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Effects of chromosomal heteromorphisms on reproductive health

Mehmet Caner Özer*[1,2], Ayşegül Karahanoğlu[1,3], Zerrin Çelik[1]

[1]Department of Medical Genetics, Faculty of Medicine, Başkent University, Ankara, Turkiye

[2]Department of Assisted Reproductive Treatment, Gülhane Training and Research Hospital, University of Health Sciences, Ankara, Turkiye

[3]Department of Medical Genetics, Ankara Training and Research Hospital, University of Health Sciences, Ankara, Turkiye

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ABSTRACT

Chromosomal heteromorphisms (CHs) are structural chromosomal variants that are generally regarded as benign. This study will examine the potential impact of CHs on reproductive health, including infertility, recurrent pregnancy loss, spermatogenesis, oogenesis, and assisted reproductive techniques technologies. A narrative review of published studies evaluating the prevalence, biological mechanisms, and reproductive implications of CHs was conducted. Although CHs are traditionally regarded as normal cytogenetic variants, several studies have reported increased frequencies among individuals with infertility, recurrent pregnancy loss, and abnormal reproductive outcomes. Proposed mechanisms include alterations in meiotic chromosome pairing, chromatin condensation, gene regulation, and genome stability. However, findings remain inconsistent across studies. Current evidence suggests a possible association between CHs and adverse reproductive outcomes; however, a definitive causal relationship has not been established. Further prospective studies are required to clarify their clinical significance.

Keywords: Chromosomal heteromorphism, chromosomal polymorphism, infertility, recurrent pregnancy loss, assisted reproductive technologies

INTRODUCTION

The term heterochromatic chromosomal variants, also known as "chromosomal heteromorphism" (CH), is used interchangeably with polymorphism or normal variant. Common cytogenetic polymorphisms identified through G-banding are considered heteromorphisms.[1] The most common variations are quantitative or positional changes in the structural DNA heterochromatin found in the centromeric regions of chromosomes 1, 9, and 16, on the long arm of the Y chromosome, and on the short arms of acrocentric chromosomes (Figure 1). These changes, known as secondary contraction regions, can involve various length patterns such as qh+ or qh- for heterochromatin blocks or may include an inversion of an entire block.[2] An increase or decrease in the short arm length of acrocentric D and G group chromosomes is called 'p±'. Meanwhile, changes in the satellites and stalks of the short arms are referred to as 'ps+/-' and 'pstk+/-', respectively (Table).[3,4]

Pericentric inversion of chromosome 9 is one of the most common chromosomal variations observed in humans.

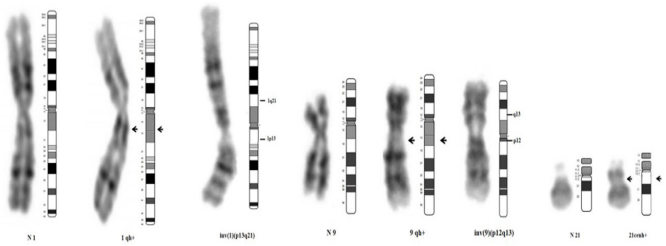

Figure 1. An increase in the long arm heterochromatin of chromosomes 1 and 9, as well as inversions considered as normal variants, are observed in chromosome 21's centromeric heterochromatin increase. The relevant regions are marked with black arrowheads (Images are taken from the archive of the Department of Medical Genetics at Başkent University)

Epidemiological data suggest its occurrence ranges from 1% to 4%. The latest version of the International System for Human Cytogenetic Nomenclature (ISCN) designates inv (9) (p12q13) as a chromosomal polymorphism with no known clinical significance (Figure 1).[3,4]

DNA sequencing and analysis of human chromosome 9 reveal that it contains the largest autosomal heterochromatin block

Table. Common chromosomal polymorphisms and banding techniques (ISCN, 2024)[38]

Method	Chromosome											
	1	2	3	9	10	13	14	15	16	21	22	Y
C-bant (+)*	qh+			qh+					qh+			q12
NOR-bant (+)						p12	p12	p12		p12	p12	
G-bant	inv (p13q21)	inv (p11.2q13)	inv (p11.2q12)	inv (p12q13)	inv (p11.2q21.2)				inv (p11.2q12.1)			inv (p11.2q11.2)

*Structural heterochromatin at the centromere is found on all chromosomes. In this table, those with frequently observed length polymorphism are included. ISCN: International System for Human Cytogenomic Nomenclature, q: Long arm, +: Increased length, qh+: The heterochromatin region on the q arm is longer than usual, NOR: Nucleolar organizer region, p: Short arm, inv: Inversion

***Corresponding Author:** Mehmet Caner Özer, mc.ozer77@gmail.com

and is structurally highly polymorphic and heteromorphic in 6-8% of human cases. Some studies have suggested associations between the inv (9) (p12q13) variant and a range of phenotypes, including recurrent pregnancy loss, intrauterine growth retardation, heart disease, amenorrhea, Down syndrome, and sexual development disorders.[5-8]

Structural heterochromatin comprises parts of the genome that are consistently highly dense and transcriptionally inactive. These regions typically contain few genes and are made up of repetitive tandem sequences. Regions rich in structural heterochromatin, like subtelomeric and pericentromeric areas, are often conserved across individuals of the same species. In humans, the size of the subcentromeric regions on chromosomes 1, 9, and 16, as well as the distal q arm of chromosome Y, can vary significantly among individuals (**Figure 2**). Most of the time, these types of variants are stable and inherited across generations.[9]

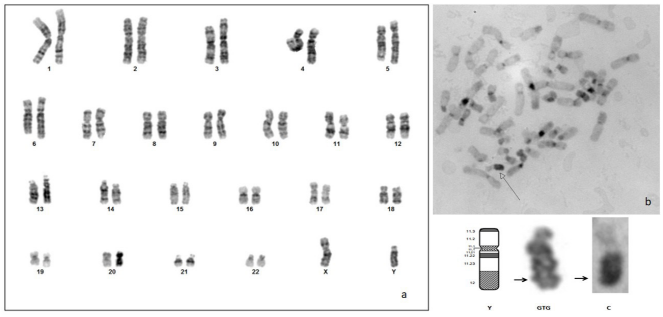

Figure 2. Karyotype (a), C-banding (b), and partial karyotype image related to length polymorphism of heterochromatin on the long arm of the Y chromosome. The Y chromosome variant is marked with an arrow in metaphase (Images are taken from the archive of the Department of Medical Genetics, Başkent University)

For a long time, structural heterochromatin was considered small chromosomal rearrangements lacking clear coding potential and not linked to abnormal phenotypes. However, some studies suggest a potential link between CH and cancer and reproductive issues. High rates of CPM have been especially observed in patients with primary infertility and recurrent pregnancy loss. Some research indicates that CHs are independently connected to the formation of multinucleated embryos,[10] and male CHs are associated with increased early pregnancy loss and decreased live birth rates after in vitro fertilization (IVF).[11] Some studies have reported that CH has no effect on IVF.[12,13]

It has been demonstrated through some studies that chromosomal heteromorphisms (CHs) in humans may have indirect effects on processes such as gametogenesis, meiotic division, and chromosome pairing in terms of reproductive health. In this context, the potential role of CH in infertility, sperm parameters, recurrent pregnancy losses, and the success of assisted reproductive techniques (ART) is noteworthy. In this review, the definition of CH, its common types, possible mechanisms of effect on reproductive functions, and the existing literature data will be examined.

Chromosomal Heteromorphisms (CHs)

CHs are microscopically visible variations involving heterochromatic segments. They are usually inherited and are most commonly observed in the pericentromeric regions of chromosomes 1, 9, and 16, as well as on the long arm of the Y chromosome. CHs are generally regarded as normal variants, and many clinical cytogenetic guidelines consider them to be of limited clinical significance.[14]

Although CHs are generally considered benign, the underlying etiological mechanisms behind some of the correlations with various diseases shown in different studies have not yet been fully understood; however, scientific research suggests that CHs may have a potential effect on genome stability and modulation. Hypotheses suggest that CHs may influence gene expression by regulating or inhibiting specific genes through position effect modifications on meiotic chromosome pairing and segregation, thereby affecting genome organization.[14]

Recent research indicates that heterochromatin associated with CHs can suppress or silence gene expression through interactions between heterochromatin and euchromatin. In different organisms, euchromatic genes located near pericentric heterochromatin show position-effect variegation, causing gene silencing in some cells where expression would typically occur, thus producing a mosaic phenotype. This phenomenon has been observed in models involving *Drosophila*, yeast, and mice.[15] Other studies also indicate that heterochromatin at centromeres is crucial for cell division. Mutations in these chromatin regions, along with defects in centromere function and cohesion, can cause problems like improper homologous chromosome pairing and disrupted cell division, potentially impacting the development of functional sperm.[4]

The impact of chromosomal polymorphisms on fertility is still not fully understood. Some studies suggest various possible mechanisms for specific types of pericentric inversions. One possibility is that the inversion could disrupt homologous chromosome pairing during meiosis. Another proposed mechanism is the interchromosomal effect. This suggests that inv (9) can affect how other chromosomes pair, since the unpaired segments of homologous chromatids might also impact other bivalent chromosomes.[16]

As seen, recent developments in molecular genetic methods have begun to reveal that DNA in heterochromatin regions possesses partial genetic functionality. Clinical observations indicate a link with several reproductive health issues, including male infertility, recurrent spontaneous miscarriages, reduced sperm quality, fetal anomalies, and disturbances in male reproductive development.[17]

Chromosomal Heteromorphisms (CHs) and Recurrent Pregnancy Loss

Repeated pregnancy loss (RPL) refers to experiencing two or more pregnancy losses before the 20th week of gestation. Female with a history of RPL have been reported to have partners exhibiting a higher incidence of sperm DNA damage compared to those without such a history.[18] The increased frequency of CHs observed in men may suggest a potential influence on chromosomal pairing and meiotic progression. Consequently, CHs may contribute to unexplained sperm DNA damage observed in some patients with RPL.[18]

In a particular study, it was observed that patients experiencing RPL exhibit a higher prevalence of CH (8-15%) compared to those with natural pregnancies (3-10%).[18,19] In a different study, it was reported that the prevalence of spontaneous abortion and preterm delivery was markedly increased in infertile female carrying CHs compared with female with

a normal karyotype. In patients experiencing unexplained recurrent pregnancy loss, CH variants such as 1qh+, inv (9), and 21 ps (s)/pstk (stk) have been reported more frequently.[18]

It is well understood that heterochromatin within chromosomes, the attachment of spindle fibers to chromosomes, the movement of chromosomes along spindle fibers, the meiotic pairing of chromosomes, and sister chromatid cohesion each confer specific benefits. Additionally, the short arm of acrocentric chromosomes also comprises heterochromatin. Any deviation exceeding acceptable limits in this region is believed to potentially result in improper chromosome segregation during karyokinesis, which may lead to RPL.[20]

Karaca et al.[21] discovered that the most common heteromorphism among female with recurrent miscarriage, infertility, and the control group is 1qh+. Additionally, they observed that female experiencing IVF failure exhibit higher frequencies of 21 chromosome variants in comparison to 1qh+. The study also found that Yqh+ was the most common heteromorphism in men within both the control and infertility groups, while Yqh- was observed in the recurrent miscarriage and IVF failure groups.

In female individuals, the chromosome 9 qh+ CH variant has been associated with an increased risk of pregnancy loss and infertility. Furthermore, the ps+ variants are predominantly observed on chromosomes 21 and 22, as well as on chromosomes 14 and 15. These variants might potentially lead to errors during meiotic segregation, resulting in reproductive failures, such as recurrent miscarriages and infertility issues, which have been highlighted in various studies.[22]

Although Karaca et al.[21] reported in their study that there is no relationship between heteromorphisms and recurrent miscarriages, Zhu et al.'s[23] study found that chromosomal polymorphic variants may negatively affect fertility. Furthermore, the unusually high frequency of acrocentric chromosome D/G group variants in female with RPL indicates that CH variants may be associated with RPL.[24]

In a study conducted by Rawal et al.,[25] elevated occurrences of satellite chromosome segments were observed in female experiencing spontaneous miscarriage and their partners. However, so far, no particular function has been identified as related to satellite segments. Nevertheless, such variations in couples may render the fetus more vulnerable to translocations, and this situation is regarded as a potential risk factor that could contribute to pregnancy loss. In the same study, patients who had experienced IVF failure and gave birth to children with malformations were also found to frequently exhibit increased centromeric heterochromatin in chromosomes 1 and 9. These variants may have contributed to mitotic instability and increased the risk of aneuploidy. Thus, heterochromatin variations in chromosomes 1 and 9 might be linked to pregnancy loss, recurrent or spontaneous miscarriages, embryonic developmental issues, and abnormal phenotypes.[25] Conversely, the research conducted by Yuan Dong et al.[26] concluded that there is no correlation between heteromorphism and reproductive failure; this conclusion is supported by the observation that heteromorphism was also present during examinations of the fathers and brothers of fertile patients. This study suggests that heteromorphisms should not be considered linked to infertility, recurrent pregnancy loss, or a history of delivering children with such conditions or malformations.

Chromosomal Heteromorphisms (CHs) and Infertility

Given the important role of heterochromatin in meiosis, it has been hypothesized that CHs may interfere with the formation of functional gametes. In CH carriers, the likelihood of embryonic aneuploidy and adverse reproductive outcomes may be increased.[2] Heterochromatin functions in polymorphic regions can suppress or inhibit gene expression, potentially affecting gametogenesis. Variations in these polymorphic chromosome regions may significantly contribute to infertility in both males and females.[27]

Chen et al.[17] reported that 14.98% of male patients attending an infertility clinic were carriers of CHs. This rate is higher than the reported prevalence of CHs in the general population.

Cheng at al.[16] study found that CHs occurred more frequently in infertile patients than in controls, with the highest rate seen in the unexplained infertility subgroup. Furthermore, the occurrence of 9qh+ was notably higher in individuals with tubal infertility, ovulation dysfunction, and unexplained infertility compared to the control group.

CH-associated heterochromatic regions are among the last chromosomal regions to complete synapsis during meiosis. It has been suggested that alterations in these regions may contribute to meiotic defects and subsequently to infertility.[15] The contribution of distinct heteromorphisms to infertility remains incompletely elucidated; however, the observation that these variants are more prevalent in infertile men than in infertile female, according to some studies, suggests that their effects may become evident during the spermatogenesis process. An unusually long heteromorphism observed in studies on infertility carriers causes the chromosome in this region to bend outward and become asynaptic during metaphase I of meiosis. This condition may contribute, at least partially, to defective spermatogenesis in some infertile men; however, these variants alone are not strongly linked to abnormal semen parameters.[9]

Chromosomal Heteromorphisms (CHs), Spermatogenesis, and Male Infertility

The literature indicates that CHs are more frequently observed in men with infertility than in female. It is thought that Y chromosome polymorphisms, accounting for nearly 20% of male chromosome polymorphisms, could be a key factor behind this discrepancy.[24]

The Yqh+ variant, characterized by an enlarged heterochromatic block on the long arm of the Y chromosome, has been proposed to contribute to chromosomal instability. This instability can disrupt the expression of euchromatin genes and the functionality of related genes, potentially affecting spermatogenesis, embryo formation, and differentiation. As a result, this condition may lead to impaired semen quality in men and fetal malformations.[28] The Y chromosome variant can lead to the deletion of heterochromatin segments near important autosomal genes (such as the AZF gene) that are crucial for gender determination and spermatogenesis. This deletion may affect gene expression or cause AZF gene microdeletions, thereby negatively impacting the production and quality of spermatogonial cells.[28]

Morales et al.[29] found that the rate of sperm aneuploidy is higher in CH carriers than in controls. It has also been shown that variation in the Y chromosome can increase the error rate in meiotic segregation and recombination. In carriers of CH with severe oligozoospermia, lower fertilization rates have been observed compared to non-carriers with severe oligozoospermia.[30] Therefore, it has been proposed that chromosomal polymorphisms may negatively impact spermatogenesis and IVF success rates.[18]

In the study by Carlos Hernandez-Nieto et al.,[2] no significant difference was found in embryo ploidy rates between CH carriers and control groups. Additionally, after accounting for patients' age and other possible confounding factors, no link was found between the presence of a CH variant and a higher risk of embryo aneuploidy.

Li et al.[31] conducted a study showing that chromosomal variants are linked to a higher risk of non-obstructive azoospermia in Chinese men. Moreover, Dul et al.[32] reported that chromosomal variants negatively impact spermatogenesis and reduce the success rates of IVF/ICSI-ET procedures.

Chromosomal Heteromorphisms (CHs), Oogenesis, and Female Infertility

Cheng et al.[16] investigated the association between CHs and female infertility and reported a higher frequency of unexplained infertility among CH carriers. In addition, female carriers may be at increased risk of adverse reproductive outcomes compared with female without CHs. Although several studies have demonstrated that CHs alone do not significantly affect embryo quality, their influence may become clinically relevant when combined with other chromosomal abnormalities. Consistent with this observation, patients carrying both chromosomal polymorphisms and translocations were found to have lower rates of high-quality embryos and higher rates of abnormal embryos than patients with translocations alone.[13,18]

Lu et al.[33] study indicated that female undergoing IVF with multiple polymorphisms and female with pstk+ variants undergoing ICSI may have an increased risk of preterm birth. The role of females CHs in increasing preterm birth risk is still unclear, and further research is needed to determine if this link is due to the negative impact of CHs on oocyte development.

Lu et al.[33] reported that CHs may negatively affect oocyte maturation. It is well established that constitutive heterochromatin plays a role in suppressing gene expression, preserving genome stability, and ensuring proper chromosome segregation.[33,34] Therefore, CHs are thought to be associated with chromosomal segregation errors and aneuploidy formation. Previous studies have shown that female carrying CHs tend to produce more aneuploid blastocysts[29] and that polymorphisms are linked to the formation of multinucleated embryos. This supports the idea that female carrying CHs might experience more meiotic errors, resulting in increased chromosomal aneuploidy in oocytes. Such errors can hinder oocyte maturation and negatively impact embryo development.[10,33]

Fewer studies have explored the link between centromeric heterochromatic variants and female infertility. However, a notable 9qh+ variant has been linked to reproductive failure. This aligns with findings that decreased recombination, especially in the oocytes of female of advanced maternal age, is associated with nondisjunction events. The impact of long heterochromatic variants on meiotic recombination in human oocytes has not been studied. If we assume they inhibit crossing over as observed in male spermatogenesis, these variants could potentially lower the overall crossing over rate in oocytes, possibly leading to fewer viable, polyploid oocytes in female of advanced maternal age.[9]

Chromosomal Heteromorphisms (CHs) and Assisted Reproductive Techniques

The impact of chromosomal polymorphisms on the results of in vitro fertilization or intracytoplasmic sperm injection (IVF/ICSI) remains inconsistent. Some studies report no influence of IVF/ICSI outcomes,[2] while others suggest that CHs are linked to adverse effects.[35,36] Zhanhui Ou and colleagues,[12] in their meta-analysis, discovered that male chromosomal polymorphisms are significantly linked to reduced fertilization rates, division rates, and the percentage of good-quality embryos.

Carlos Hernandez-Nieto et al.[2] reported that CHs do not significantly affect the outcomes of assisted reproductive technologies. In another study, lower fertilization rates were reported in men carrying CHs and severe oligozoospermia compared with non-carriers who also had severe oligozoospermia. Therefore, CHs may negatively affect spermatogenesis and IVF outcomes.[35]

Although many recent publications have proposed that long heterochromatic variants could be inherited by offspring of infertile couples using assisted reproductive technologies, Wilson et al.[9] reported no statistically significant difference in the occurrence of heterochromatin variants between children conceived through these technologies and normal controls. Additionally, studies indicate that children born through assisted reproductive technology are not more likely to inherit long Y variants compared to those conceived naturally. Therefore, even if these variants play a role in infertility, children conceived through assisted methods who inherit the long Y variant are not at increased risk of negative effects from it.

A study suggests that the presence of various types of CHs can influence patients' clinical features, including IVF failure, infertility, and recurrent miscarriages. It also indicates potential interchromosomal interactions between polymorphic chromosomes and other chromosomes,[21] which may further complicate the understanding of infertility and the effectiveness of assisted reproductive technologies. Another study, after excluding individuals with complex chromosomal anomalies and clear causes of infertility, found that ICSI's impact on pregnancy outcomes depends on the gender of polymorphism carriers. Specifically, in males, carrying these polymorphisms leads to the development of poorer quality embryos.[18]

Several mechanisms have been proposed to explain the adverse effects of male CHs on ART outcomes. It has been suggested that heterochromatin on the Y chromosome's long arm might affect sperm function and that variations on the Y chromosome could lead to microdeletions and male infertility. Thus, it has been determined that chromosomal polymorphisms reduce semen quality and subsequently affect the fertilization rate.

Secondly, heterochromatin associated with chromosomal polymorphisms may potentially suppress or even silence euchromatin gene expression. Thirdly, heterochromatin clusters at the centromeres; thus, heterochromatin can lead to errors in meiotic cell division and interfere with the development of functional spermatozoa. Fourthly, structural heterochromatin mainly gathers in the telomeric, centromeric, and pericentromeric regions of chromosomes, where it stays condensed throughout the cell cycle. This organization is vital to maintaining genome stability and ensuring proper chromosome segregation. Variations in heterochromatin can disrupt these mechanisms. All of these mechanisms can affect the developmental potential of the embryo.[12]

According to Lu et al.,[33] female carrying qh+ and undergoing IVF showed higher fertilization, clinical pregnancy, and live birth rates. Another study found that female with chromosomal polymorphisms also experienced increased clinical pregnancy and live birth rates.[4] However, this study did not specifically investigate how different types of polymorphisms affect IVF and ICSI outcomes separately or analyze their distinct impacts.

Li et al.[3] in their study found that patients with inv (9) had a lower division rate in IVF compared to control patients, but no significant difference was observed when ICSI was used. Additionally, it has been reported that these patients may have a higher rate of early pregnancy loss in both ICSI and IVF groups.

In a study investigating the rate of unbalanced chromosomal rearrangements in patients with inv (9) undergoing IVF with preimplantation genetic testing (PGT-SR) prior to structural reorganization, it was found that pericentric inversions of chromosome 9 did not lead to unbalanced structural rearrangements in embryo samples on days 5/6.[3,37]

Using ICSI in men with chromosomal polymorphisms may improve fertilization rates compared to traditional IVF. Male carriers tend to lower success rates by decreasing fertilization, good-quality embryo development, clinical pregnancies, and live births, while raising biochemical pregnancy rates. In female carriers, this impact mainly manifests as a slower embryo division rate.[18]

Although several studies have reported associations between CHs and infertility, recurrent pregnancy loss, and adverse ART outcomes, the current evidence remains insufficient to support changes in routine clinical management.[2,9,33] At present, the identification of CHs should not automatically alter IVF/ICSI treatment strategies, embryo selection, or reproductive decision-making. Instead, these findings should be interpreted within the broader clinical context and considered alongside other established reproductive risk factors.

It is also important to acknowledge that reproductive outcomes may be influenced by multiple factors, including maternal age, ovarian reserve, semen quality, embryo quality, and underlying causes of infertility.[2,13,18] Therefore, the independent contribution of CHs to reproductive failure remains difficult to determine.

Future prospective studies with larger patient populations are needed to clarify the impact of specific CH variants on embryo development, implantation, pregnancy outcomes, and live birth rates.

The presence of CHs should not be considered an independent cause of reproductive failure, nor should it lead to unnecessary concern among carriers. However, given the growing body of evidence suggesting potential associations with adverse reproductive outcomes, individualized genetic counseling and careful clinical evaluation remain important. Understanding the potential implications of CHs may improve reproductive counseling, facilitate informed clinical decision-making, and support personalized management strategies for affected individuals and couples.[28] Such an approach may help ensure appropriate clinical management and comprehensive patient-centered care.

CONCLUSION

CHs are generally regarded as benign cytogenetic variants; however, they have frequently been investigated in association with reproductive failure. The potential effects of CHs on reproductive health may be explained through several proposed mechanisms: an increase or decrease in heterochromatin blocks may hinder meiotic pairing and disrupt chromatin condensation during spermatogenesis; additionally, since it contains many non-epigenetic repetitive sequences, it may affect epigenetic regulation. However, there is a noticeable inconsistency among the studies in the literature. While many studies have found an increased carrier rate, these findings do not fully establish a cause-and-effect relationship. Additionally, many studies have methodological limitations such as differences in sample sizes and control groups. Therefore, it is more accurate to state that strong prospective data is necessary for definitive classification as a risk factor. In individuals with unexplained infertility, recurrent pregnancy losses, or ART failure, the evaluation of CHs as part of conventional karyotype analysis may be considered. When emphasizing personalized genetic counseling, it is crucial to meticulously address the presence of CHs in relation to the individual's comprehensive clinical profile, and to comprehensively elucidate the potential implications.

ETHICAL DECLARATIONS

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

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REFERENCES

1. Sahin FI, Yilmaz Z, Yuregir OO, Bulakbasi T, Ozer O, Zeyneloglu HB. Chromosome heteromorphisms: an impact on infertility. *J Assist Reprod Genet.* 2008;25(5):191-195. doi:10.1007/s10815-008-9216-3
2. Hernandez-Nieto C, Gayete-Lafuente S, Alkon-Meadows T, et al. Parental chromosomal heteromorphisms are not associated with an increased risk of embryo aneuploidy. *JBRA Assist Reprod.* 2021;25(4):575-580. doi:10.5935/1518-0557.20210011
3. Li SJ, Cheng YX, Ye-Shang, et al. Chromosomal polymorphisms associated with reproductive outcomes after IVF-ET. *J Assist Reprod Genet.* 2020;37(7):1703-1710. doi:10.1007/s10815-020-01793-8
4. Zhao J, Huang B, Hao J, Xu B, Li Y. Chromosomal polymorphisms have no negative effect on reproductive outcomes after IVF/ICSI-ET/FET. *Sci Rep.* 2022;12(1):19052. doi:10.1038/s41598-022-20132-8
5. Madan K. Chromosome heteromorphisms: critical literature review finds no convincing evidence of harm. *Eur J Med Genet.* 2025;78:105056. doi:10.1016/j.ejmg.2025.105056
6. Mešanović S, Perić M, Vareškić A. Prevalence and possible effects of pericentric inversion of chromosome 9 on reproductive failure in a human population of Northeast Bosnia and Herzegovina: a 10-year retrospective study. *Eur J Med Health Sci.* 2023;5(2):1-4. doi:10.24018/ejmed.2023.5.2.1662
7. Azonbakin S, Ouedraogo A, Ouedraogo A, et al. Chromosome polymorphism and human pathology: about 27 cases of chromosome 9 inversion in the Beninese population. *Open J Genet.* 2021;11(3):23-31. doi:10.4236/ojgen.2021.113003
8. Yuksel S, Savaci S, Ekici C, Kurtoglu EL, Korkmaz S, Yesilada E. Prevalence of pericentric inversion of chromosome 9 in Eastern Anatolia region and relationship to reproductive efficiency. *EJMO.* 2018;2(1):40-42. doi:10.14744/ejmo.2017.06978
9. Wilson A, Watt K, Ma S. The incidence of long heterochromatic polymorphism variants in infants conceived through assisted reproductive technologies. *Reprod Biomed Online.* 2017;35(2):219-224. doi:10.1016/j.rbmo.2017.04.008
10. Sun L, Chen ZH, Yang L, Yi CX, Liu J, Ou CQ. Chromosomal polymorphisms are independently associated with multinucleated embryo formation. *J Assist Reprod Genet.* 2018;35(1):149-156. doi:10.1007/s10815-017-1037-9
11. Ni T, Li J, Chen H, et al. Male chromosomal polymorphisms reduce cumulative live birth rate for IVF couples. *J Assist Reprod Genet.* 2017;34(8):1017-1025. doi:10.1007/s10815-017-0951-1
12. Ou Z, Yin M, Chen Z, Sun L. Meta-analysis of the association between chromosomal polymorphisms and outcomes of embryo transfer following in vitro fertilization and/or intracytoplasmic sperm injection. *Int J Gynaecol Obstet.* 2019;144(2):135-142. doi:10.1002/ijgo.12702
13. Li G, Shi W, Niu W, et al. The influence of chromosomal polymorphism on embryo development and embryonic molecular karyotype in preimplantation genetic testing for chromosomal translocation. *Front Physiol.* 2020;11:543188. doi:10.3389/fphys.2020.543188
14. Pires S, Jorge P, Liehr T, Oliva-Teles N. Challenges in classifying human chromosomal heteromorphisms using banding cytogenetics: from controversial guidelines to the need for a universal scoring system. *Hum Genome Var.* 2024;11(1):38. doi:10.1038/s41439-024-00295-8
15. Christofolini DM, Mafra FA, Neto RP, et al. Correlation between chromosomal variants and male infertility in a population of Brazilian infertile men. *Reprod Syst Sex Disord.* 2012;1(1):105. doi:10.4172/2161-038X.1000105
16. Cheng R, Ma Y, Nie Y, et al. Chromosomal polymorphisms are associated with female infertility and adverse reproductive outcomes after infertility treatment: a 7-year retrospective study. *Reprod Biomed Online.* 2017;35(1):72-80. doi:10.1016/j.rbmo.2017.03.022
17. Chen C, Jiang J, Yang Q, Cheng X, Wang G. The relationship between chromosomal polymorphism and male reproductive abnormalities. *Reprod Sci.* 2024;31(8):2425-2432. doi:10.1007/s43032-024-01530-x
18. Cao M, Zhang Q, Zhou W, Zhu Y, Li H, Yan J. Analysis of aneuploidy rate and pregnancy outcomes in unexplained recurrent pregnancy loss couples with chromosome polymorphism after PGT-A. *Front Med (Lausanne).* 2022;9:803988. doi:10.3389/fmed.2022.803988
19. Wang Y, Li G, Zuo MZ, et al. Y chromosome polymorphisms may contribute to an increased risk of male-induced unexplained recurrent miscarriage. *Biosci Rep.* 2017;37(2):BSR20160528. doi:10.1042/BSR20160528
20. Chakraborty A, Kar S, Mohapatra PC, Banerjee B. A case-control study identifying the frequency and spectrum of chromosomal anomalies and variants in a cohort of 1000 couples with a known history of recurrent pregnancy loss in the Eastern region of India. *J Hum Reprod Sci.* 2021;14(4):422-430. doi:10.4103/jhrs.jhrs_68_21
21. Karaca Y, Pariltay E, Mardan L, et al. Co-occurrences of polymorphic heterochromatin regions of chromosomes and effect on reproductive failure. *Reprod Biol.* 2020;20(1):42-47. doi:10.1016/j.repbio.2019.12.006
22. Trieu ST, Pham MD, Le H, et al. Survey of structural autosomal abnormalities and autosomal variants in infertile patients treated at some IVF centers in Vietnam. *Appl Clin Genet.* 2025;18:29-40. doi:10.2147/TACG.S510933
23. Feng X, Liu J, Wang Y, et al. Acrocentric chromosome polymorphic variants on Chinese female have possible association with unexplained recurrent pregnancy loss. *Reprod Sci.* 2021;28(2):575-584. doi:10.1007/s43032-020-00332-1
24. Zhu S, Zhang Q, Hu M, et al. Karyotypic analysis of 62,587 Han Chinese infertile couples undergoing assisted reproductive technology treatments: insights into chromosomal variations. *BMC Genomics.* 2025;26(1):640. doi:10.1186/s12864-025-11851-z
25. Rawal L, Kumar S, Mishra SR, Lal V, Bhattacharya SK. Clinical manifestations of chromosomal anomalies and polymorphic variations in patients suffering from reproductive failure. *J Hum Reprod Sci.* 2020;13(3):209-215. doi:10.4103/jhrs.JHRS_46_19
26. Dong Y, Jiang YT, Du RC, Zhang HG, Li LL, Liu RZ. Impact of chromosomal heteromorphisms on reproductive failure and analysis of 38 heteromorphic pedigrees in Northeast China. *J Assist Reprod Genet.* 2013;30(2):275-281. doi:10.1007/s10815-012-9910-z
27. Ralapanawe MSB, Gajaweera SL, Karunaratne N, et al. A comprehensive analysis of chromosomal polymorphic variants on reproductive outcomes after intracytoplasmic sperm injection treatment. *Sci Rep.* 2023;13(1):1319. doi:10.1038/s41598-023-28552-w
28. Rodriguez F, Cruz M, Requena A. Impact of parental chromosomal polymorphisms on the incidence of congenital anomalies and perinatal complications in a cohort of newborns conceived after ICSI + PGT-A. *Reprod Biol Endocrinol.* 2022;20(1):145. doi:10.1186/s12958-022-01012-2
29. Morales R, Lledó B, Ortiz JA, Ten J, Llácer J, Bernabeu R. Chromosomal polymorphic variants increase aneuploidies in male gametes and embryos. *Syst Biol Reprod Med.* 2016;62(5):317-324. doi:10.1080/19396368.2016.1212949
30. Šípek A Jr, Mihalová R, Panczak A, et al. Heterochromatin variants in human karyotypes: a possible association with reproductive failure. *Reprod Biomed Online.* 2014;29(2):245-250. doi:10.1016/j.rbmo.2014.04.021
31. Li JP, Zhang FB, Li LJ, et al. Y chromosome polymorphisms contribute to an increased risk of non-obstructive azoospermia: a retrospective study of 32,055 Chinese men. *J Assist Reprod Genet.* 2024;41(3):757-765. doi:10.1007/s10815-024-03022-y
32. Dul EC, Groen H, van Ravenswaaij-Arts CMA, Dijkhuizen T, van Echten-Arends J, Land JA. The prevalence of chromosomal abnormalities in subgroups of infertile men. *Hum Reprod.* 2012;27(1):36-43. doi:10.1093/humrep/der374
33. Lu Y, Tian T, Chen L, Yan L, Chang L, Qiao J. Diverse impacts of female chromosomal polymorphisms on assisted reproduction outcomes: a retrospective cohort study. *BMC Pregnancy Childbirth.* 2024;24(1):331. doi:10.1186/s12884-024-06532-w
34. van de Werken C, van der Heijden GW, Eleveld C, et al. Paternal heterochromatin formation in human embryos is H3K9/HP1 directed and primed by sperm-derived histone modifications. *Nat Commun.* 2014;5:5868. doi:10.1038/ncomms6868
35. Guo T, Qin Y, Gao X, et al. The role of male chromosomal polymorphism played in spermatogenesis and the outcome of IVF/ICSI-ET treatment. *Int J Androl.* 2012;35(6):802-809. doi:10.1111/j.1365-2605.2012.01284.x
36. Liang J, Zhang Y, Yu Y, Sun W, Jing J, Liu R. Effect of chromosomal polymorphisms of different genders on fertilization rate of fresh IVF-ICSI embryo transfer cycles. *Reprod Biomed Online.* 2014;29(4):436-444. doi:10.1016/j.rbmo.2014.06.011
37. Merrion K, Maisenbacher M. Pericentric inversion (Inv) 9 variant-reproductive risk factor or benign finding? *J Assist Reprod Genet.* 2019;36(12):2557-2561. doi:10.1007/s10815-019-01601-y
38. ISCN 2024: an International System for Human Cytogenomic Nomenclature (2024). *Cytogenet Genome Res.* 2024;164(suppl 1):1-224. doi:10.1159/000538512