 14 had 47,XXY and related variants (47,XXY/48,XXXY mosaicism), 2 had 47,XYY, 3 had Y chromosome deletions, and 7 carried balanced rearrangements. The most prevalent sex chromosomal abnormality was 47,XXY, and its variants, consistent with Klinefelter Syndrome. Among the autosomal anomalies, 7 males presented with balanced rearrangement, comprising 5 Robertsonian translocations and 2 reciprocal translocations. Furthermore, an unbalanced rearrangement was noted in three patients, consisting of mosaic and non- mosaic deletions of Yq as illustrated in figure 1.

Association of various types of chromosomal polymorphic variants in male infertility: A detailed investigation was carried out to assess the prevalence of various polymorphic variants in males experiencing infertility issues. Out of 650 infertile men, 156 were found to have various types of chromosomal polymorphisms. The preva-lence of these polymorphic variants was signifi-cantly higher ($p<0.001$) in infertile males (24%) compared to fertile males (8%) (Table 2). Figure 2 illustrates the visualization of the constitutive heteromorphic region (acro region) on the short p-arm of acrocentric chromosomes and the visualization of the heteromorphic variant region on the long q-arm of a non-acrocentric chromosome.

The detailed assessment was conducted based on the categories of variations identified in the current investigation. Polymorphic variants were classified into several groups, including: qh+/- CPVs, qh+ double CPVs, inversion of chromosome 9, inversion of chromosome Y, ps+ CPVs, ps+ double CPVs, ps+ triple CPVs, ps+ multiple

Table 1. A comprehensive overview of different chromosomal anomalies and variations in 650 infertile and 150 fertile individuals

Cytogenetic outcome	Prevalence (%) Infertile Male (n=650)	Prevalence (%) Control group (n=150)
Normal karyotype 46,XY	71.84%(n=467)	92% (n=92)
Chromosomal alteration	28.15% (n=183)	08% (n=12)
Major chromosomal anomaly	4.15% (n=27)	-
Numerical anomalies	2.61% (n=17)	-
47,XYY	0.30% (n=02)	-
47,XXY	2.15% (n=14)	-
47,XXY/48,XXXY	0.15% (n=01)	-
Structural anomalies	1.53% (n=10)	-
46,X,delY	0.15% (n=01)	-
46,Xdel(Y)/46,XY	0.15% (n=01)	-
45,X/46,X,del(Y)	0.15% (n=01)	-
46,XY,der(13;14)	0.46% (n=03)	-
46,XY,der(14;22)	0.30% (n=02)	-
46,XY,t(1;15)	0.15% (n=01)	-
46,XY,t(11;22)	0.15% (n=01)	-
Polymorphic variants	24% (n=156)	08% (n=12)

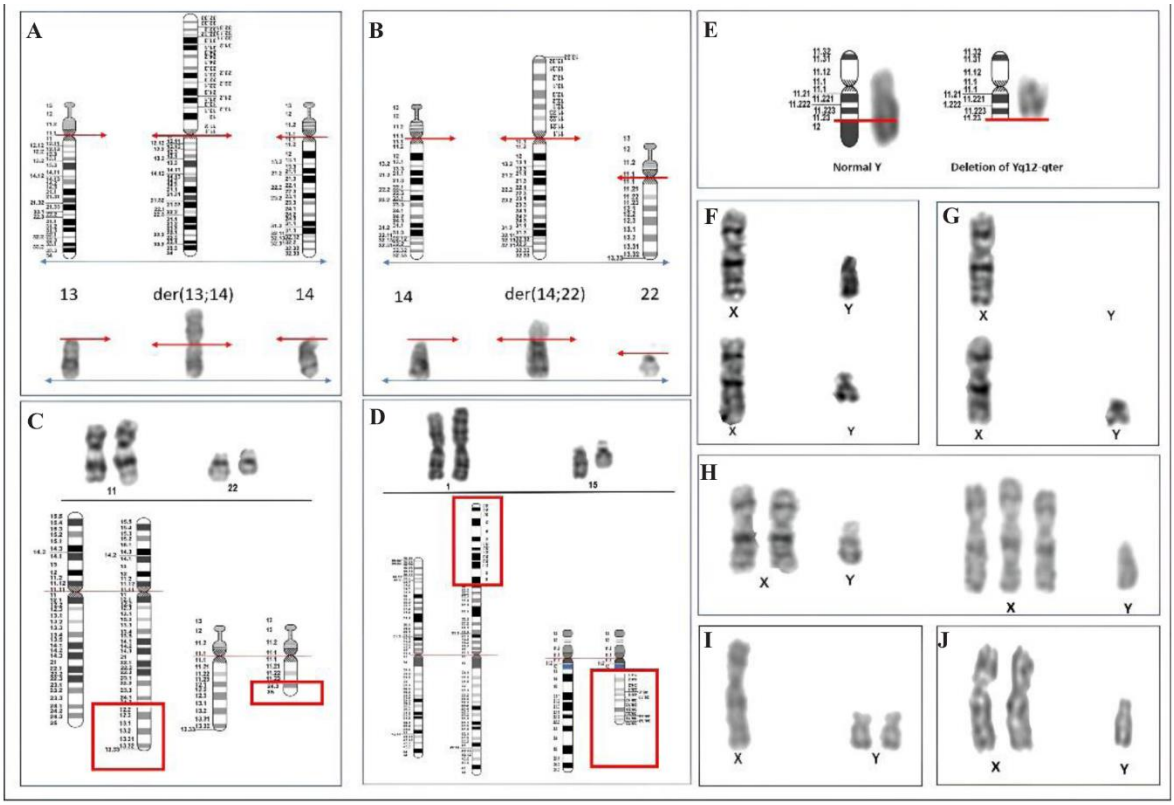

Figure 1. Images representing different chromosomal variants identified in men experiencing infertility. A: balanced Robertsonian translocation; B: balanced Robertsonian translocation; C: balanced reciprocal translocation; D: balanced reciprocal translocation; E: deletion on long arm (q) of chromosome Y; F: a mosaic karyotype exhibiting both a normal cell line and a cell line with a deletion on the long arm (q) of chromosome Y; G: mosaic karyotype with loss of chromosome Y and deletion of long arm (q) of chromosome Y; H: 47,XXY/48,XXXY; I: 47,XYY; J: 47,XXY

Table 2. Prevalence of non-acrocentric and acrocentric chromosomal polymorphic variants

Groups	Chromosomal polymorphic variants	Prevalence of chromosomal polymorphic variants (%)								
		Non-acrocentric							Acrocentric	Combination of non-acrocentric and acrocentric
		1qh+	Inv (9)	9qh+	16qh+	Yqh+	Yqh-	inv(Y)	D/G group	
Infertile (n=650)	156 (24%)	0.15 (n=01)	1.69 (n=11)	4.15 (n=27)	0.15 (n=01)	7.85 (n=51)	0.61 (n=04)	1.38 (n=09)	7.54 (n=49)	0.46 (n=03)
Fertile (n=150)	12 (08%)	-	-	0.66 (n=01)	-	2 (n=03)	-	-	4.67 (n=07)	0.66 (n=01)
p-value	<0.05*	-	0.11	0.0.35*	-	0.010*	0.00*	0.14	0.21	0.74

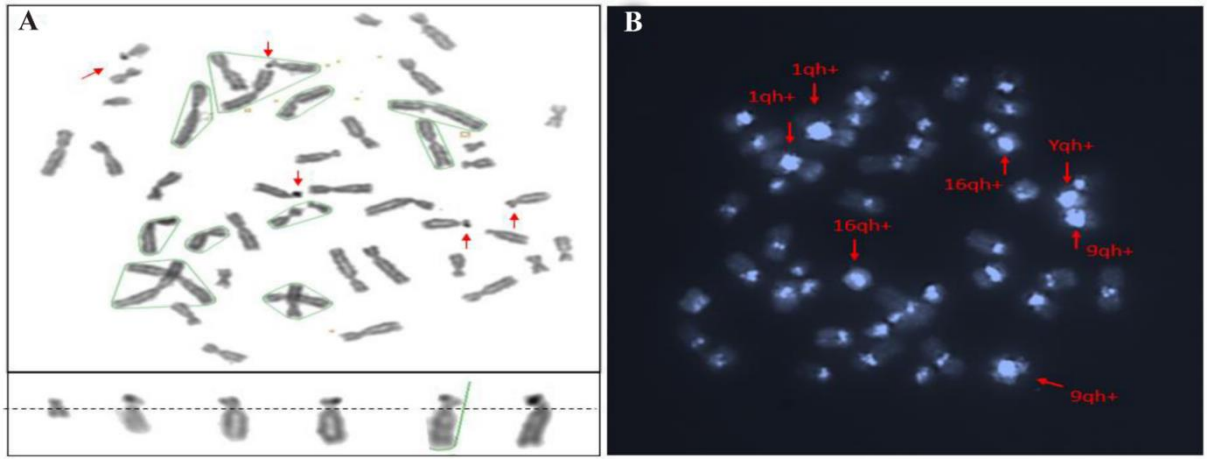

Figure 2. A) representative karyotype illustrating a chromosomal variant on the NOR region of the short p-arm of an acrocentric chromosome and B) karyotype representation illustrating a chromosomal heteromorphic variant region on the long q-arm of a non-acrocentric chromosome, utilizing inverted DAPI staining

CPVs, pstk+ CPVs, and pstk+ double CPVs. These categories are illustrated in figure 3.

Various types of non-acrocentric heteromorphic variants in infertile versus fertile males: A comprehensive analysis of chromosomal polymorphic variations revealed that the frequencies of heterochromatin regions 9qh+ (4.15%), Yqh+ (7.85%), 1qh+ (0.15%), 16qh+ (0.15%), and Yqh- (0.61%) were much higher than those seen in fertile males. Additionally, the prevalence of inversion 9 (1.69%) and Y (1.38%) polymorphic variations was notably higher in the infertile group, as seen in table 3. The prevalence of qh+/-, qh+ double CPVs, and the inversion of chromosomes 9 and Y were significantly higher ($p<0.05$) in the infertile group, with an odds ratio (OR) of 7.03 (95%CI: 2.55-19.40).

Various types of acrocentric heteromorphic variants in infertile versus fertile males: Subsequent analysis revealed that the infertile cohort had a higher frequency of polymorphic variations (ps+) belonging to the D/G groups (6.15%) compared to fertile males (4.67%). The prevalence of the 15ps+ subtype polymorphism was significantly higher in the acro ps+ group, with an OR of 1.85 (95% CI: 0.23-14.95). Additionally, the prevalence of other variants such as 13ps+, 14ps+, 21ps+, 22ps+, double ps+, triple ps+, and various ps+ polymorphic variants was higher in the infertile group compared to fertile males. Overall, the occurrence of ps+, ps+ double, and ps+ multiple candidate polymorphic variants was higher in the infertile group, with an OR of 1.33 (95%CI: 0.58-3.05).

The analysis showed that the infertile group had

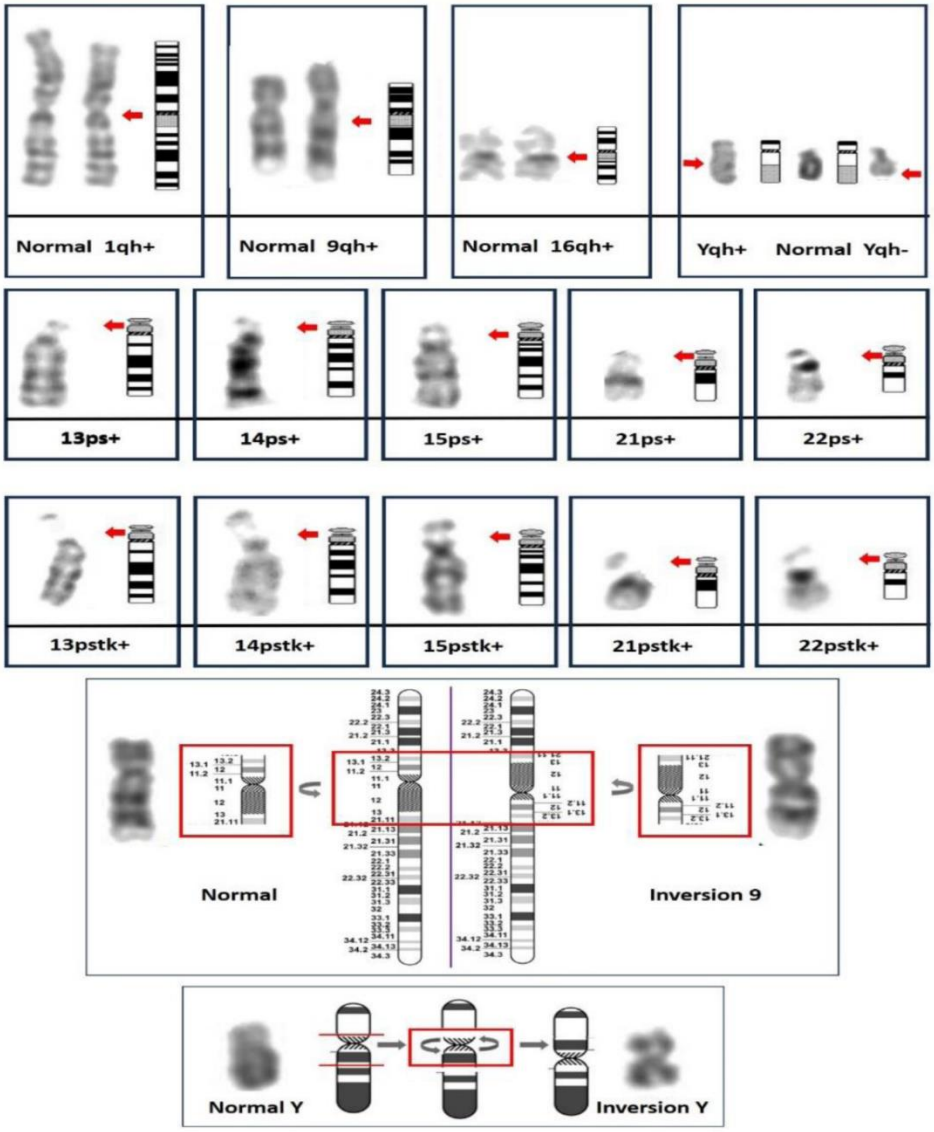

Figure 3. Representative illustration of different types of chromosomal polymorphism observed

Table 3. Distribution and prevalence of various types of non-acrocentric heteromorphic variants detected in group I (infertile group) and the group II (fertile group)

Non-acrocentric heteromorphic variants								
Type of variant	**Chromosomal polymorphism**	**Group I (n=650)**	**Composition ratio (%)**	**Group II (n=150)**	**Composition ratio (%)**	**p-value**	**OR**	**95%CI**
qh+	1qh+	01	0.15	00	00	0.627	Ref	Ref
	9qh+	27	4.15	01	0.67	0.035*	6.45	0.87-47.90
	16qh+	01	0.15	00	00	0.627	Ref	Ref
	Yqh+	51	7.85	03	2.00	0.010*	4.17	1.28-13.55
qh-	Yqh-	04	0.61	00	00	p<0.001***	Ref	Ref
qh+ (double)	9,Y	01	0.15	00	00	0.627	Ref	Ref
Inversions	Inv(9)	11	1.69	00	00	0.11	Ref	Ref
	Inv(Y)	09	1.38	00	00	0.14	Ref	Ref
Total		105	16.15	04	2.67	<0.05*	7.03	2.55-19.40

Test used: Chi-square or Fisher's exact test (if any frequency <5). * Represents a significant p-value <0.05

a comparatively higher frequency of polymorphism variations (pstk+) associated with the D/G groups (1.38%) compared to fertile group.

Combination of non-acrocentric heteromorphic and acrocentric heteromorphic variants in infertile versus fertile males: The frequency of the combination of acrocentric and non-acrocentric polymorphic variants was higher in the studied group compared to group II. Overall, the occurrence of the combination of acrocentric and non-acrocentric CPVs was comparatively higher in the infertile group, with an OR of 0.69 (95%CI: 0.07-6.68).

Discussion

Various chromosomal anomalies have emerged as a significant genetic causative factor in male infertility and it makes cytogenetic analysis a crucial part of the infertility evaluation process. In this investigation, cytogenetic analysis was carried out on 650 individuals with a history of infertility. The analysis revealed that the major chromosomal anomalies in 4.15% of the cases, which falls within the expected range of 2-5%, are attributed to genetic causes, according to established standards for assessing and managing infertility in couples. In addition to these major chromosomal anomalies, variations in chromosomal polymorphisms are also believed to make a substantial contribution to male infertility. Numerous studies published in recent years have investigated the probable correlation between infertility and specific chromosomal polymorphism variations (13).

A review carried out by Bhasin et al. on 24 published research studies, which included a total of 73,013 patients globally, revealed that the prevalence of acrocentric D-group polymorphic variants was 2.58%, while acrocentric G-group polymorphic variants were recorded at 1.38%. Consequently, the combined prevalence of acrocentric D and G group polymorphic variations was 3.96% (14). In the present study, 650 infertile men showed a singular acrocentric D or G group polymorphic variant in 6.01% (39 out of 650) of cases, while more than one variant was found in another 1.53% (10 out of 650) of cases. The prevalence of acrocentric D and G group polymorphic variants in this investigation was therefore 7.54% (49/650). In the current study, a polymorphism of the Y chromosome was identified in 7.84% (51 out of 650) of the cases. Additionally, pooled data from 7,995 individuals across 34 studies reported the prevalence of the 9qh+ variant among 2.44% of cases (14). In contrast, the present investigation showed the 9qh+ variant in 4.15% (27 out of 650) of cases. Furthermore, a polymorphism of the Y chromosome classified as Yqh- was found in 0.62% (4/650) of the cases.

The debate over the importance of constitutive heterochromatin has been contentious for an extended period. It was previously regarded as "junk DNA". The "selfish DNA hypothesis" suggested that the commonly satellite DNA sequences linked to heterochromatin served little purpose for the organism (15, 16). Previous data from cell biology and epigenetics suggests that polymorphic heterochromatic region can take part in chromatin organization, stress responsive transcription activity, and nuclear architecture (17-23). These findings should be interpreted as contextual rather than causative; however, they offer a plausible biological framework for interpreting our results. Moreover, several investigations, particularly those assessing assisted reproductive technology (ART) and in vitro fertilization (IVF) outcomes, have reported no significant adverse impact of heteromorphic polymorphic variants on fertilization rates, the embryo development process, or pregnancy outcomes (24-29). The apparently conflicting findings may reflect differences in the study design, outcome measures, patient selection, and the use of ART, which can partially bypass natural reproductive barriers. In contrast, the present investigation emphasized on natural infertility phenotypes, where subtle chromosomal or epigenetic alternation may exert greater influence during spermatogenesis rather than the post-fertilization process.

It is important to highlight that our investigation did not directly evaluate molecular mechanisms underlying these association. Instead, our investigation provided epidemiological evidence of an elevated prevalence of these polymorphic variants but did not establish a causal role in male infertility. Thus, our results do not support the conclusion that all chromosomal polymorphic variations have pathogenic consequences. Rather, they indicate that in a subgroup of infertile men, specific heterochromatic and NOR-associated variations might serve as susceptibility indicators or risk modifiers. Instead of routinely classifying these variants as clinically insignificant, the observed enrichment of these variants underscores the necessity for thorough documentation and re-evaluation.

The present study, being a first line retrospective study, has several limitations. The first limitation

is the assessment of infertility as a single composite outcome, without stratification based on semen profiling or precise clinical diagnoses. Infertility comprises a heterogenous spectrum of conditions. Due to the retrospective design and insufficient clinical information, subgroup analysis was not feasible. Second, certain subtle duplications and deletions were overlooked due to the limited resolution of conventional G-banding. Additionally, while FISH and microarray analyses are not commonly performed in cases of reproductive failure, the possibility of cryptic translocations, microdeletions, and microduplications cannot be excluded.

Conclusion

The current study underscores the potential clinical relevance of the increased prevalence of chromosomal polymorphic variants identified in infertile men. The presence of chromosomal polymorphic variants among infertile men may have significant cellular functions, including but not limited to transcriptional activation of constitutive heterochromatin, nucleolar segregation, and capping during transcriptional inhibition. These factors may significantly influence male infertility. Therefore, routine cytogenetic analysis may not be sufficient, making high-resolution NOR banding analysis essential for detecting these polymorphic variants, which may act as crucial contributors in identifying the probable etiology for male infertility. This practice will facilitate their re-evaluation and serve as a valuable resource for future reference. An accurate diagnosis of the constitutional karyotype is crucial, as it plays an important role in the early management of patients undergoing fertility evaluations. Polymorphic variants should not uniformly be considered 'normal', as they may serve important cellular functions that are not yet fully understood and warrant further longitudinal investigation. To better understand their biological and clinical implication, future research must integrate cytogenetics with functional, epigenetic, and reproductive outcome data.

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Conflict of Interest

The authors declare no conflicts of interest.

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