

Association Between Pericentric Inversion in Chromosome 9 and Congenital Heart Defects

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ABSTRACT Congenital heart disease (CHD) is the leading cause of mortality in the first year of life. Prevalence of CHD worldwide is found to range from 1.0 to 50.89 per 1000 livebirths including India. The association of these defects with chromosomal anomalies varies between 4 to 12%. In the present investigation, we report two different cases of pericentric inversion of chromosome 9 [inv(9)(p11-q13)], associated with Total Anomalous Pulmonary Venous Connection (TAPVC) and Tetralogy of Fallot (TOF). In one of the cases (TOF), the mother had similar inversion without CHD. We predict here that, the genes responsible for the normal heart development could be present on chromosome 9 around p11-q13 region, which might have been defective during the process of inversion and thereby resulted in CHD. To our knowledge, this is the maiden report of association of inversion with CHD from South India.

INTRODUCTION

Congenital heart disease (CHD) is the malformations of the heart or the large blood vessels associated with the heart, affecting various parts or function. It is one of the leading causes of death in the first year of life (Srivastava 2001). Prevalence of CHD worldwide is found to range from 1.0 to 50.89 per 1000 livebirths including India (Smitha et al. 2006). These are grouped as multifactorial defects, however about 4 to 12% of the CHDs are found to be associated with various chromosomal anomalies (Smitha and Ramachandra 2005).

Cytogenetic aberrations on chromosome 9 (aneuploidy, deletions, translocations, inversions) have been reported to be one of the most frequent abnormalities. The range of phenotypic consequences found to be associated with these abnormalities are mild growth retardation, malformations of the skull and facial (craniofacial) region, abnormalities of the hands and fingers, skeletal malformations, and/or cardiac defects

(Boby et al. 1994; Mokhtar 1997; McAuliffe et al. 2005).

Among these anomalies pericentric inversion of chromosome 9 is one of the most common balanced structural chromosomal aberrations found in 1 to 3% of the general population (Nielson and Silesen 1975; Ko et al. 1992; Teo et al. 1995; Humphray et al. 2004). However, there are several conflicting reports on the association of this inversions with subfertility, sterility, recurrent miscarriage, schizophrenia, congenital myotonic dystrophy, cerebral cyst, dysmorphic signs, mental retardation, psychiatric disorders and other abnormal clinical conditions (Krishna et al. 1992; Scarinci et al. 1992; Teo et al. 1995; Gardner and Sultherland 1996; Kunugi et al. 1999; Davalos et al. 2000; Parmar and Sira 2003; Srebniak et al. 2004). This particular pericentric inversion has also been implicated as a possible predisposing factor for nondisjunction and interchromosomal effect (Krishna et al. 1992). Individuals carrying such inversions have an increased risk of unbalanced progeny ranging from 1 to 10% (Gardner and Sultherland 1996).

In the present investigation, we report two cases of pericentric inversion of chromosome 9 in heterozygous condition with CHDs of which, one is a familial case.

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MATERIALS AND METHODS

Case Report

Case 1: The male proband was the first-born child of nonconsanguineous parents, spontaneously delivered after an uneventful pregnancy with a birth weight of 2.5 kilograms. Clinical investigations revealed the presence of CHDs with no other clinical abnormalities. Echocardiographic examination of the proband confirmed the presence of total anomalous pulmonary venous connection as the defect (TAPVC). For further investigations, the proband was referred for cytogenetic investigation.

Case 2: The male proband was the second twin child born to nonconsanguineous parents (Fig. 1), delivered by caesarean operation after an uneventful pregnancy with a birth weight of 2 kilograms. Clinical investigations of the proband revealed the presence of CHD. Echocardiographic studies confirmed the CHD as tetralogy

of fallot (TOF). The proband was further referred for echocardiographic examination and cytogenetic analysis.

Cytogenetic Studies

With the consent of the family members, chromosomal analysis for both the probands and parents of case two was carried out on peripheral blood lymphocyte culture using standard protocol of Seabright (1971), with little modifications. Giemsa banded metaphases were screened using Leica DMRA2 research microscope. A total of 50 well-banded metaphase plates were analyzed and karyotyped according to the International System for Human Cytogenetic Nomenclature (ISCN 1995).

RESULTS

Case 1: Pedigree analysis revealed that there was no history of birth defects or genetic defects

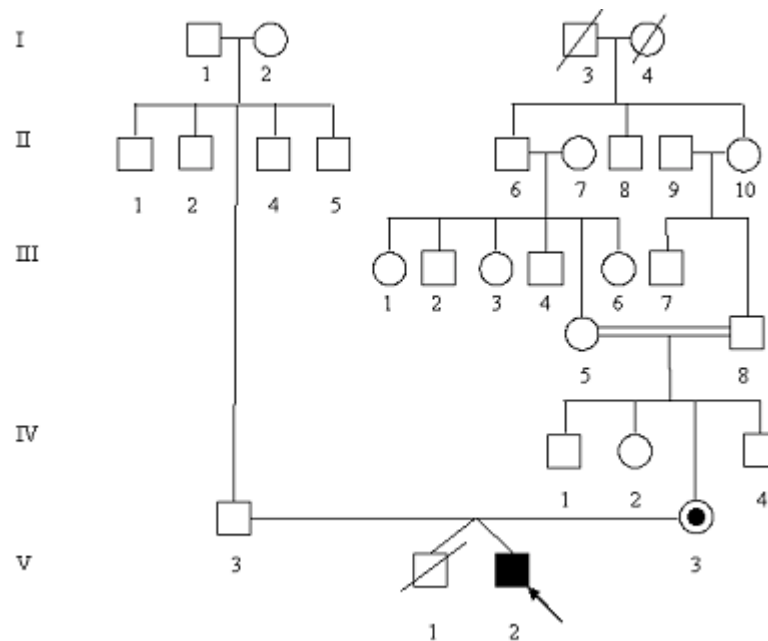


Fig. 1. Pedigree of the family of case two with $inv(9)(p11-q13)$ in the proband and the mother

The symbols which are square indicate males and circle indicate females; the arrow directed to the shaded symbol represents the proband, the shaded dot in the circle denotes the inversion carrier mother. The Roman number in the left side of the figure indicates the number of generations. The Arabic number below the symbol denotes the number of individuals in that generation. The double line between the maternal grandparents of the proband indicates the consanguineous marriage (first cousin marriage). The crossed line on the symbols indicates the individual as deceased.

in the family. Conventional cytogenetics (G-banding) revealed 46,XY,inv(9)(p11-q13) in all the 50 metaphase plates screened (Fig. 2). Chromosomal investigations could not be carried out on the parents as they declined to take part in the investigation.

Case 2: Pedigree analysis revealed that there was no history of birth defects or genetic defects in the family. However, clinically the first twin who had not shown any symptoms of CHD, died after few days of birth due to continuous refusal of feed. It was also seen that maternal grand-parents were related (first cousin consanguineous marriage). Conventional cytogenetics on the probands chromosomes revealed 46,XY,inv(9)(p11-q13) in all the 50 metaphase plates screened (Fig. 3). Cytogenetic investigation in the mother also revealed 46,XX,inv(9)(p11-q13) (Fig. 4), whereas the father revealed normal karyotype. Echocardiographic examinations in the parents did not reveal any CHD or any other abnormalities.

DISCUSSION

Congenital heart anomalies constitute a major malformation leading to significant morbidity and mortality eventually affecting the clinical outcome of the affected individuals. There are several reports of CHDs associated with chromosomal variations like trisomies, deletions, duplications and translocations (see, Smitha and Ramachandra 2005). However, there are no reports of association of pericentric inversion of chromosome 9 [inv(9)(p11-q13)] with CHDs. This pericentric inversion is believed to be a frequent occurrence in the general population and inherited in a Mendelian fashion or might appear for the first time in a child without any apparent phenotypic consequences (Nielson and Silesen 1975; Ko et al. 1992; Luke et al. 1992; Teo et al. 1995; Humphray et al. 2004). Interestingly, in the present findings, we found the association of same inversion with two different CHDs (1.70%) of the total 117 CHD cases studied. In the first case study, the proband was diagnosed clinically with TAPVC and cytogenetically with the inv(9)(p11-q13). In the second case study, proband was diagnosed clinically with TOF and cytogenetically with the inv(9)(p11-q13). When parents were screened clinically by echocardiographic examination none of them had CHD, but cytogenetic investigation revealed the inv(9)(p11-q13) only in mother.

One of the possible explanations for the presence of CHD in the second case with this inversion could be that the mother might have this pericentric inversion due to *de novo* event, which the proband inherited. However, during the process of inheritance of the inversion some gene/s, which is required for the normal development of the heart, might have undergone mutation resulting in CHD in the proband. To support this hypothesis, there are several studies, which state that the individuals carrying, such inversions have an increased risk of unbalanced progenies (Gardner and Sultherland 1996) and this inversion is a possible predisposing factor for nondisjunction and interchromosomal effect (Krishna et al. 1992).

We predict here that this pericentric inversion of chromosome 9 and associated mutations have resulted in the occurrence of CHDs in both the probands. In support of this, there are reports about abnormalities of chromosome 9 associated with several cardiac anomalies which includes truncus arteriosus, truncal valve stenosis, single carotid trunk, subclavian arteries arising from the distal part of the aortic arch, atrial and ventricular septal defects, atrioventricular septal defect, pulmonary arteria, right ventricular hypertrophy and hypoplastic left pulmonary artery (Roberts et al. 1993; Nekarda et al. 1997; Sepulveda et al. 2003). In particular, the chromosome 9p is found to be associated with series of CHDs, like ventricular septal defect with pulmonary valve stenosis and a marked hypoplasia of the pulmonary trunk (Schimmenti et al. 1995; Leichtman et al. 1996; Nakagawa et al. 1999).

Although, development of the heart involves cascade of events involving several genes on different chromosomes, which includes Nkx2-5, Gata4, Tbx5, etc. (Srivastava 2001), studies on molecular level to unravel the gene/s on chromosome 9 which might contribute to the development of the heart, have limited success. Apart from the studies by Scott et al. (1998) who mapped the ZNF216 gene within a 1.5-Mb DFNb7/11 interval in 9q13-q21 region, which was found to express highly in brain, muscle, eye, and heart in mouse studies and the present study, no other studies have reported the contribution of chromosome 9 in the heart development. However, these reports indicate that there are genes in this particular region whose contribution to the normal development of the heart is vital and any structural abnormality in the chromosome 9 will lead to CHD.

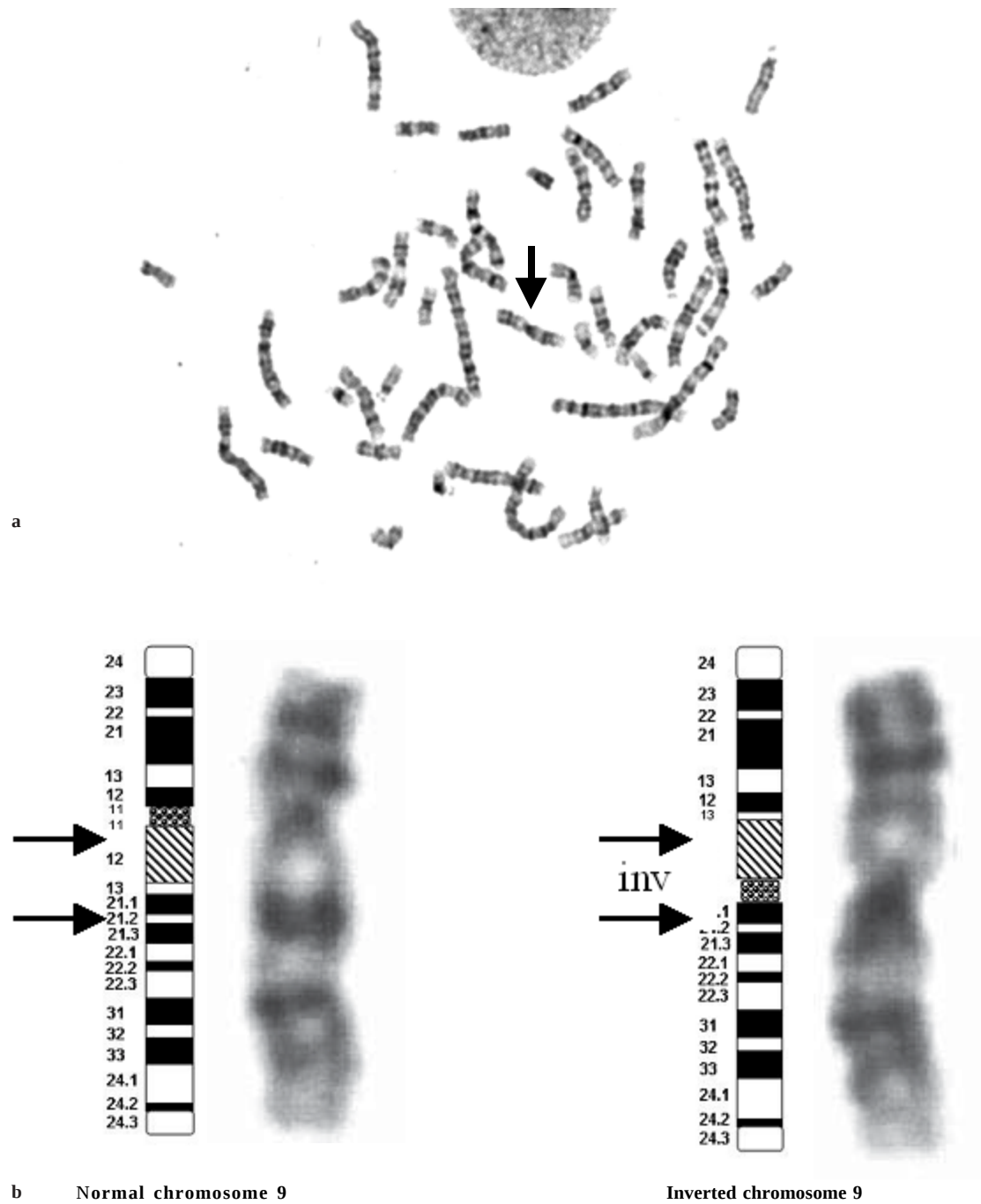


Fig. 2. G banded Chromosomes of the case one proband with inv(9)(p11-q13)
 (a) G banded metaphase plate showing inv(9)(p11-q13) (arrow), (b) enlarged view of chromosome 9 without and with inversion along with the respective ideogram.

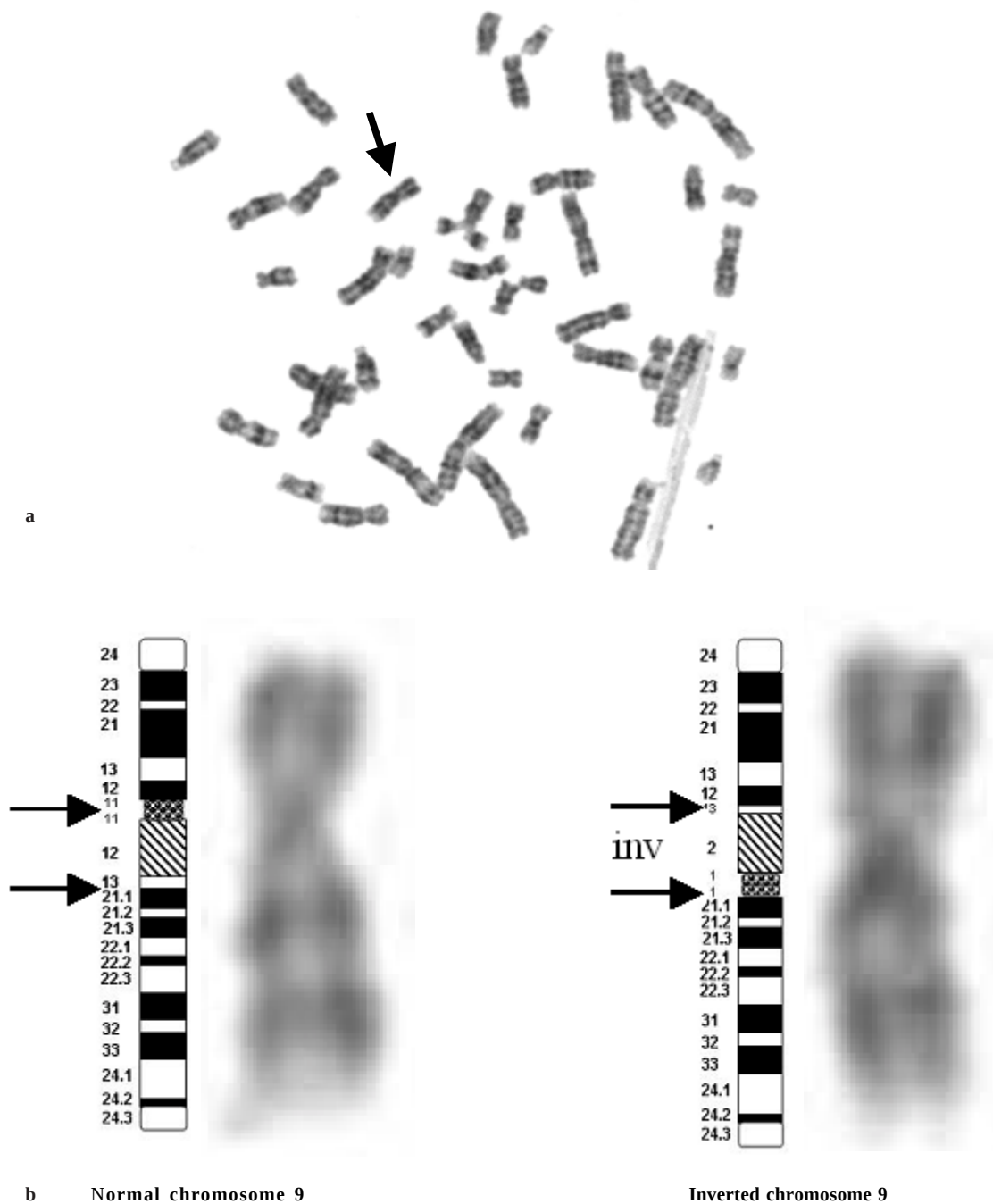


Fig. 3. Chromosomes of the case 2 proband with inv(9)(p11-q13)
 (a) G banded metaphase plate showing inv(9)(p11-q13) (arrow), (b) enlarged view of chromosome 9 without and with inversion along with the respective ideogram.

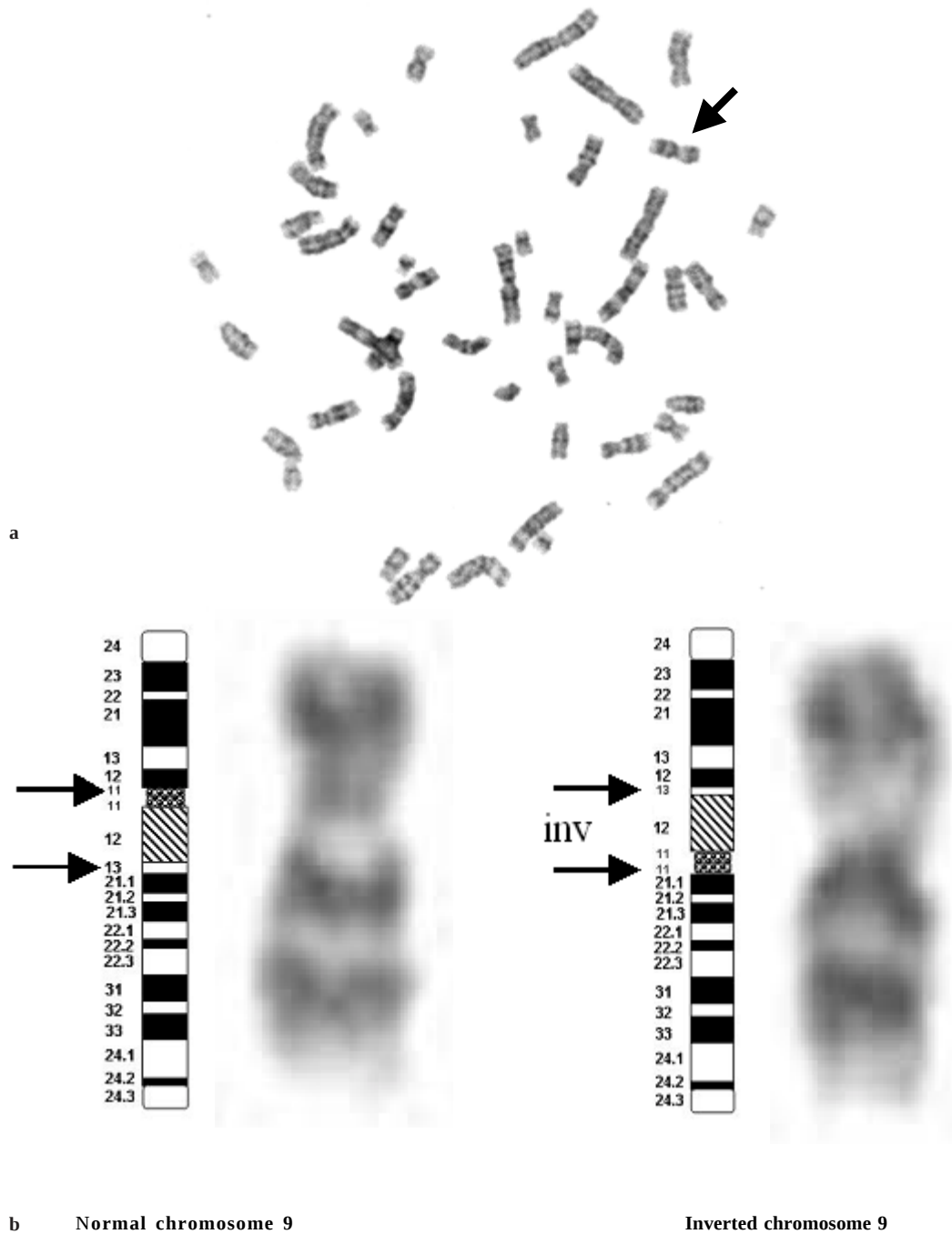


Fig. 4. Chromosomes of the mother of case 2 with inv(9)(p11-q13)
 (a) G banded metaphase plate showing inv(9)(p11-q13) (arrow), (b) enlarged view of chromosome 9 without and with inversion along with the respective ideogram.

There are several reports of the association of this inversion with several abnormal clinical conditions like schizophrenia, congenital myotonic dystrophy, cerebral cyst, dysmorphic signs, mental retardation, psychiatric disorders and other abnormal clinical conditions (Krishna et al. 1992; Scarinci et al. 1992; Teo et al. 1995; Gardner and Sultherland 1996; Kunugi et al. 1999; Davalos et al. 2000; Parmar and Sira 2003). and the adult carriers are subfertile and suffer recurrent miscarriages (Srebnik et al. 2004). In contrast to this, in our investigations apart from CHDs in both the probands there were no other clinical abnormalities. In the second case study, the mother did not suffer any miscarriage or any other abnormalities although she had this particular inversion.

Reports are also available concerning carriers of pericentric inversion of chromosome 9 showing different clinical anomalies (Scarinci et al. 1992). However, there are no reports of such inversion associated with CHD. To our knowledge, this is the maiden report of association of inversion with CHDs from South India. We predict here, that the genes responsible for the normal heart development could be present on chromosome 9 around p11-q13 region, which might have been defective during the process of inversion and thereby resulted in CHD.

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