Original Article

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Genetics Section

Homozygosity and Heterozygosity of the Pericentric Inversion of Chromosome 9 and Its Clinical Impact

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ABSTRACT

Introduction: This paper presents a detailed study of inversion in chromosome 9 and its correlation with sub-fertility amongst 26 couples. Until now, there have been conflicting views on the clinical outcome of the pericentric inversion in chromosome 9. Many researchers consider this anomaly as a predisposing factor for infertility.

Methods: In the present study, the karyotyping analysis of 500 couples was carried out to investigate the genetic basis for infertility in these subjects.

Results and Conclusion: It was observed that a significant fraction (5.2%) of the total group had a pericentric inversion in chromosome 9 as the only known abnormality. The incidence of this abnormality in infertile patients was significantly higher than the reported value of 1%-3% in the normal population. Moreover, it was observed that the incidence of the inv (9) karyotype in the male patients was 2.5 times higher than that in females. These correlations clearly indicated that the inv (9) karyotype was not a normal karyotype but that it had a harmful effect on fertility.

Key Words: Homozygosity, Pericentric inversion, Chromosome 9, Heterochromatin, Infertility

INTRODUCTION

The most common form of inversion which is encountered in human chromosomes is a pericentric inversion of chromosome 9 (inv 9), that occurs in 1%-1.65% of the general population [1]. In the Asian population, the incidence of this anomaly is projected to be lower than that in other ethnic groups. Various studies have estimated it to be in the range of 0.25% [2].

In some of the previous reports, the clinical investigators had associated the pericentric inversion of chromosome 9 (inv 9) with various abnormalities which had included infertility, miscarriages, sub-fertility, birth defects, abnormal pregnancies like intrauterine growth retardation, etc [3-15]. On the other hand, there have been some reports which have denied the correlation between the minor polymorphic chromosomal variants and reproductive failure [16,17]. Apart from infertility related problems, inv (9) has also been associated with problems such as chromosomal aberrations [18-22] psychiatric disorders [23], ectodermal dysplasia [24] and azoospermia [25].

In our experience, we have observed a higher incidence of the inv 9 karyotype in patients with infertility related problems. Recently, we have come across two extremely rare cases of homozygosity for the pericentric inv (9). Both the patients had fertility related problems. These cases were instrumental in strengthening our belief that the pericentric inv (9) karyotype could not be categorized as a normal karyotype but that it had clinical implications. Therefore, in order to investigate the harmful effects of pericentric inv 9 on fertility, we analyzed the cases of 500 infertile couples that were referred for infertility in the recent 3 years (2009-2011) to the Dr. Lal Pathlabs, India.

MATERIALS AND METHODS

Subjects: Couples of Indian origin (n=500) with no known cause of infertility (idiopathic) were subjected to a karyotyping analysis. The mean age of the patients was 33 years and their age range was between 23-42 years. Also, 4500 normal subjects were analyzed cytogenetically as the control group. The data which was generated for the control group reflected the occurrence of inversion 9 in the general population. An informed consent was taken from all the subjects before blood was collected from all of them.

The karyotyping investigations were carried out on the cultures of the peripheral blood lymphocytes by using standard cytogenetics techniques. Short-term cultures of peripheral blood or were established and they were arrested in the metaphase stage. The metaphase spreads were analyzed by the standard GTG-banding technique [26].

The chromosomal abnormalities which were observed in the data set were reported in accordance with the ISCN guidelines (International System for Human Cytogenetic Nomenclature [27].

RESULTS

This study involved 500 infertile couples (1000 individuals). 2 cases were diagnosed with homozygosity and 24 cases were diagnosed with heterozygosity for pericentric inv (9) [Table/Fig-1]. Out of 25 couples who had infertility and inv (9) as the only cytogenetic anomaly, 18 male partners carried the inv (9) karyotype while the females were normal. Only in 7 couples, infertility was observed in the female partners with inv (9) karyotype. It was observed that the infertility could be expressed as primary or secondary infertility. However, 84% (21 out of 25) cases were of secondary infertility [Table/Fig-2].

DISCUSSION

Inv (9) regarded as a normal polymorphic form of chromosome 9. The breakpoints are preferentially located in the 9p12 or the 9q13-21.1 regions. Starke *et al.,* 2002 [28] studied the heterochromatin organization in the pericentromeric region and the proximal long

SN	Sex	Age	Karyotype	Type of infertility
Cases of homozygosity				
1	F	23	46, XX, inv (9)(p11q13)x 2	Fetus with diagnosed with Down's syndrome
2	M	39	46, XY, inv (9)(p11q13)x 2	Primary infertility
Cases of primary infertility with heterozygosity with inv (9)				
1	F	35	46,XX,inv(9)(p11q13)	Primary Infertility
2	M	26	46,XY,inv(9)(p11q13)	Primary infertility
3	M	32	46,XY,inv(9)(p11q13)	Primary infertility
Cases of secondary infertility with heterozygosity with inv (9)				
1	F	23	46,XX,inv(9)(p11q13)	Sec. Infertility
2	F	27	46,XX,inv(9)(p11q13)	Sec. Infertility
3	F	30	46,XX,inv(9)(p11q13)	Sec. Infertility
4	F	31	46,XX,inv(9)(p11q13)	Sec. Infertility
5	F	38	46,XX,inv(9)(p11q13)	Sec. Infertility
6	F	41	46,XX,inv(9)(p11q13)	Sec. Infertility
7	M	21	46,XY,inv(9)(p11q13)	Sec. Infertility
8	M	24	46,XY,inv(9)(p11q13)	Sec. Infertility
9	M	24	46,XY,inv(9)(p11q13)	Sec. Infertility
10	M	25	46,XY,inv(9)(p11q13)	Sec. Infertility
11	M	26	46,XY,inv(9)(p11q13)	Sec. Infertility
12	M	28	46,XY,inv(9)(p11q13)	Sec. Infertility
13	M	32	46,XY,inv(9)(p11q13)	Sec. Infertility
14	M	32	46,XY,inv(9)(p11q13)	Sec. Infertility
15	M	34	46,XY,inv(9)(p11q13)	Sec. Infertility
16	M	34	46,XY,inv(9)(p11q13)	Sec. Infertility
17	M	35	46,XY,inv(9)(p11q13)	Sec. Infertility
18	M	36	46,XY,inv(9)(p11q13)	Sec. Infertility
19	M	36	46,XY,inv(9)(p11q13)	Sec. Infertility
20	M	38	46,XY,inv(9)(p11q13)	Sec. Infertility
21	M	42	46,XY,inv(9)(p11q13)	Sec. Infertility

[Table/Fig-1]: Details of the patients that were diagnosed with inversion in chromosome 9.

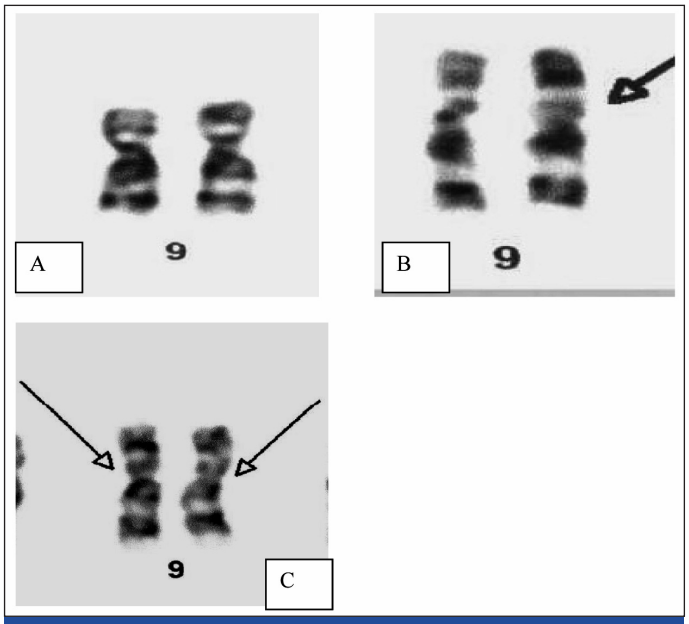
(q) and short (p) arms of human chromosome 9. They observed regions of sequence homology between the 9p12 and the 9q13-21.1 bands.

The Cases of Homozygosity for the Pericentric Inversion Chromosome 9

The homozygosity for inv (9) is extremely rare and therefore the reporting and the documentation of such cases is valuable.

Case 1: A couple was referred for the investigation of primary infertility. Here, the female was found to be normal, while the karyotype of the husband was found to be 46, XY, inv (9) (p11q13)x 2 (Table/Fig-2). The cytogenetic analysis of the parents of the patient could not be carried out due to the non-availability of samples.

Case 2: The patient was a 23 years old pregnant (28 weeks) female. The pregnancy had to be terminated due to the diagnosis of Down's syndrome in the foetus. The karyotyping for the aborted foetus confirmed the presence of trisomy 21. The patient's blood was sent for chromosomal analysis. The karyogram revealed a very rare case of homozygosity of the inversion in chromosome



[Table/Fig-2]: The karyogram showing (A) normal chromosome 9 (B) heterozygosity of INV (9) chromosome (C) homozygosity of INV (9) chromosome in the Case 1.

9. The karyotype was found as 46, XX, inv (9) (p11q13) x 2. In this case, no other abnormality was reported. The karyotype of the patient's husband was found to be normal. A higher incidence of a Down's syndrome offspring where one of the parents had inv (9) had been documented in the past [29].

The study of Case 1 and Case 2 gave strong evidences on the correlation of the abnormal phenotypes with homozygosity for the pericentric inversion of chromosome 9. This abnormality could be expressed as infertility or abnormality in the progeny.

Previous case reports involving homozygosity of the pericentric inversion of chromosome 9. Most of the cases had suffered from infertility. Khaleghian and Azimi (2006) [30] reported a case of a female patient with homozygosity of the pericentric inversion of chromosome 9. The patient was a 23-year female with a 28-week stillbirth (secondary infertility). Ceylan (2008) [31] discussed a case of a 27 year old male with primary infertility. Guven (2011) [32] reported a case of infertility which was caused by oligoasthenoteratozoospermia in a man with homozygosity of the pericentric inv (9). Cotter *et al.,* (1997) [33] studied the incidence of inv (9) in foetuses. He reported the incidence of homozygosity for inv (9) in two cases. One of the foetuses suffered from severe intra-uterine growth retardation (IUGR) and oligohydrominous, leading to foetal death and the other foetus was born as a normal term healthy baby. The baby had a normal life for the next five years. However, the study did not extend till its adult life to make any conclusion on its fertility.

Rarity of the homozygosity for inv (9) makes it difficult to analyze and compare the data. However, a higher prevalence of infertility in the subjects who had heterozygosity of inv (9) has been reported by many researchers. In the following section, we studied the impact of the heterozygosity for pericentric inversion 9 in the given study group.

The Effect of Heterozygosity for the Pericentric Inversion of Chromosome 9

Based on the study on the 4500 individuals of Indian origin, we have estimated the incidence of the pericentric inversion in chromosome 9 to be about 0.73% in the general population (unpublished data). In the present data set, out of the total 500 couples, 2 subjects were diagnosed with homozygosity for inv (9) and 24 subjects were diagnosed with heterozygosity for the pericentric inv (9).

In our study, 5.2% of the total cases who were examined for infertility had inv (9) as the only cytogenetic abnormality. It has to be noted that previous population studies which had involved the general population had estimated the prevalence of inv (9) to be 1%-3%, with the lowest incidence in the Asian population (around 0.25%). The other cytogenetic abnormalities together formed another 5.2% of the total, whereas in 89.6% of the patients, no detectable cytogenetic abnormality was found. The occurrence of inv (9) in patients with infertility was therefore significantly higher than the incidence of inv (9) as well as other cytogenetic abnormalities in the general population. This result clearly indicated the association of this anomaly with infertility.

In the above study, we considered the cases of 25 infertile couples, with one of the partner having inv (9) as the only cytogenetic anomaly [Table/Fig-1]. It was observed that in 18 couples, the male partners had carried the inv (9) karyotype while the female partner was normal. Whereas in 7 couples, the female partner had carried the inv (9) karyotype. Therefore, it can be said that the infertility was not specific to a particular sex. However, the ratio of the infertility in males and females was 2.57. It meant that men were 2.57 times more likely to suffer from infertility related problems due to the inv (9) karyotype as compared to the female subjects. In most of the previously reported cases, the incidence of infertility with the inv (9) karyotype in the male population was higher than that in the female patients. Similarly, Mozdarani *et al.* (2007) [13] had investigated the cases of 300 infertile couples. They had discovered a significantly higher incidence of inversion 9 in the male subjects and even in female subjects of a normal population and had concluded that the presence of inv (9) in the male population could lead to infertility due to spermatogenic disturbances. Uehara *et al.* (1992) [34] had carried out the chromosomal analyses of foetuses and infertile couples. The analysis of the infertile couples had revealed that the incidence of such an inversion in the males was significantly higher than the incidence in the normal population. The karyotyping of the foetuses revealed that the occurance of this inversion was higher in the foetuses of the parents with a history of clinically abnormal offsprings.

It was observed that infertility could be expressed as primary or secondary infertility. A significantly high percentage (84% i.e., 21 out of 25 cases) of the cases were of secondary infertility. This was in accordance with previous reports in which it was said that the carriers of balanced structural aberrations had an increased risk of having progenies with an unbalanced karyotype, resulting in spontaneous abortions in the 1st and second trimesters. Farcas *et al.* (2007) [35], studied the cases of 354 couples who had a history of recurrent miscarriages. They found out that inv (9) was the most frequent chromosomal anomaly which was observed amongst the study lot. Similarly, Turleau *et al.* 1979 [4] studied 413 couples with a history of spontaneous abortions. They observed a significantly higher prevalence of pericentric inversions in the patients.

Case reports which have described the association of pericentric inv (9) and infertility as well as other problems, have been documented in the literature. Ghasemi *et al.,* 2007 [36] reported two cases of inv (9) in one of partners from two sub fertile couples with no other abnormalities. Rossodivita *et al.,* 1997 [37] documented two cases with structural variations of chromosome 9 which were associated with hypogonadotrophic hypogonadism and azoospermia. Akbas *et al.,* [15] reported inv (9) in a 17 month old, mentally retarded, male child with a micropenis and other defects.

Inv (9) has been considered as a predisposing factor for nondisjunction and an interchromosomal effect [38]. Gardner and Sultherland (1996) [39], found out that the individuals who carried such inversions had an increased risk of having an unbalanced progeny, at a range of 1% to 10%. Similar observations were made by Ford and Lester (1978) [40], where they reported a high frequency of mitotic non-disjunction in the inv (9) cases.

The predominant cause of secondary infertility is said to be numerical aberrations in the foetuses and immunological factors [41]. Serra *et al.* 2005 [29] studied the prevalence of Down's syndrome in a parent with an inv (9) karyotype and observed that the presence of inv (9) in a parent increased by a factor of about 3 the incidence of extrachromosome 21 in the offspring. Kaiser [42], 1988 proposed that small inversions might lead to recombinants with a fatal deletion or an addition of a large fragment. Rao *et al.* (2006) [43] detected a high frequency of inv(9) (p12q13) in children with dysmorphic features and concluded that inv(9) definitely played a role in the abnormal phenotype development. They hypothesized that during an inversion event, there might be loss or suppression of the euchromatin chromosome region, leading to abnormalities.

Inv (9) has been considered to be a normal polymorph, as it mainly consists of centromeric heterochromatin with no known coding regions. Recent studies are now suggesting an important role of heterochromatin [44]. Hsu (1975) [45] proposed that heterochromatin plays the passive role of an immune bodyguard. The transcription potential of a gene can also be susceptible to heterochromatic silencing by position effect variegation [46]. Also, it has been proposed that the harmful effect of the inversion may be brought about by changes in the expression of the genes which are responsible for fertility and foetal growth. Using the advanced approaches of genomics and proteomics and applying the advanced gene expression techniques could help in finding out the causative mechanisms of infertility.

Garcia_Peiro *et al.,* 2011 [47] used flow cytometry and the SCD test to analyze the sperm DNA integrity in the case of a patient with infertility and the inv (9) karyotype. They discovered significant meiotic alterations, anomalous aneuploidy rates, high-sperm DNA fragmentation, and altered seminogram parameters in the patient.

Yashuhara *et al.* (2005) [48] studied the case of an ovarian cancer patient with the inv (9) karyotype. DNA sequence analysis and southern blot analysis showed multiple FGF7-like genes in the 9p11 region which were also duplicated to the 9q13 region on the aberrant chromosome 9. Surgical specimens of ovarian cancer with the reverse transcription-polymerase chain reaction and immunohistochemical staining showed overexpression of the FGF7 gene in the patient as well as other ovarian cancer patients. FGF 7 signalling plays a crucial role in the regulation and the maintenance of the male reproductive system (Cotton *et al.*

2008) [49]. This aspect needs to be investigated deeply to know the mechanism by which the fertility is affected.

Finally, based on this clinical study, it can be concluded that the pericentric inv (9) (p11q13) is not an uneventful rearrangement and that it leads to a relatively higher possibility of various clinical problems, such as reproductive failure and the occurrence of abnormalities in the offspring. It can be hypothesized that the susceptibility locus for infertility and other abnormalities may be located at the breakpoint of the inversion on chromosome 9, which may lead to the cloning of a susceptibility gene for the unspecified abnormalities. These findings have paved the way for further research at the molecular level, to find out the physiological effects of inv (9) which lead to infertility.

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