

## Two Familial Cases of Robertsonian Translocations 13; 14 and Its Clinical Consequences

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### Abstract

Two familial cases of Robertsonian translocation 13;14 [rob t(13;14)] and its clinical manifestation in children are discussed in present report. In case-1, father and child both were having [rob t(13;14)] with karyotype [45,XY,rob(13;14)(q10;q10)] and [46,XY,rob(13;14)(q10;q10),+21] respectively. The child was presented with clinical characteristics of Down syndrome (DS) due to trisomy 21. The child and father both were having soft sub-mucous cleft palate. In case-2, child and mother both were having rob t(13;14) with karyotype [45,XX,rob(13;14)(q10;q10)]. Mother was phenotypically normal but both of her children were presented with gross developmental delay for all the four areas, i.e., gross motor, adaptive, language and personal social behavior. Interestingly all the carriers of [rob t(13;14)] showed abnormal clinical features: like soft sub-mucous cleft palate with DS in case-1 child, soft sub-mucous cleft palate and Inter Chromosomal Effect (ICE) in case-1 father, miscarriage and birth of children with congenital problem in case-2 mother and gross developmental delay in case-2 child. It was assumed that the co-occurrence of [rob t(13;14)] and trisomy 21 in case-1 child was due to phenomenon of ICE in father carrying [45,XY,rob(13;14)(q10;q10)].

**Keywords:** Robertsonian translocation; Familial case of robertsonian translocation; Robertsonian translocation with down syndrome; Congenital anomalies; Submucous cleft palate

### Introduction

Robertsonian translocation is due to distinct constellation of the five acrocentric chromosomes (13, 14, 15, 21 and 22) among them [rob t(13;14)] attributed to 75% of the cases. Its incidence in population has been reported to be 1.23 in 1000 live births [1]. Phenotypically, carriers of [rob t(13;14)] are normal but they are at higher risk for producing unbalanced gametes resulting in to monosomic or trisomic fetuses [2]. They are often met with fertility problems, unfavorable pregnancy outcome like miscarriages, stillbirths, offspring with mental retardation, uniparental disomy (UPD) or UPD-related imprinting disorders [3-6]. Aneuploidy in offspring of [rob t(13;14)] carriers is because of Inter Chromosomal Effect (ICE) in which during gametes formation at meiosis I, a trivalent structure is formed by pairing of translocated chromosome and two corresponding normal chromosomes. The trivalent structure undergoes three modes of segregation: Alternate mode producing normal balanced gametes, adjacent and a rare 3:0 patterns of segregation both generating unbalanced type of gametes [7]. To the best of our knowledge, this is the first case of coincidence of [46,XY,rob(13;14)(q10;q10),+21] with soft sub-mucous cleft palate.

In present paper with two familial cases of [rob t(13;14)], heterogeneity in clinical outcome of [rob t(13;14)] carriers and the phenomenon of ICE observed in the cases are discussed.

### Materials and Method

The cases were referred from Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi. Detailed clinical history of both cases was recorded. Parents in both cases had given their written consent for the study. For whole blood culture, about 2 ml peripheral blood was drawn in a heparinized sterile syringe. Whole blood cultures were performed in RPMI-1640 pH 7.2 (Sigma-Aldrich, Inc., St. Louis, MI, USA) culture media supplemented with 10% fetal bovine serum (Himedia), India and stimulated by phytohaemagglutinin-M (Sigma-Aldrich, Inc., St. Louis, MI, USA). Cultures were incubated at 37°C for 72 hours. Cultures were treated with colchicine (Sigma-

Aldrich, Inc., St. Louis, MI, USA) at 70 hours at a concentration of 0.02 µg/ml of culture to arrest the cells at metaphase. Harvesting of cultures was performed following 12 minutes treatment with hypotonic (44.9 mg/mL Potassium Chloride and 4.0 mg/mL Sodium Citrate). Cells were fixed with fixative (Methanol and Acetic Acid in 3:1 ratio) and further processed to clear cell suspension. Slides were prepared by dropping the suspension from height and flame dried. G-banding was performed by Saline-Trypsin-Geimsa method. 30-50 metaphases were captured with the help of microscope and karyotyping was done with 450 G-banding resolution using Ikaros karyotyping system-Metasytems software (Carl Zeiss Microscopy GmbH, Göttingen, Germany). Chromosomes were analysed following guidelines provided by the International System for Human Cytogenetic Nomenclature (ISCN 2013) [8].

### Results

#### Case presentation

**Case-1:** Paternal transmission of [rob t(13;14)] in a child with Down syndrome and soft sub-mucous cleft palate.

A 02 years-old male child was presented with typical clinical characteristics of DS like dismorphic face including short neck, up slanting of palpebral fissure, strabismus, wide open mouth, protruding tongue and serrated mouth corners. The child was having developmental problem which included inability to speak, delayed sitting, delayed walking and muscular hypotonia. The child and the father both had soft sub-mucous cleft palate. Age of father and mother at the time of child

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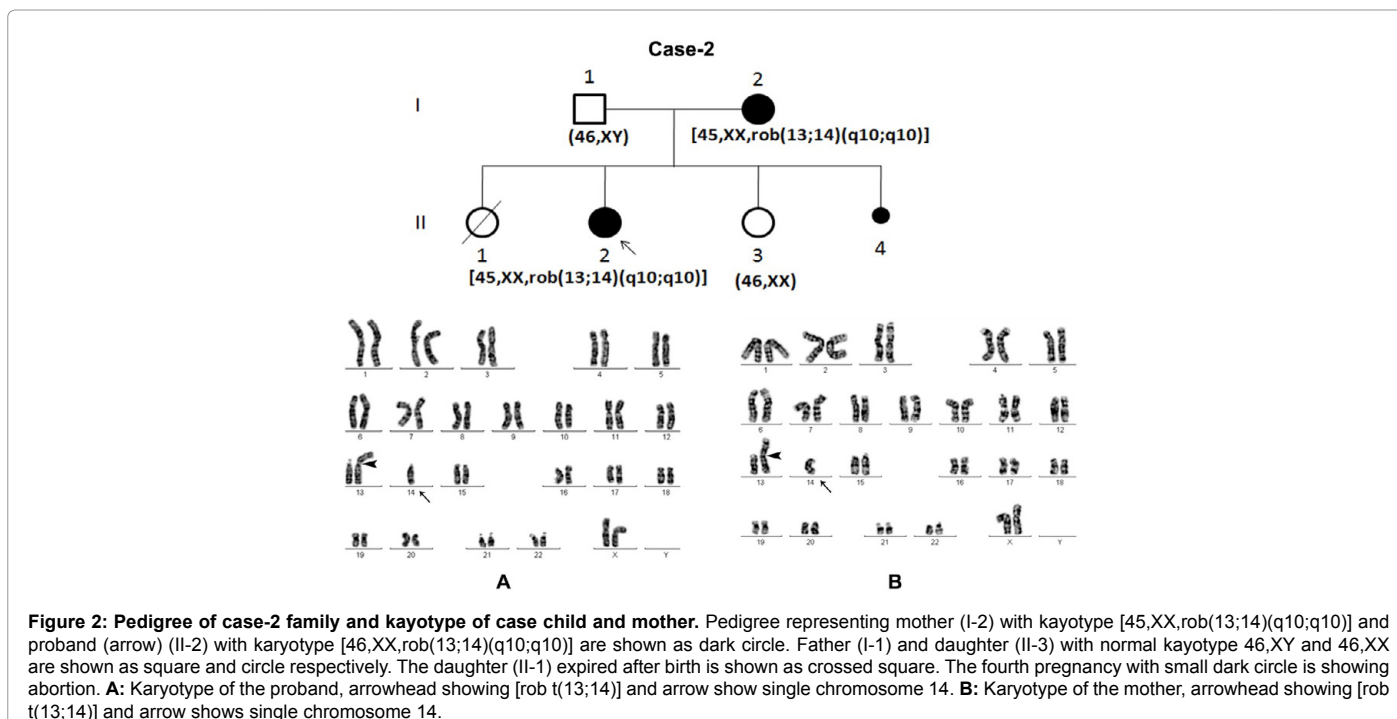
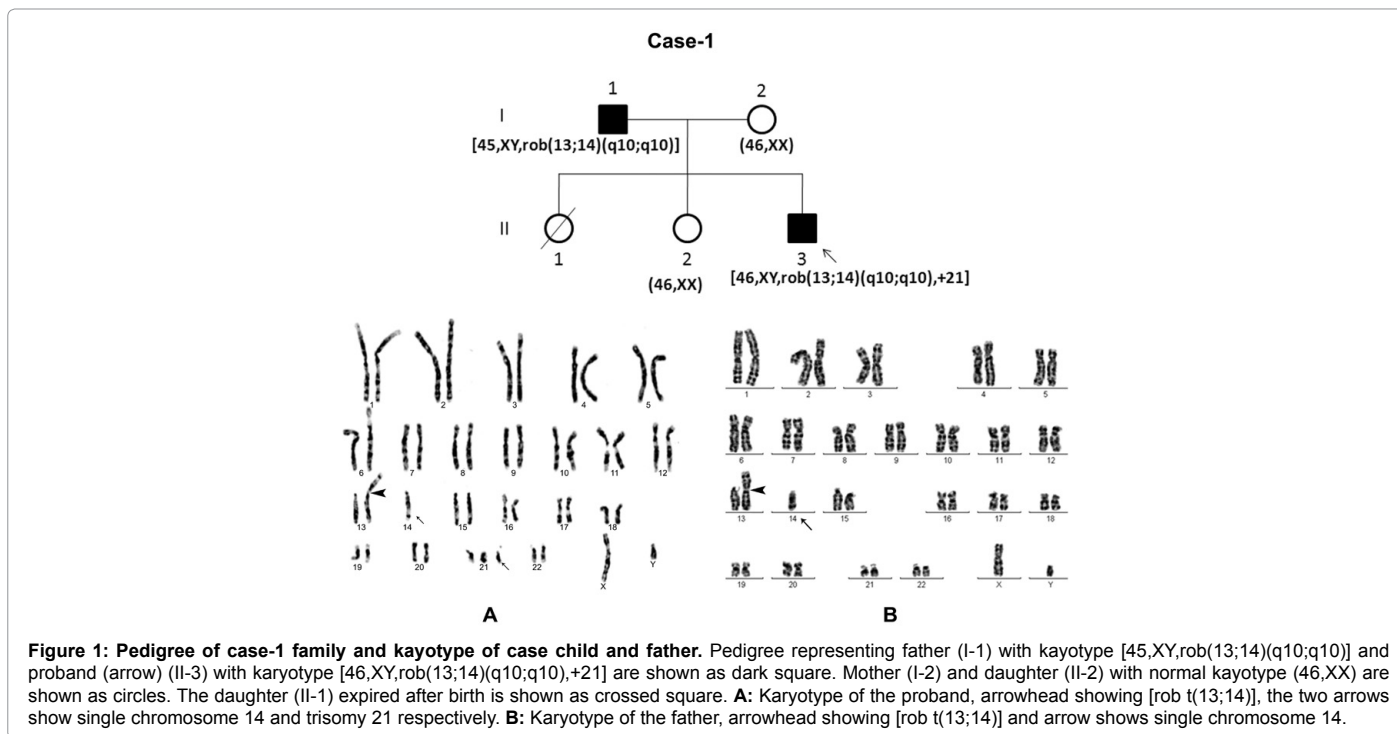
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birth was 35 and 25 years respectively. The first child of the parents expired at age of 05 months; the reason of her death was not exactly explained to us by parents. Second child was apparently healthy without any obvious clinical complication (Figure 1). Karyotyping of the child revealed [46,XY,rob(13;14)(q10;q10),+21] in all observed metaphases (Figure 1A). The chromosome analysis of father also showed balanced Robertsonian translocation with karyotype [45,XY, rob(13;14)(q10;q10)] in all metaphases (Figure 1B). Karyotyping of the mothers

was normal (46,XX) (not shown). Therefore, we considered the [rob t(13;14)] in the child was transmitted from the father.

**Case-2:** Maternal transmission of [rob t(13;14)] in child with gross developmental delay.

A 03 years old female child was second baby of apparently healthy mother with four pregnancies (Figure 2). Age of the mother and father at the time case presentation was 25 and 29 years respectively. The first



child of the couple died on same day of her birth. As per information given by parents she was having neonatal jaundice. The second child (case child) was also presented with complaint of developmental delay. She had suffered from diarrhea at the age of one year and pneumonia at the age of 1.5 months. She was unable to speak, not able to balance her body during movement and even she was not able to do her daily activity by own. The third female child (aged 1.5 years) was also having complaint of developmental delay along with macrocephally, not gaining weight and frequent cough. Mother had a history abortion of fourth pregnancy. On developmental scale both second and third child showed gross developmental delay for all the four areas, i.e., gross motor, adaptive, language and personal social behavior [9]. Overall developmental quotient for second and third child was 43.75 and 27.25 respectively. Their behavior was assessed using child behavior checklist (CBCL) [10]. The second child scored normal on the dimensions of CBCL. Though she scored higher on CBCL domains but her behavior was within normal range. The third child showed externalizing behavior problems in borderline range of CBCL. Externalizing behavior problems are negative behaviors that are directed towards the external environment. It comprises two dimensions of CBCL, i.e., attention problems and aggression. Karyotyping of second and third child revealed [45,XX,rob(13;14)(q10;q10)] (Figure 2A) and (46,XX) (not shown) respectively in all observed cells. Mother was also having same translocation with karyotype [45,XY rob(13;14)(q10;q10)] (Figure 2B). Karyotype of father (46,XY) and younger sister (46,XX) was normal. We observed [rob t(13;14)] in second child was transmitted from mother.

## Discussion

In present report we presented karyotype-phenotype correlation of [rob t(13;14)] in two familial cases. All the individuals with [rob t(13;14)] showed abnormal features like soft sub-mucous cleft palate with DS in case-1 child, soft sub-mucous cleft palate and ICE in case-1 father, miscarriage and birth of children with congenital problem in case-2 mother and gross developmental delay in case-2 child. The features observed in our cases are reflection of observation that the clinical features vary with location of breakpoint during translocation when acrocentric chromosomes fuse near centromere with loss of short arm [11].

Although, carrier of [rob t(13;14)] are phenotypically normal, there is greater chance of infertility, aneuploid gametes formation, spontaneous abortions, progenies with multiple congenital anomalies, mental retardation and uniparental disomy related complication [2,12]. Recently, a study from Chinese population on 872 cases of Robertsonian translocations revealed 93% of the balanced translocations were having problem of infertility, miscarriage, or offspring(s) with known chromosomal abnormalities [13]. In our study, both the carrier of [rob t(13;14)], i.e., father in case-1 and mother in case-2 (Figures 1A and 1B) were phenotypically normal (except soft sub-mucous cleft palate with father in case-1). Consequence of this [rob t(13;14)] in case-1 was observed with two congenital anomalies; trisomy 21 and soft sub-mucous cleft palate in child. We are not exactly aware of reason for death of first child in this family. There could be probability of congenital anomalies for non-survivor of the child. Two different case studies reported paternal transmission of [rob t(13;14)]; a 9 years old boy with severe mental retardation, peculiar faces, osseous dysplasia (including clinodactylism), urogenital and skin abnormalities, congenital heart disease and a 3 years old boy with severe scrotal hypospadias [14,15]. There have been limited reports on familial cases of [rob t(13;14)] with clinical correlation. Mother with [rob t(13;14)] in our case-2 (Figure 2B) was phenotypically normal but gross developmental delay was

observed in both of her children. The first child expired at the time of birth, was not diagnosed for any congenital anomalies. The mother also had an abortion of fourth pregnancy. Therefore, there seemed higher propensity of transmission of genetic imbalances due to [rob t(13;14)] leading to congenital anomalies in these abnormal progenies.

Co-occurrence of [rob t(13;14)] and trisomy 21 (Figure 1A) together with soft sub-mucous cleft palate observed in our case-1 child is probably first report to the best of our knowledge. Inheritance of [rob t(13;14)] and co-occurrence trisomy 21 in this child is uncommon finding of nondisjunction which seems as a consequence of ICE. Several studies have shown aneuploid gametes formation due to phenomenon of ICE in male carriers of Robertsonian translocations [16-18] while others opposed [19-21]. Co-occurrence of [rob t(13;14)] with trisomy 21 is rarely reported [22-26]. Among familial cases, a case of [rob t(13;14)] being inherited in four generations along with co-occurrence of trisomy 21 and maternal inheritance of [rob t(13;14)] in a child with trisomy 21 have been reported [27,28].

Therefore, genetic counseling is important for the carriers of [rob t(13;14)] especially in familial cases. Pre-implantation genetic diagnosis (PGD) has been shown to be effective strategy for carriers of these chromosomal rearrangements. In order to avoid abnormal pregnancy, normal or balanced embryo should be selected for transfer by PGD analysis of translocation chromosomes. As the carrier of a balanced [rob t(13;14)] are usually normal, possible heterogeneity in clinical outcome of the [rob t(13;14)] might be due to variable genetic imbalances. Further delineation of this heterogeneity in clinical features would be possible by fine mapping of break points involved in these translocations.

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## Conflict of Interest

The authors declare no Conflict of Interest.

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