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Case Report

New Discovery of a Rare Robertsonian Translocation (15;22) - A Case Report from India

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Abstract

The rob(15;22) is one of the rarest translocations which accounts for only 0.6% of the entire Robertsonian translocations reported in humans. A case of rob(15;22) in association with trisomy 21 still has not been reported. In the present study, a case of a 3-year 6-month-old male child with rob(15;22) with trisomy 21 is focused. The phenotype comprises generalized hypotonia, delayed developmental milestones, simian crease, dysmorphic facies, etc. Chromosome analysis with peripheral blood was executed and the karyotype was interpreted as 46,XY,der(15;22)(q10;q10)+21. To analyse whether the chromosomal translocation was de-novo or inherited, the chromosome analysis with the peripheral blood of his parents was performed. The karyotype of the father was interpreted as 46,XY, and of the mother was 45,XX,der(15;22). It was concluded that the rob(15;22) was inherited from his mother, although trisomy 21 was a de novo incidence. Hence, this case study can be proven useful in the understanding of rob(15;22) in solo and rob(15;22) in association with trisomy 21.

More Information

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Introduction

Robertsonian translocations are one of the most frequent structural chromosomal rearrangements witnessed in humans. The occurrence is about 0.1% in the general population [1], whereas rob(15; 22) is very sporadic and accounts for only 0.6% of the entire Robertsonian translocations [2]. Additionally, rob(15;22) in association with trisomy 21 is still unfocused. In this case study rob(15;22) with trisomy 21 in which the phenotype includes generalized hypotonia, delayed developmental milestone, a single line across the palm (simian crease), dysmorphic facies, etc. is discussed (Figure 1). In addition, an extensive review of the literature on the rob(15;22) cases reported so far is included.

Case report

The proband (The first individual in a family to obtain genetic counseling and/or testing for suspected hereditary risk) is a 3-year-6-month-old male child of an unrelated Indian parent from a rural village in West Bengal. His father and mother were 30 and 25 years of age at the time of his birth, respectively. Her mother had mild polyhydramnios

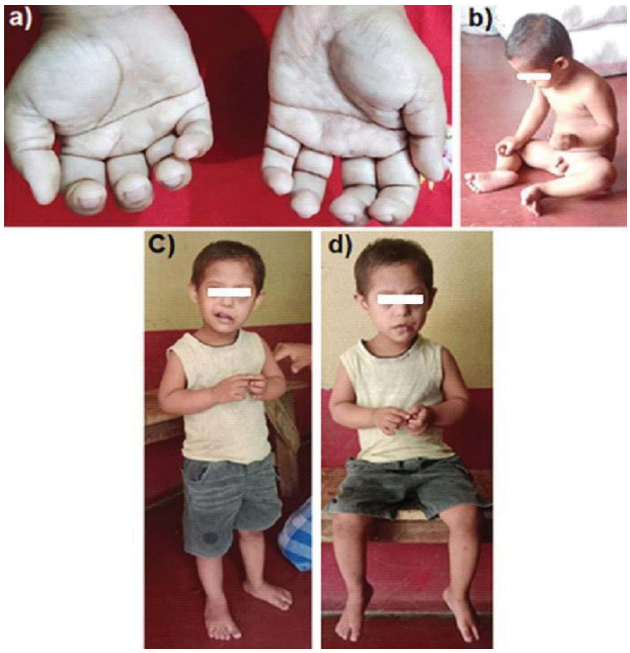

Figure 1: Showing the phenotypical features of the child, a) simian crease, b) normal external genitalia, c) improper response and laughter, and d) dysmorphic facies like Down syndrome.

at 30 weeks of gestation. The child was born after a full-term pregnancy at 37 weeks 4 days of gestation period following vaginal birth. His birth weight was 2.78 kg. No more information about the child at the birth time is available. There was also consanguineous marriage in the family history. As he grew up his physical development, intellectual ability, speech ability, learning ability, etc. was delayed, due to which his parents went to the clinician.

His present weight is 9.92 kg, height is 79.68 cm and head circumference is 18.50 inches. The clinical examination of the child showed persistent generalized hypotonia, an unresponsive face with syndromic facies with a high-arched palate, almond-shaped eyes, reduced reflex response of skeletal muscles (hyporeflexia), etc. The atrioventricular septal defect was also present in the radiological study. He has a low neckline and small ears but his external genitalia are normally developed. His behaviour was abnormal (laughter not associated with happiness), restless, and stubborn. Chromosome analysis with peripheral blood was accomplished with appropriate ethical consent from his parent (as the child was a minor) at Nirnayan Health Care Pvt. Ltd, Kolkata on May 2023 as a part of the investigation of hypotonia and dysmorphic facies.

Cytogenetics analysis of 20 metaphases from Phytoheamagglutinin-stimulated 72-hour blood cell culture shows an abnormal male chromosome complement with an extra chromosome 21 (trisomy 21), consistent with the clinical diagnosis of Down syndrome. Also, there is an additional abnormality of balanced Robertsonian translocation between the long arms (q-arm) of chromosomes 15 and 22. The karyotype was interpreted as 46,XY,der(15;22)(q10;q10)+21(Figure 2). Parents were convinced for the chromosomal study to be performed. It is to determine whether der(15;22) rearrangement is inherited or a de novo event.

Clearly the 15;22 Robertsonian translocation was inherited from his mother (Figure 3). The mother of the child was leading a healthy life. Trisomy 21 was a de novo incidence. A total of 20 metaphases were observed in each case. The translocation was present in all twenty cells observed.

Discussion

Robertsonian translocation (centric-fusion) is a form of chromosomal translocation in which two long arms of acrocentric chromosomes are fused to form one metacentric or sub-metacentric chromosome and the two short arms are lost [3]. These translocations decrease the number of chromosomes at the same time preserving existing genes [3]. As no significant genetic material is lost, the person is generally normal despite having such translocation. However, such persons are at risk of infertility, miscarriage, or even an offspring with chromosomal imbalance because their chromosome count does not match with their partners [4,5]. Robertsonian translocation is considered to be the key player of speciation, which means the formation of new and distinct species in the course of evolution [6,7]. For example, a Robertsonian evolutionary fusion, which may have happened in the common ancestor of humans and other great apes, is the cause of humans having 46 chromosomes whereas other primates have 48. Generally balanced Robertsonian translocations involve two different chromosomes (a heterologous translocation) [8]. There are three potential mechanisms for the formation of balanced heterologous translocation. Fusion at the centromere union subsequent breakage in one short arm and one long arm (in essence, a whole arm reciprocal translocation), and union succeeding breaks in both short arms [8]. The first two mechanisms are infrequent and would yield a translocation chromosome with one centromere (monocentric), whereas the third results in a chromosome along with two centromeres (dicentric).

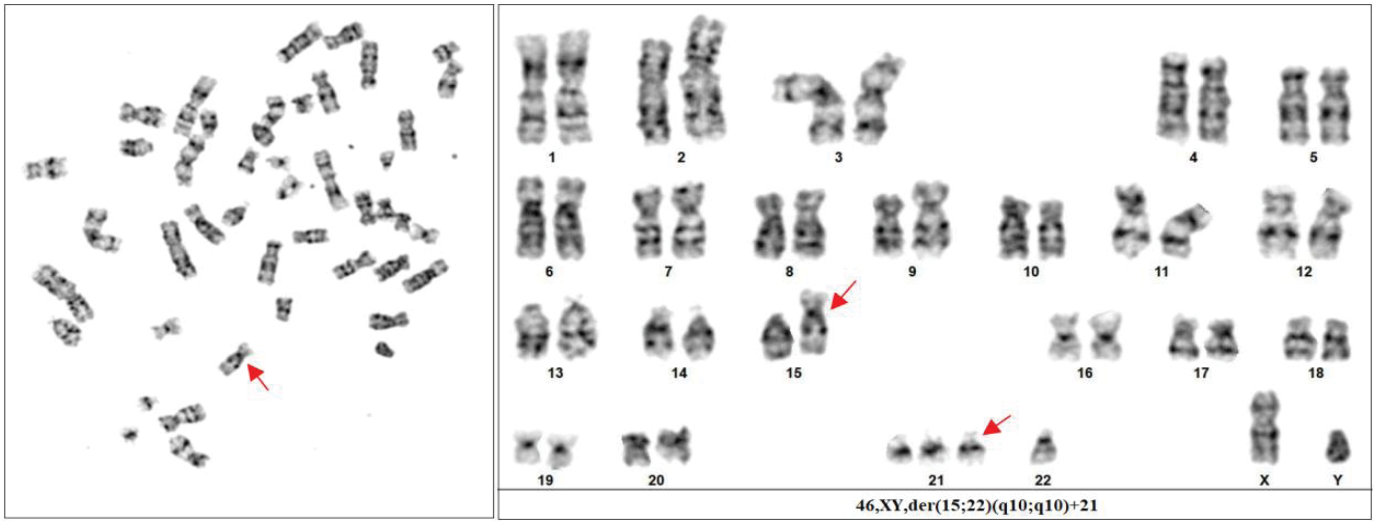

Figure 2: Showing the metaphase plate (left) and the karyotype [46,XY,der(15;22)(q10;q10)+21] at the (right). The translocated chromosome [t(15;22)] and trisomy 21 is indicated by the red arrow. The metaphase proves the authenticity of the study.

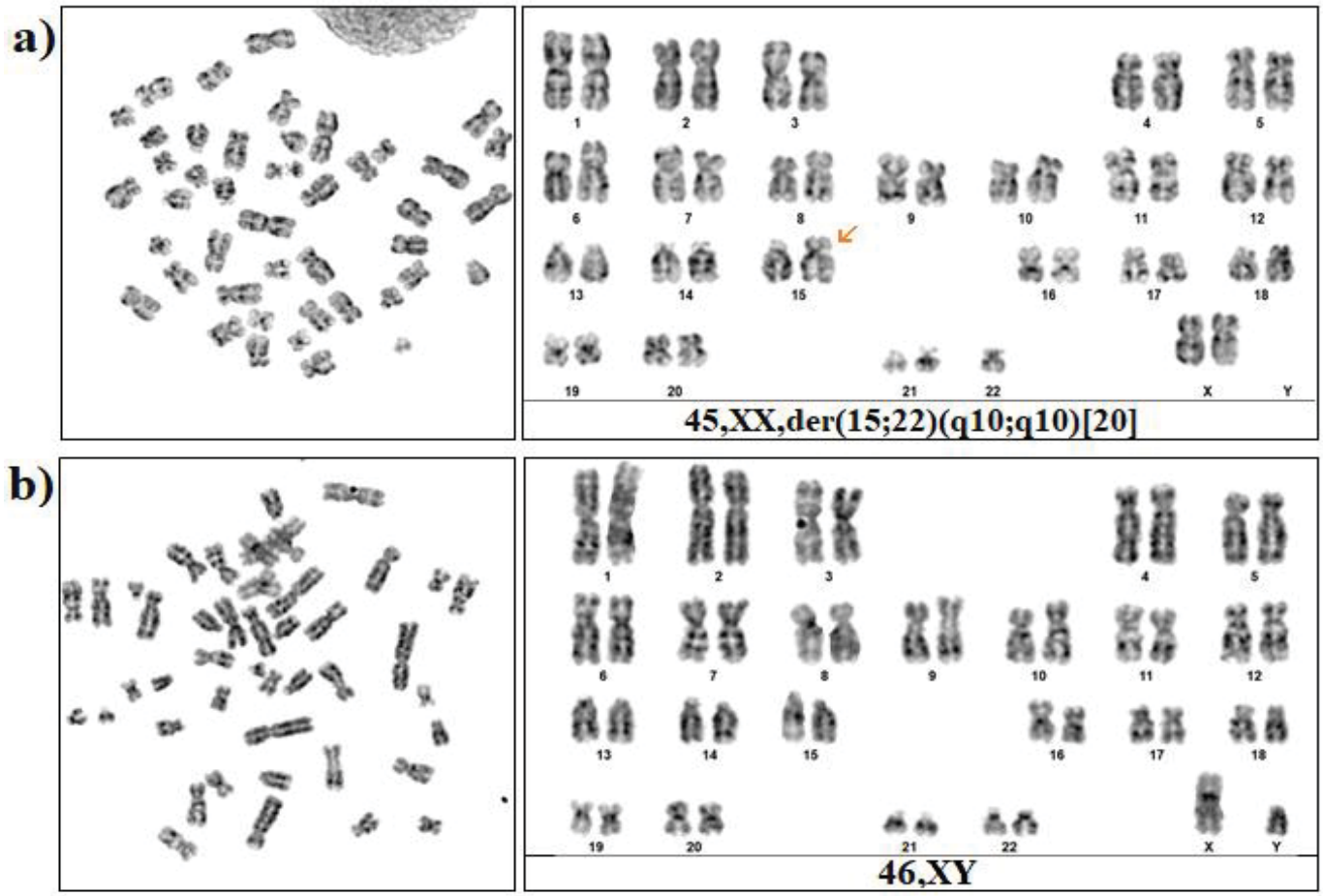

Figure 3: Showing the metaphase and karyotype of the mother (a) [45.XXder(15;22)(q10;q10)] and the metaphase and karyotype of the father [46,XY] (b).

To the best of our knowledge, worldwide there were only four cytogenetic studies in which rob(15;22) was clearly identified [9,11-13].

This particular translocation was first reported in 1987. The chromosomal study showed a constitutional Robertsonian translocation in a Philadelphia (Ph) chromosome-positive chronic myelocytic leukaemia (CML) patient [9]. However, a more complex karyotype 9;22;15 was observed in Ph Chromosome positive CML patients in ostensive lymphoid cells of blastic crisis. The translocation was from 15 to 9q. Subsequently, with improved karyotypes, it became apparent that most of 22q had been translocated to the centromeric portion of 15 [10]. In 1992 Robertsonian 15;22 translocations with the cardio-facial-cutaneous (CFC) syndrome were reported [11]. In 2010, 15;22 translocation was reported in a Turner syndrome (monosomy X) patient [12]. In 2016, 45,XX,der(15;22)(q10;q10) was reported with hypotonia, respiratory distress, and abnormal face [13]. Our case can explain 45,XX,der(15;22)(q10;q10) (mother of the child) as well as 46,XY der(15;22)(q10;q10),+21 (present case).

Three dissimilar neurodevelopmental disorders ascend mainly from deletions or duplications that happen at the 15q11-q13 locus: Prader-Willi syndrome (PWS), Angelman Syndrome (AS), and 15q11-q13 duplication syndrome (Dup15q syndrome) [14] (Figure 4). Each of these disorders is a consequence of the loss of function or over-expression of a minimum of one imprinted gene. Similarly, DiGeorge syndrome and Velocardiofacial syndrome are linked with 22q11.2 deletion [15] (Figure 4). Medical glitches frequently related to 22q11.2 deletion syndrome embrace heart defects, reduced immune system activity, a cleft palate, low levels of calcium in the blood, and delayed development with behavioural and emotional complications.

Again, laboratory findings on leukaemia patients suggested that abnormal chromosomal clones expand in an anomalous cytokine milieu rich with G-CSF in leukaemia [16]. The existence of a short G-CSF receptor isoform provides a signal of proliferation, but not differentiation. This can explain why the various clones are obtained in the bone marrow cytogenetics. Since 1987, no other study of Leukaemia patients has been reported with constitutional t(15;22) [9]. In this study, the translocation was clearly visible in all twenty metaphases observed. The entire q arm of chromosome 15 from 15q11 and the entire q arm of chromosome 22 from 22q11was present in the translocated chromosome. But both the 15p and 22p arms were lost in the child as well as in his mother.

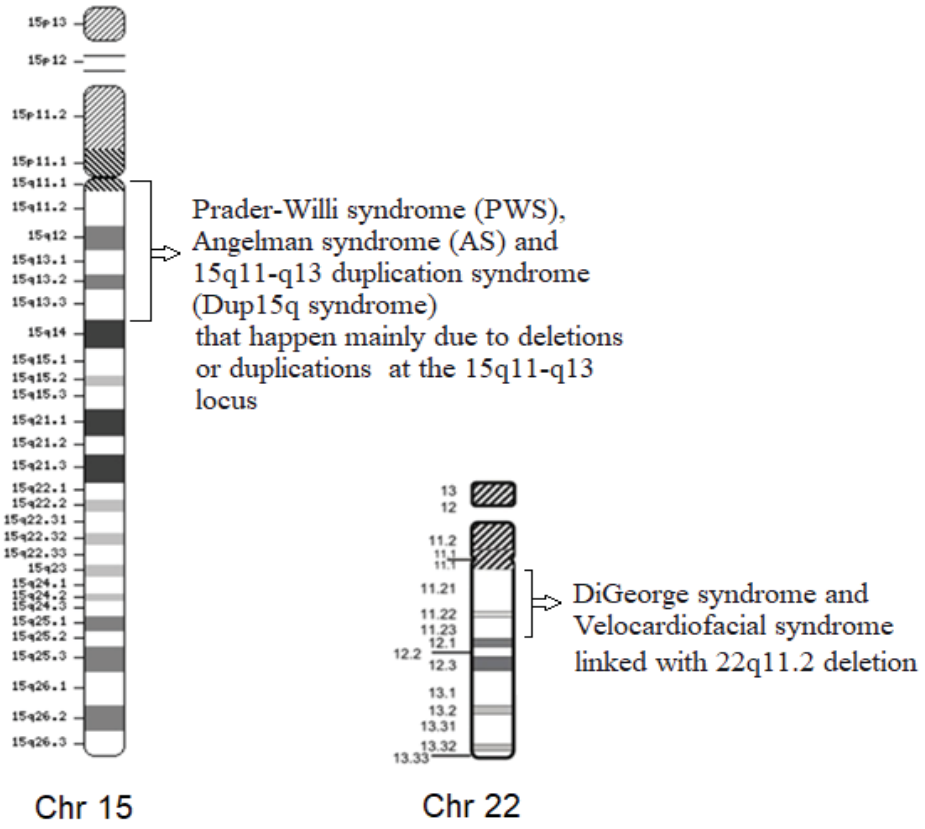

Figure 4: Showing the ideogram of chromosome15 and 22. Prader-Willi Syndrome (PWS), Angelman Syndrome (AS), and 15q11-q13 duplication syndrome (Dup15q syndrome) are linked with the q arm of chromosome 15, and DiGeorge syndrome and Velocardiofacial syndrome are linked with the q arm of chromosome 22 [19].

In conclusion, we have presented the cytogenetic analysis of a 3-years-6-months-old male child with hypotonia, an unresponsive face with syndromic facies with a high arched palate, almond-shaped eyes, hyporeflexia, etc. This study is rather evoking a big question about the true pathogenicity of the t(15;22). There is a similarity between Mario et al. 2010 and the present case. In Mario, et al. 2010, the patient was having t(15;22) with monosomy X like this case where trisomy 21 is associated. From Table 1 it can be assumed that the symptoms the patients are exhibiting are very close to pure Turner syndrome and Down syndrome. Hence, a question is arising, whether this translocation has any pathogenicity or not. Another question is that if the loss of the gene of p arms of chromosomes 15 and 22 is so important that it can show pathogenicity as mentioned in Cho, et al. 2016 then how the mother of the child is leading absolutely a normal life? She is phenotypically normal. This raises another question the pathogenicity of the child in Cho, et al. 2016 may be due to some other genetic involvement. Parents denied the molecular study (chromosomal microarray or FISH study) to be done due to financial constrain. The presence of the whole q arm of chromosomes 15 and 22 in the child can nullify the probability of having pathogenic mutations (in this case deletion/duplication). Again the mother has the translocated chromosome [t(15;22)] and the genes that are present on the translocated chromosome are functionally normal which means not mutated (deletion/duplication). Genetic counselling was recommended to the parents for the management and upbringing of the child. Prenatal genetic counselling is also suggested in case of further pregnancy.

Although, studies like array-CGH (CMA), Whole Exome Sequencing (WES), and FISH can be performed for the investigation of the breakpoints in infants with suspicion of genetic disease with Robertsonian translocation. FISH studies with the probes on the stalk regions of involved chromosomes could be considered and applied for a better understanding of the presence/absence of the p-arm's genes. In most cases, Robertsonian translocation involves the acrocentric chromosomes like 13, 14, 15, 21, 22, and Y [17]. It is known the p arm of the acrocentric chromosome has very few genes. Thus the bearer does not face any physiological issues daily but infertility, miscarriage, or offspring with chromosomal abnormality may happen due to mismatched chromosome number. There may be the possibility of further complications arising in the offspring if one of the parents has such translocation (here trisomy 21). The p-arms of the five human acrocentric chromosomes bear nucleolar organizer regions (NORs) comprising ribosomal gene (rDNA) repeats that are organized in a homogeneous tandem array and transcribed

Table 1: Cytogenetic and clinical findings of the reported cases with Robertsonian translocation (15;22).

Case No.	Authors (year of eporting)	Age and sex	Karyotype in Peripheral Blood	Clinical findings at presentation
1	Becher, et al. [9]	40Y/M	45,XY,der(15;22)(q10;q10)	Phenotypically normal, Ph-positive, CML developed
2	Fryns, et al. [11]	5Y6 M/F	45,XX,-15,-22,t(15;22) (p11;q11)mat	Polyhydramnios during the third trimester; Cardio-Facio- Cutaneous Syndrome (severe growth retardation, coarse)
3	Mario, et al. [12]	11Y/F	44,X,der(15;22)(q10;q10)	Short stature, low hairline, broad neck, high palate, broad thorax, wide-spaced nipples, hyperconvex nails with shortening of the 4th and 5th metacarpals, numerous nevis located mainly at the thorax and the back
4	Cho, et al. [13]	5Y/M	45,XX,der(15;22)(q10;q10)	Generalized hypotonia, respiratory distress, tent-shaped upper lips, hyporeflexia, and single umbilical artery
5	This case	3Y6M/M	46,XY der(15;22)(q10;q10),+21	Hypotonia, an unresponsive face with syndromic facies with a high arched palate, almond-shaped eyes, skeletal muscles a reduced reflex response (hyporeflexia)

in a telomere-to-centromere direction [18]. Thus chance of being pathogenic is less as nucleolar organizer regions (NORs) genes from other acrocentric chromosomes may be compensatory. More study is required on the rob(15;22) and deletion of chromosomes 15-p and 22-p to come to any flawless conclusion to find whether the pathogenicity is an after-event of translocation or the mutation.

Conclusion

Robertsonian translocations are a precise class of translocations in which two acrocentric chromosomes marge at their centric ends. In humans, chromosomes 13, 14, 15, 21, and 22 are acrocentric chromosomes and are generally related to Robertsonian translocations. The short arms of the acrocentric chromosomes comprise plentiful copies of the genes coding for rRNA. Because counting the number of centromeres in a metaphase spread evaluates chromosome number, persons with a Robertsonian translocation have 45 chromosomes. The tiny reciprocal product, which encompasses the fragments of the short arms (p) of the two fused chromosomes, is eventually lost. Loss of the short arms (p) of two acrocentric chromosomes is not lethal and persons with this kind of rearrangement are mostly phenotypically normal. These rearrangements can be categorised into two types: (a) common Robertsonian translocations such as the der(13;14) and the der(14;21), and (b) rare Robertsonian translocations. Genetically balanced carriers of these translocations have an amplified occurrence of infertility and risk for genetic imbalances between their offspring like Down syndrome (tri 21) and Patau syndrome (tri 13) etc. Thus Robertsonian translocation carriers are at increased risk for having infertility, miscarriage, or children with anomalies either because of mal-segregation of the translocation chromosome or as a consequence of Uniparental Disomy.

The take-home message of this study is a basic conventional chromosomal study (Karyotyping) of the partners before marriage or before planning a child can be a saviour. Because in such cases the entire family suffers a tremendous mental trauma for the child. Again, in case any couple has any such Robertsonian translocation in the test report of karyotyping, genetic counseling can be a good option before planning for a baby. In case of pregnancy, prenatal genetic screening may be performed under a doctor's supervision.

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Consent statement

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy. The patient is a child of 3 years and 6 months, written consent was obtained from the child's father.

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