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Review article

Chromosomal Heteromorphism with Reference to Cancer and Reproduction in Human: An Appraisal

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Abstract

Background and Objectives: Human cell nucleus has, the genome consisting of euchromatin and heterochromatin. The euchromatin has gene-rich and actively functional. The heterochromatin has two components namely constitutive and facultative, where the former is highly polymorphic. It is related to numerous diseases like cancer and infertility which is now well known, though it was earlier thought to be inactive; hence the implication of these polymorphic variants of chromosomes is reviewed with respect to acrocentric and non- acrocentric types. ***Methodologies:*** The polymorphic variants can be detected by C, G, Q and R banding techniques. We usually follow G band preparation of karyotypes following World Health Organisation (WHO) manuals and their role in cancer and reproduction is reviewed. ***Review and Conclusion:*** It is emphasized that most of the p and q arms of 1, 9, 16, D and G groups and X, Y chromosomes exhibited polymorphism which are related to cancerous and infertile conditions in both sexes. Data on few non-acrocentric chromosomes like 2, 4, 8, 10, 12, 18, 19 and 20 are not available. Our review however indicated that the evaluation of specific heteromorphic variants needs to be detected using specific probes for confirmation of anomaly to assist affected cases, though earlier data indicated ambiguous information with few cases analyzed regarding assisted reproductive technologies and malignancy condition. This appraisal thus would play a key role in human chromosomal heteromorphic abnormalities and recommend genetic tests and counseling ultimately made available to the affected cases.

Keywords: ***Acrocentric and non acrocentric chromosomes, Heterochromatin, Heteromorphic, Human, Infertility, Karyotypes, Malignancy.***

Introduction

Recent studies on cell nucleus have revealed that the nuclear genome has euchromatin and heterochromatin, two functional units present on chromosomes. The euchromatin has the most active portions of genome with gene rich. The heterochromatin has two types i.e. Constitutive and facultative. The constitutive type is a stable form, composed of satellite DNA I, II or III units and is known to be highly polymorphic not coding the protein and unstable. Facultative is not rich with satellite DNA and is not very polymorphic like inactive X chromosome (Barr body). The role of heterochromatin in human genome is remained unknown as it has no functional and phenotype effect including cancer.[1,2] It now is known that heterochromatin is not inert and has multiple functions in a cell and organismal viability in multi-cellular eukaryotes. Genes required for viability, fertility and cancer are thought to be present in it required for chromosomal inheritance. It also plays a role in spindle attachment and chromosome movement, meiotic pairing and sister chromatid cohesion.[3-7]

Methodology and Classification

Studies on human chromosomes had revealed that there was a great deals of polymorphism with certain pairs of complement in particular pairs of 1, 9, 16, and Y as well as D and G groups which are of interesting. Others also exhibit to certain level[4,7] Thus these chromosomes included are non-acrocentric (usually paracentric, acrocentric, and distal region of Y chromosome). The term heteromorphism is especially applicable to normal variants observed before Q, C, R and G banding techniques.[8] In 1960/ 1966, chromosomes were divided into A-G groups based on their relative sizes and position of the centromere. The X-chromosome fell in the C group, whereas Y was in G group due to lack of satellite and distinctive morphology. In 1963 prominent secondary constrictions were identified near centromere of chromosome 1 in group A, 9 (in group C) and 16 (in group E). By 1966, it was generally noticed that these regions and the variable length of Y including variations in short arms of the D/G chromosomes using Q, G and C-bandings became widely used.[9] The Q and C bandings are possible to localize regions variable in size and staining to specific chromosomes. These bandings revealed distinct classes of heteromorphisms. The most listing heteromorphism by the use of Q banding was observed in variations in length of long arm of Y, 3, 4, 13-15 and 21-22,[10-13] although G banding

technique became generally used for identification of chromosomes.[5,8]

As these are highly polymorphic, we call it as polymorphic heterochromatin sites. This phenomenon is familial and follow Mendelian inheritance with low mutation rate.[3] These polymorphic variants occur due to the following reasons; short arm with them and secondary constriction sites, satellite stalks satellite themselves short arm with genes and breakages are exchangeable of leading to Robertsonian and structural rearrangement in man. These chromosomal heteromorphisms also include various sizes of repeated DNA sequences in the genome like various sizes of heterochromatin blocks as cited earlier. These are commonly seen on non-acrocentric chromosomes on long arms (q) of 1, 9, 16, short arms (p) of acrocentric chromosomes and distal heterochromatin of Y chromosome. Thus increase/decrease in length of heterochromatin region of above chromosomes like 1qh+, 9qh+ and 9qh- and short arm of D and G groups such as 13Ppsk+, 13ps+, 14ps+, 21ps+,Yp+ etc. are notified.[7,14,15] This frequency occurs in more individuals[3] and cause reproductive anomalies, mental retardation and cancer.[16-18] Chromosomal heteromorphisms are also important in paternity testing, maternal cell contamination during amniocentesis, chorionic villus sampling (CVS) and in tracing the origin of the extra chromosomes in trisomies and other types. Heterochromatin hence mainly plays a role in genome function, which needs to be searched, though still the genes present in these DNA units are to be identified and their role in unclear gene functions pose a challenge in molecular biology.

Cancer

The possible role of constitutive heteromorphism in the development of neoplasia has been explored by many researchers, using G and C banding methods.[9,19,20,21,22] Many workers have found the correlation between constitutive heterochromatin heteromorphism in chromosome 1 and development of different types of neoplasms, such as ovarian cancer, carcinoma of cervix, breast cancer, malignancies of the head and neck, solid tumors, carcinoma of the colon and rectum, bladder carcinoma, chronic myeloid leukemia (CML), acute myeloid leukemia (AML) and multiple myeloma.[22-28] Contrast results were also noticed by Kivi and Mekelsaar[24] in regard to ovarian and testicular tumors. Some of the studies report also support association of malignancy with heteromorphism of chromosome 9 and 16.[22] Berger et al[17] noticed heteromorphism of constitutive heterochromatin with G band positive in human chromosome 1, 9, 16 in peripheral lymphocytes of 54 breast cancer cases. Heteromorphism of C bands on chromosome 1, 9 and 16 with different premalignant and malignant diseases were reported in the form of solid tumors and hematologic disorders in literature by Berger et al.[17] The parameters of heterochromatic regions analysed were of relative size, symmetry-asymmetry within homologous pairs and prevalence of inversions. These authors found differences between control and diseased cases with respect to C band size of chromosomes #1, #9 and #16 and incidence of inversions.[17] Suciu[29] in his study in patients with solid tumors (101) and along with controls (85) found that C bands of constitutive heterochromatin polymorphism associations were between #1 and #9 chromosomes and between chromosome #9 and D acrocentrics. It also concluded the involvement of constitutive heterochromatin of #1 in malignant disease in solid tumor patients. Chromosome analysis was carried out in G and C banding from PBLCs of 19 families with familial occurrence of cancer. Distinct heteromorphism in the chromosome 1qh+ (Fig.2A,B) was detected in 15 (79%) of them.[22] We also noticed heterochromatin polymorphism in #1 chromosome in hematologic neoplasia cases recently.[30] Earlier the frequency of heterochromatin polymorphisms in patients with malignant disease in blood cultures of 23 patients and with controls having free of cancer and same sex were also included. It concluded that no significant differences were noticed in both groups, except with #1 chromosome in breast cancer.[25] However other chromosomes 9 and 16 were also reported in varieties of cancer types,[17,22] where it is more prone to disease.[22] Atkin[19] studied first heteromorphism with C - banding positivity to ovarian carcinoma. Much work needs to be tackled on the role of heterochromatin in molecular oncology.

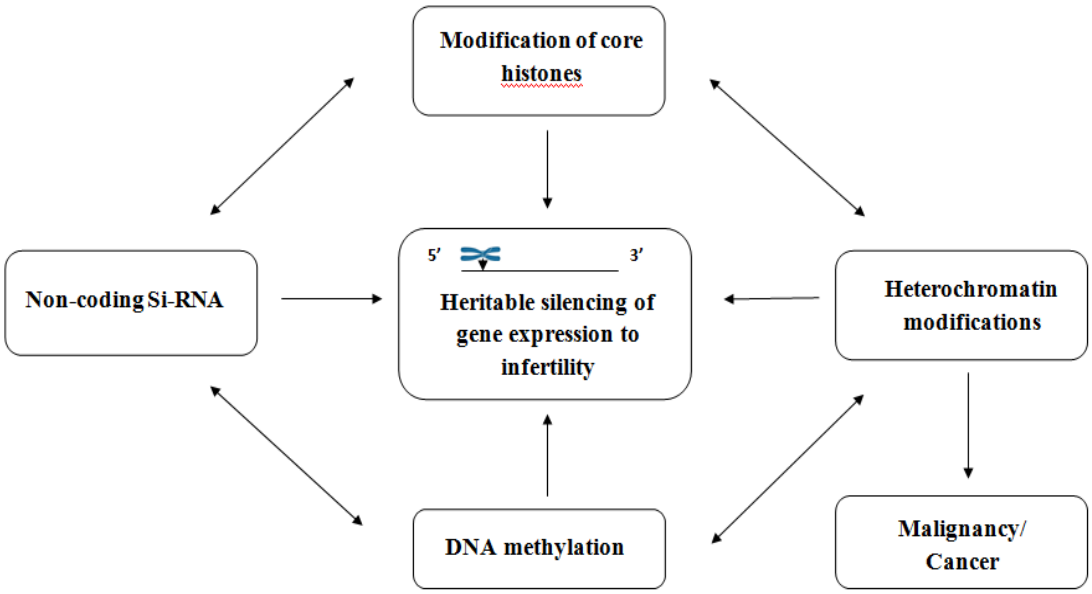
The role of constitutive heterochromatin is unclear at present in cancer, but a review of literature reveals that a trend in cytogenetic studies favoring an association between malignancies and heteromorphism distribution differences in cancer patient and controls. This poses a question regarding the transpositions of DNA sequences in repetitive DNA of heterochromatin. Another consequence is that heterochromatin plays a role in mitotic as well as in meiotic pairing and segregation. These conditions indicate that heterochromatin polymorphism might thus be related to aneuploidy or partial homozygosity reported[17] in malignant tissue samples [Fig.1, Table-1].

Table 1: Summary of chromosomal heteromorphism in cancer and reproduction

Chromosome no.	Heterochromatic region	Possible effects/ dysfunction	References (2000 onwards)
01	1qh+/1qh-, 1qh, inversion	Miscarriage/Azoospermia premalignant/malignant disease	[3][5][6][8][14][15][32][45]
03	Inv.3	BOH	[7][14]
05	Inv 5	Reproductive effects	[15][37]
06	Inv.6	Infertility in female, Miscarriage	[32]
07	Inv.7	Reproductive effects	[15][37]
09	9qh+, 9qh- and inv 9.	Cancer, Infertility	[2][4][5][6][7][8][14][15][34][36] [37][45][58][60][74]
11	11q ins.	No effects	[45]
13	ps+	Reproductive effects	[2][3][4][7][14][15][32][42][64][74]
14	ps+	RMC, Pregnancy loss, Other reproductive effects	[2][3][4][7][15][32][36][42][64][74]
15*	ps+	Pregnancy loss, BOH, Reproductive failure	[2][4][7][14][15][32][36][42][64][74]
16	qh+, qh-, inversion	Recurrent miscarriage, Infertility, Premalignant/malignant disease	[4][5][6][8][14][15][32][45][74]
17	Inversion	No reproductive effect	[33]
21	ps+	Reproductive effect	[7][32][42][74]
22	ps+	Pregnancy loss, BOH, Reproductive failure	[7][32][42][74]

Y	qh+, Yp+, inversion, Large (Y)	ART failure, Trisomy 21 risk, infertility, Abortion	[7][32][49][50][51][52][72][74]
X	Inactivation	Gene expression alteration	[1][2][3][4][7]

BOH : Bad obstetric history ; Chromosome variants of 2,4,8,10,12,18,19 and 20 are unavailable.



*Non-acrocentric and acrocentric chromosomes

Figure 1: Chromosome heteromorphism*, cancer and infertility association modified from berger et al [17] and minocherhomji et al [4] respectively.

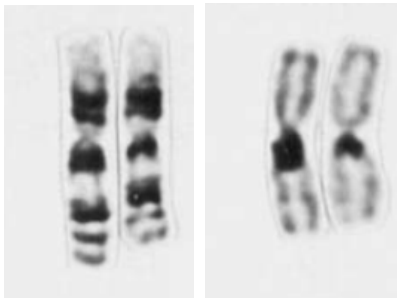


Figure. 2A, Figure. 2B

Figure 2: 1qh Heteromorphism in cancer with g-banding(a) and c-banding(b) [22]

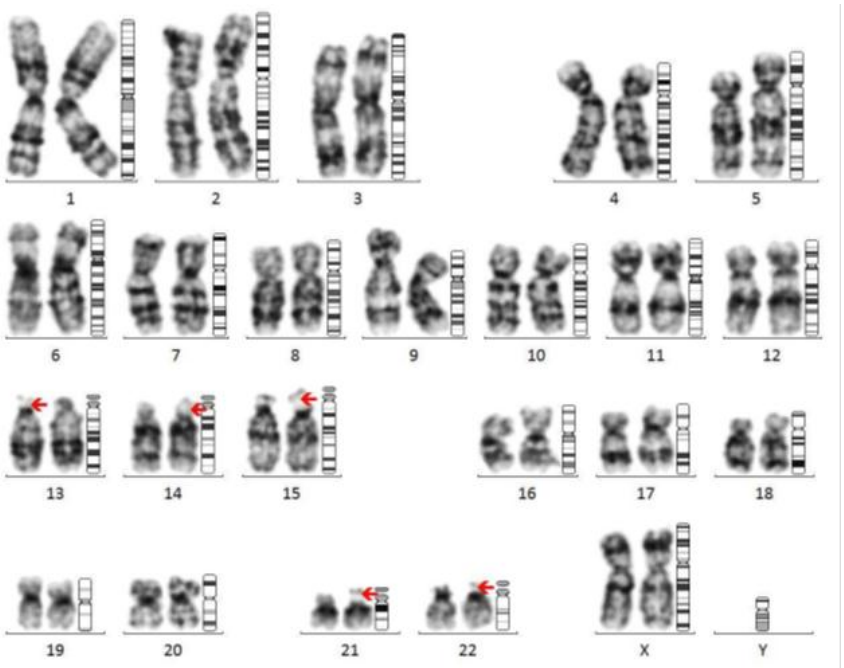


Figure 3: D and G group heteromorphism in a female with infertility- g banding [7].

Development and Reproduction

Using quantitative analysis of C - band heteromorphism of chromosomes 1, 9, 16 in 200 Delhi new borns showed no significance differences between sexes, but polymorphic variants occur in newborn also.[31] This report has the possible role of the heteromorphism in ethnical/racial ovarian and in developmental disturbances in human population with C - banding. Euchromatin heteromorphism is less whereas, more heteromorphic variants have been described.[6] Saran et al.[32] showed in their result that 1ph+ of chromosome 1 is related to recurrent miscarriages in addition to malignancy. Additionally, inversion/inverted segment of chromosome 1 might lead to synaptic failure during homologous chromosome pairing leading to male infertility.[15,32] Chromosomal polymorphism of 1, 7, 11, 17 autosomes with D and G groups were added in their studies too. Heteromorphism of 17 in a case was reported by insertion of q12 leading a novel chromosomal variant,[33] but no effect on fertility. Normal spermatogenesis occurs. The polymorphic 16qh+/- detected by Saran et al.[32] and Pokale[15] was correlated with infertility in females particularly T21 risk in pregnant woman during the analysis of infertile and amniocentesis cases, but number is restricted to few (3/230, 1/463) respectively.

Variants of chromosome 9 including inv(9) depicted maximum variations which included 9qh+/- and inv(9) in their studies of Saran et al.[32], Pokale[15], Vaghasia et al.[7], Mierla and Stoian[34], Purandare et al.[14], Dana and Stoian[35], Christofolini et al.[36] and Rao et al.[37] using GTG banding. Further, inv(9) is known to occur in 1-3% population but inv(9) (p12q13) was related to dysmorphic features and congenital anomalies. Purandare et al.[14] coined that inv(9) contributed 16% of total inversions (25%) comparatively. In BOH couples, its frequency was more. Hence, pericentric inv(9) is associated with recurrent miscarriages, infertility and congenital anomalies.[2,38-45] Inv(9) has been associated with chromosomal non-disjunction and has variable effects on spermatogenesis from azoospermia to severely altered sperm count, morphology, motility and meiosis segregation. During meiosis-I, a loop (tetrad formation/chiasmata) is formed in chromosomes with inversion and this can lead to production of abnormal gametes. Carriers of such inversions are at risk of abnormal karyotype in offsprings. Such inv(9) might lead to meiotic disturbances and it is known to be associated with T21 and mosaic T21.[2] Pericentric inv(3), inv(5), inv(6), inv(7) are also less in frequency and need to be studied with other molecular methods to understand disease association[15,37] along with chromosome 11.[6,33] Polymorphic variants of non acrocentric chromosomes 2, 4, 8, 10, 12,18, 19 and 20 are not yet available in the literature to review so far as our knowledge is concerned.

Large polymorphic variations in the length of centromeric heterochromatin on ‘q’ arms of chromosome 1, 9, 16 and Y were documented (1qh+, 9qh+, 16qh+, Yqh+, inv(Y), inv(16)) and these were less in frequency comparable to inv(9).[15] Yp+ and Yqh+ variants were reported, while reporting polymorphic variants of Y chromosome.[7,46] Purandare et al.[14] showed that inv(Y) was related to BOH leading to first trimester foetal loss in their respective studies. Similarly a highly statistically significant increase in frequency of Yqh+ was observed in men whose wives had BOH. Vaghasia et al.[7] reported inv(Y) and Yp+ were related to infertility. Previous studies have suggested indirect effects such as higher incidence of spontaneous abortions with striking chromosomal variants such as large Y. Though pericentric inversions in Y are considered to be as normal variant with no possible effect on fertility,[47,48] but a few cases have reported showing infertility.[49-52]

D/G groups of chromosomes include 13, 14, 15 (D group), 21 and 22 (G group) are the common heteromorphisms showing increased heterochromatin in the chromosome telomere, the short arm and the nuclear organisation region (NOR). Heterochromatin localized in centromere region has an essential role in spindle attachment and chromosome movement, meiotic pairing and sister chromatid cohesion. Chromatin in these regions causes defects in centromere function and kinetochore assembly, abnormal homologous chromosome pairing and impacts on cell division, affecting gamete formation.[2,3,4,53] These groups have higher amounts of heterochromatin in short arms and satellite regions (15ps+, 21ps+, 13psk+).[54,55] The stalks contain 18s and 28s rRNA and ribosomal proteins to form nude RNA (NOR).[56] Therefore polymorphism in this region suggests positive association with clinical anomalies as reported by numerous investigators[3,4,7,14,15,35-37,43,57,59] particularly in relation to infertility, BOH and other reproductive anomalies in assisted reproductive results like In-vitro fertilisation (IVF), Pre-implantation genetic diagnosis (PGD), Pre-implantation genetic screening (PGS).

Chromosomal analysis has been done in larger groups of infertile patients recently.[2,4,7,14,15,36,60-63] Most of these reports claimed that chromosome polymorphism is higher in infertile and other abnormal cases than in normal population.[2,64] Others had given little or no importance of heteromorphism in reproductive anomalies[46,53] as cited earlier. Comparatively, numerous researchers gave almost importance of it and correlated to loss of reproductive function in both sexes[7,14,15,32] and these variants are associated with abnormalities of human reproduction.[62,54] The most frequent types of heteromorphism in the infertile group was inv(9) and ‘D’ group variants followed by Yqh+/Yqh- and ‘G’ group variants.[7,15,32] Their study documented that D/G group variants of chromosomes are contributors to infertility in both male and females (Fig.3) as noted by Purandare et al.[7,14] Heterochromatin variations mostly of chromosome 1 and 9 inversions and qh+ are significantly higher in couples with BOH in their study. Pregnancy losses were also higher in couples with 22ps+ and 15ps+. Thus, the study has called for counseling of couples with BOH.[14] Hence, the overall prevalence of chromosomal polymorphisms in infertile couples and IVF cases further needs to be confirmed with new investigations and larger study population to delineate the role of harmless chromosomal variants in the etiology of infertility.[34,42,60]

Studies carried out by Hong et al.[53] and Dang et al.[46] in their studies from China and North East China claimed that heteromorphism of chromosomes of ‘D’ and ‘G’ groups including ‘Y’ and their multiples have no much impact on reproductive failure[53] and have no impact on outcome of IVF and also embryo transfer treatment. Therefore more number of samples and better sensitive techniques are needed in this study[46] in relation to infertility. So these heterochromatic regions have importance for clinical disorders like sterility, cancer and developmental problems in the field of clinical genetics in future.

Mechanisms

Heterochromatic region are considered to be present in 1.9.16,Y, D/G groups of chromosomes in common as identified by GTG banding. It contains junk repeats of DNA.[2] Recently, it also contains genes for regulation of cell function, chromosomal movements and infertility including cancer cited earlier[4,7,17,19,22] with DNA modification and other mechanism. In acrocentric

chromosomes, nuclear organization region (NOR) contains of rRNA while short arms have heterochromatin. Chromatin modification, including histone core protein changes non coding of small interfering RNA (SiRNA)- related to silencing of gene expression and reverse DNA methylation affect the gene expression which form part of epigenetic alteration (Fig.1).

Certain non acrocentric, heterochromatin regions are related to malignancy/ cancer aneuploidy leading to various types of cancers. The association of constructive heterochromatin and malignancies might reflect on heterochromatin distribution in patients and controls. It also plays a role in chromosomal segregation, pairing and cell division. This has a role in formation of aneuploidies in infertility[17,60,65] and would also be probable cause of cancer types (Fig.1). Certain regions of heterochromatin proteins are also associated with stress stimuli such as heat shock proteins (hsps), which may result in suppression of gene activity/ expression.[66] Pericentric heterochromatin induces silencing effect on euchromatic genes when brought together in a subset of cells in which these genes would otherwise be normally expressed.[2,4,55,67]

Further, junk DNA formed by infolding may affect gene coding. This was further referred by Macera et al.[68]. The non-coding DNA has a role in the suppression of genes based on biochemical and genetic analysis. It is possible that heterochromatin and euchromatin have inter- convertible nature. Hence, repressed DNA segments of heterochromatin and euchromatin (having expressed/ active segments) are expression of the degree of nuclear differentiation within individually differentiated cells.[69,70] Cellular processes involving depression of previously repressed gene include the activating/ expression of sperm genome in the embryo, viral oncogenesis and alteration of 'Y' genes during fetal development.[71] Similarly, X chromosome inactivation is one of the two XX chromosomes in female animals in response to certain cellular stimuli, which equalizes the expression of X-linked genes in female (XX) and male (XY) embryos.[71] The mechanism for association of chromosomal polymorphic variants with cell functional defects like infertility, malignancy remains to be answered. Data from cytogenetic studies on association of chromosomal variants and clinical conditions like infertility, cancer should not be ignored despite the earlier consensus pointed out that these polymorphic variants are unimportant.[7,72,74]

Conclusion

In conclusion, [Table-1] based on the data available on transcriptional activation of constitutive heterochromatin, the role of heat shock transcription factors nucleolar segregation and capping during transcription inhibition is known. The use of NOR in differentiating malignant and benign tumours and polymorphic chromosome variants and couples with reproductive dysfunction, it would be postulated that NOR and heterochromatin could play a role in certain clinical condition. It is further stressed that chromosome variants should not be ignored by cytogeneticists and clinicians, but should be evaluated for future use as all these variants may not be normal, still infertile couples with variants including aneuploidy and repeated failures may stand better chance with screened gametes. Further development of FISH probes which detect specific variants could enhance the selection of embryos by pre-implantation genetic screening (PGS) and pre implantation genetic diagnosis (PGD) and other clinical conditions in future. For new genetic tests and counseling, more governmental organizations (GO's) and nongovernmental organizations (NGO's) join together to monitor heterochromatic variants in field of assisted reproductive technology (ART) and cancer as well as their role for betterment of the society.[5,17,30,74,75-80]

Recommendations

Chromosomal heteromorphism detection is important in routine karyotypic analysis. Its anomalies cannot be ignored in present molecular technology. Hence, appropriate evaluation of polymorphic variants is necessary using FISH probes to assist the society in future for the affected cases, though few studies indicated ignorance earlier in regard to heterochromatin DNA blocks.

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