Research Article

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Association of Pericentric Inversion of Chromosome 9 with Periodontal Disease in an Indian family

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ABSTRACT

Background: Oral health may be indicative of systemic health and *vice versa*. Genetic make of an individual influence both the oral and systemic health as well as the phenotypic features of individuals. Therefore, obtaining genetic information of an individual enable a clinician to better understand the problem for clinical management and also guide them on an occasion of a hereditary pattern of clinical condition. A strong genetic correlation is seen to be associated to the inflammatory periodontal disease (PD) among patients and their family initiating researchers to search for information regarding the same. The present report describes a family with periodontal disease through three generations. A routine somatic karyotyping in peripheral blood had detected a pericentric inversion in one chromosome 9 i.e., inv (9) in members of the two generations, which was speculated to be associated with periodontal disease present in the family. However, the third member with PD didn't have the inversion, though the likelihood of genetic recombination with the inv (9) during meiotic cell division exists for gametogenesis. Inv (9) is associated with a number of clinical conditions; however, it is not considered as a marker of clinical expression. The present case with association of PD and inv (9), and hereditary condition of PD might attract molecular researchers for deciphering the genetic condition of hereditary and/or *de novo* PD, which might throw some light on genetic understanding of dental management clinically.

Keywords: Periodontal disease, pericentric inversion, chromosome 9, copy number variation.

INTRODUCTION

The study of human chromosomes plays an important role in the diagnosis of clinico-phenotypic expression of every individual. Genetic make of an individual is contributed by each parent in 1:1 ratio, meaning 50% of the genetic material is inherited from each parent. Numerical and/or structural alteration in chromosomes can significantly contribute to phenotypic and clinical variations, including craniofacial morphology and dentition[1]. Dental pattern is largely responsible for overall shaping up of the lower half of the face and defining the pattern of smile of an individual. Genetic alteration leads to altered expression at biochemical level in the form of proteins or enzymes. The combined effect of anomalous dental pattern and oral biochemistry favour plaque formation and periodontal inflammation owing to the deleterious effects of oral bio-flora [2,3].

Periodontitis is an inflammatory disease of periodontium that causes eventual loss of tooth if not treated at an appropriate time. Periodontal destruction is initiated by bacterial challenge that triggers a susceptible host immune response. The etiology of many common oral diseases including periodontitis appears to be multi-factorial involving environmental factors along with genetic alterations[4]. A unique finding of a related study showed that the genetic variances for probing depth and attachment loss could not be attributed to disease-related behaviours such as smoking and oral hygiene habits[4]. The heritable factor of

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dentition and subsequent development of periodontitis, therefore, reflects genetically determined variations in immunological host defences.

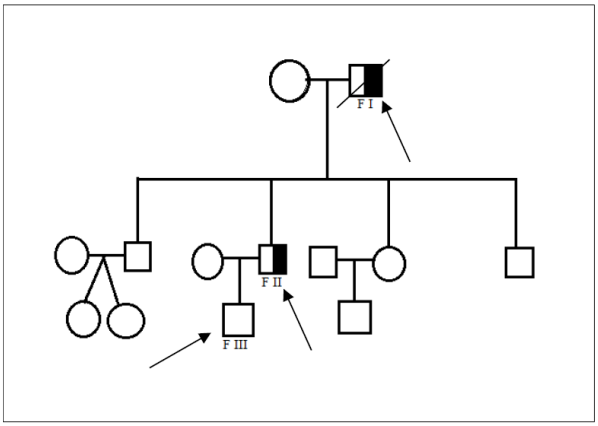
We present a report of a family having pericentric inversion in one chromosome 9 i.e. inv(9) associated with anomalous dental pattern and mild cranio-facial dysmorphism in two generations. However, the third-generation progeny, though having similar dental phenotype, does not possess the chromosomal rearrangement. This has raised a concern of genotype-phenotype association of inv(9) and chronic periodontitis with malocclusion and presence of supernumerary teeth causing poor oral hygiene and halitosis in the family. The pericentric inversion is one kind of intra-chromosomal balanced rearrangement and often considered as a normal variant in the general population. The carriers of balanced chromosomal alteration do not generally present significant clinical or phenotypic manifestation since balanced rearrangements do not apparently cause loss of nucleotides or genetic material. Such cases remain undetected life-long or detected at the adult age having reproductive as a common manifestation failure[5]. Several reports have documented association of this inversion with infertility, sub-fertility, recurrent miscarriages, birth defects, hydatidiform moles, congenital anomalies, growth retardation, and infrequently abnormal phenotype [6,7,8,9]. Approximately, 2.3% of all infertility is caused by inv(9), and that is prevalent in females. The incidence of inv(9)(p11q13), is reported to be about 1% to 1.65% in the general population[10].

Apart from the above, inv (9) has also been associated with psychiatric disorders[11], ectodermal dysplasia[12] and azoospermia[13]. The present family has the history of abnormal dentation resulting in periodontitis and mild impact on facial expression.

CASE REPORT

The present report describes about periodontitis in three members of the three generations (Fig. 1), of which FI and FII members had inv(9) in their genomic karyotype.

The proband, (FII), a 58 year old man, had reported with the chief complain of foul odour from oral cavity and dryness of mouth. Previously advocated twice daily brushing followed by chlorhexidine rinse was being done.



Heterozygous carrier of inv(9); Normal karyotype.

Karyotyping was not performed for members without arrow

Fig 1: Pedigree of the reported family.

On oral examination, there were significant local contributing factors like plaque and calculus (Fig.2). The patient also showed grade I mobility with respect to 31, 32, 41 and 42. There was presence of generalized probing pocket depth of 5 to 7 mm. The patient showed presence of mesiodens which was lost following first oral prophylaxis work up. On radiographic examination, generalized horizontal bone loss was observed (Fig.2). The patient had no systemic history and did not report presence of any deleterious habit. The proband had to undergo frequent scaling and polishing to combat halitosis and improve oral hygiene.

Phase I therapy was carried out for the member of the FI generation and he was recalled after 6 – 8 weeks for follow up evaluation and assessment. However, grade I mobility was persistent with respect to 31, 32, 41 and 42 in conjunction with generalized probing pocket depths of 5 to 7mm. Also, the patient had complaint of halitosis. The patient reported that his father (FI) also had mal-positioned teeth and one extra supernumerary tooth, and he too had experienced halitosis on several occasions. The FI member was otherwise systemically healthy with proper oral hygiene habits.

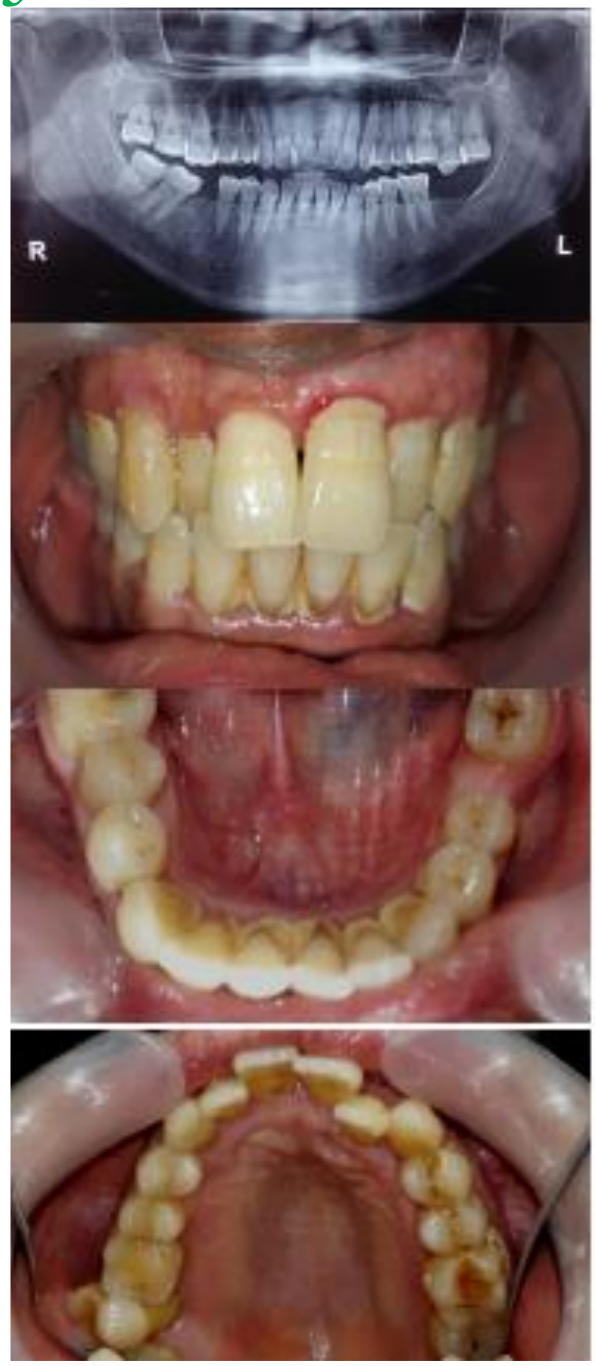


Fig. 2. Dental pattern and calculi: a. Orthopantamogram show loss of horizontal bone, and missing of 37 and 46; b. Frontal view of teeth showing crowding, plaque and calculus within one month of scaling and polishing, gingival inflammation; c. calculus around the lower anterior teeth and recession; d. malalignment in the maxillary arch.

Phenotypically, the facial appearance was similar in FI and FII generations with elongated face and tapered chin since childhood. However, the third-generation progeny (FIII) (25 year old male), though had a round facial structure, developed similar elongated facial characteristics at the adolescent age. Also, the FIII reported similar problems of mal-positioned teeth and halitosis despite following oral hygiene protocols on regular basis. On examination, similar plaque and calculus were observed. The FIII member also developed two supernumerary teeth (Fig. 3).

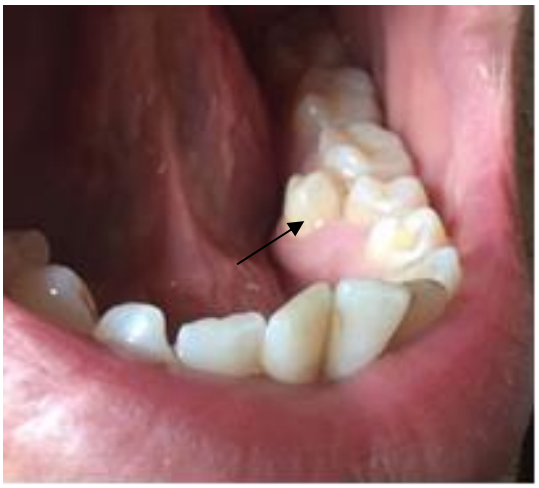


Fig 3: Supernumerary teeth in the F III member.

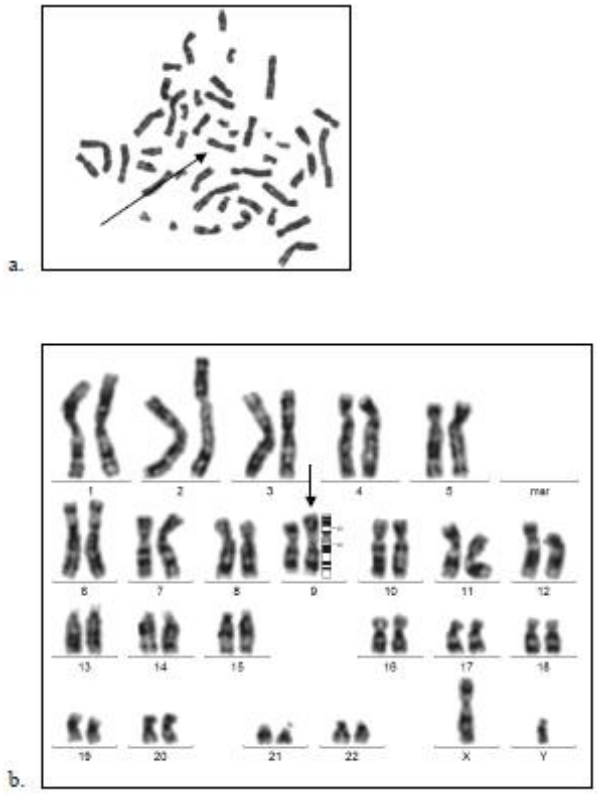


Fig 4: Karyotype showing the pericentric inversion in chromosome 9 (arrowed): a. metaphase; b. karyogram.

The hereditary pattern of periodontal problems, halitosis and presence of supernumerary teeth in all the three generations propelled for a genetic testing, which consisted of cytogenetic analysis in peripheral blood for all three members. Peripheral whole blood culture was processed in RPMI 1640 medium supplemented with fetal bovine serum and phytohaemagglutinin (all from GIBCO, USA) for 72h at 37°C for genomic karyotyping of all three members of the three generations[14]. Metaphase chromosome preparation was performed using standard colchicine-hypotonic-fixation technique. Conventional cytogenetic analysis was carried out on G-banded chromosomes following International System for Human Cytogenetic Nomenclature (ISCN 2016). Imaging of 30 metaphases with the help of IKAROS software (MetaSystems, Germany) revealed male karyotype with 46,XY,inv(9)(p11q13) pattern in all 30 cells evaluated for the FI and FII members (Fig.4a). A pericentric inversion in one chromosome 9 was present as a constitutional abnormality. However, the FIII member had apparently normal male karyotype with 46,XY pattern (Fig. 4b).

DISCUSSION

It has been established based on clinical and scientific reports that genetic factors are important determinants of periodontitis susceptibility and disease progression. The studies carried out on animals and humans indicate that genetic factors influence inflammatory and immune responses in general, and periodontitis experience specifically[15]. The periodontal diseases are initiated by microbial plaque, which accumulates in the cervical region of teeth and induces an inflammatory response. Periodontal therapy which aims in reducing the tissue inflammation caused by bacterial plaque, preventing further loss of attachment also aims in regenerating the anatomical bone structures around teeth by physiologic method[16].

Pericentric inversion requires two chromosome breaks on 'p' and 'q' arms of a chromosome respectively and rejoining of the interstitial broken segments in inverted position, which results in the alteration in morphology of the chromosome owing to involvement of the centromere[17]. Such intra-chromosomal rearrangement leads to changes in the sequence of nucleotides and genes on the two re-joining sites of the two arms. Although loss of chromosomal segments on the two arms has not been recognized in the present study, loss of nucleotides could be apparent due to breaks, and that might lead to copy number variation (CNV) in the inverted chromosome.

Human chromosomal patterns show extensive polymorphism with respect to CNVs[18]. CNVs contribute to variation between individuals, underlying human evolution and diseases including cancer. Meiotic recombination during crossing over between the homologous chromosomes may also contribute to CNV resulting in polymorphism[18]. Recent concepts hypothesize perturbation of DNA replication and replication of non-contiguous DNA segments, including repair of the broken replication forks, switches under stress from high-fidelity homologous recombinational to non-homologous repair that produces CNVs[18]. Similar mechanism might have worked for the FIII member of the present report, who didn't have the inverted 9 but had similar dentition which was observed in the two previous generations. One of the normal 9 was paternally inherited by FIII member, which might contain recombination of genes from the inv(9) due to crossing over during gametogenesis[19]. Pericentric inversion of chromosome 9 is frequently reported to cause infertility[20], which was not evidenced in the present family. However, inv(9) has contributed in dental pattern in three consecutive generations in the present report.

While microbial and ecological factors are believed to instigate and modulate periodontal disease progression, there now exists strong supporting evidence that genes play a role in the predisposition to and progression of periodontal diseases[21,22].

The present report has described association of inv(9) with dentition and periodontitis in two generations. The recombination in second and apparently normal 9 might have caused similar dental problem in the FIII generation. Therefore, the genes present in the broken segments on the two arms or the rearranged segments following rejoining could be underlying factor for the present dental pattern, which established a favoured environment for the microorganisms. However, further studies are required for deciphering the genetic rearrangement post-rejoining and its association with cranio-facial and dental deformities.

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CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

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