

A Novel Translocation t(2;9)(p23;q13) in Female with Short Stature

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KEYWORDS Chromosome. Height. Balanced. Reciprocal. 2p, 9q

ABSTRACT Short stature has, for long time, been a diagnostic dilemma for clinicians and a major concern for females and their parents. Although short stature has been observed in individuals with Turner syndrome (45,X) and its variants, there are very few reports on autosomal anomalies being present in individuals with short stature. We present the first case of a 12 years old female with short stature, slightly elevated FSH (10.08 mIU/ml), small sized uterus and ovaries that revealed a balanced reciprocal translocation between chromosomes 2 and 9 [t(2;9)(p23;q13)]. The present case suggests that genes for human height could be mapped to short arm of chromosome 2 and/or long arm of chromosome 9.

INTRODUCTION

Short stature, one of the most observed features in Turner syndrome (45,X), is a major concern for females and their parents. Few females with short stature have normal karyotypes and present as diagnostic challenges to clinicians. Various genes like *UDP7*, *FGFR3*, *SHOX*, *GH1* and so on (Kant et al. 2003; Kuznetzova et al. 1994) have also been extensively studied in such cases. However, there are very few reports on other chromosomal anomalies being present in females with short stature.

We present the first case of a 12 years old female with short stature, slightly elevated FSH, small sized uterus and ovaries that revealed a translocation between chromosomes 2 and 9, that is, t(2;9)(p23;q13).

CASE REPORT

The proband, 12 years old female was the first in birth order and was succeeded by a 10 years old male child. The height of the proband was 125 cm while the father and mother were 171 cm and 170 cm in height, respectively. The female weighed 25 kg and revealed no development of secondary sexual characters. The bone age of the proband was 12 years while her height age (as per the Indian Council for Medical Re-

search guidelines) (Khadilkar et al. 2007) was 8 years. The vitals, hemogram, urine analysis, renal and liver function tests revealed results within normal limits.

The ultrasound findings revealed a relatively small and anteverted uterus (40x16x29 mm) with homogenous echo pattern and relatively small ovaries. The right ovary measured 17x11 mm in size while the left ovary measured 18x13 mm in size. Both the ovaries had normal echo pattern. The skull radiographs revealed copper beaten appearance that was suggestive of raised intra-cranial tension (ICT). Hormonal analysis revealed slightly raised FSH values (10.08 mIU/ml) while TSH (3.32 µIU/ml) and tissue transglutaminase IgA (3.8 U/ml) were within normal limits [p<0.1].

MATERIAL AND METHODS

Cytogenetic analysis was done using standard protocols wherein chromosome preparations were obtained from 72 hours lymphocyte cultures (Roulston and Beau 1997). These chromosomal preparations were then subjected to GTG-banding after which karyotyping was done according to the standard ISCN nomenclature (ISCN 1995). Fluorescence *In Situ* Hybridization (FISH) analysis using Vysis LSI *bcr/abl* extra signal (es) probe was also performed on metaphases obtained from 72 hours lymphocyte culture to confirm the translocation of region of chromosome 9 to short arm of chromosome 2.

RESULTS

Cytogenetic analysis revealed 46,XX,t(2;9)(p23;q13) karyotype in all the 30 cells analyzed

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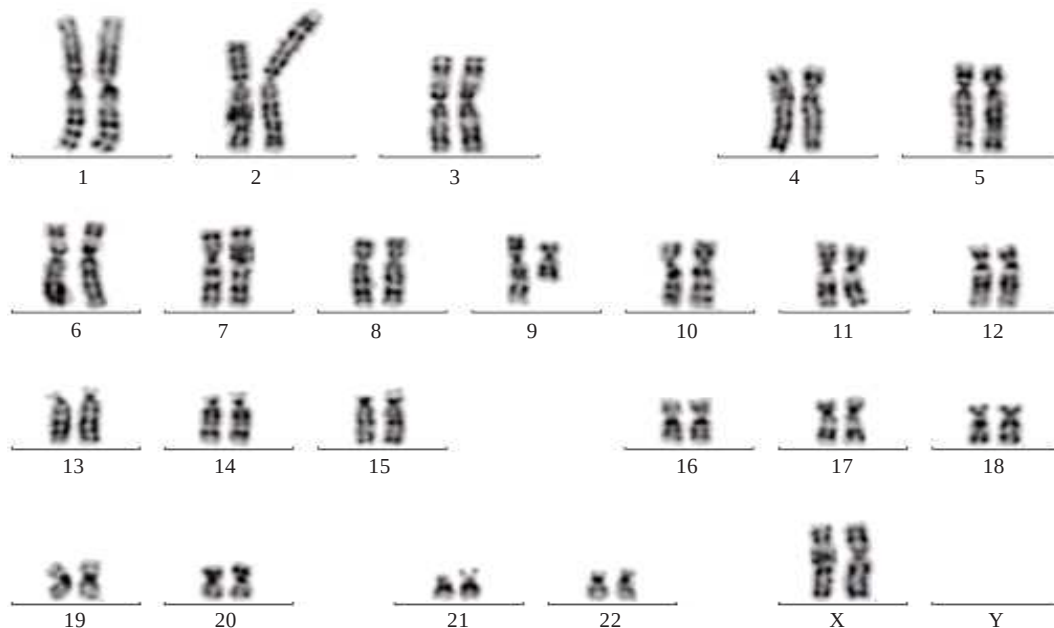


Fig. 1. GTG-banded karyotype revealing t(2;9)(p23;q13)

at a minimum of 550 band resolution (Fig. 1). The breakpoint was at band 23 in the short arm of chromosomes 2 and band 13 in the long arm of chromosome 9. FISH analysis revealed translocation of *abl* gene (9q34) onto short arm of chromosome 2 (Fig. 2).

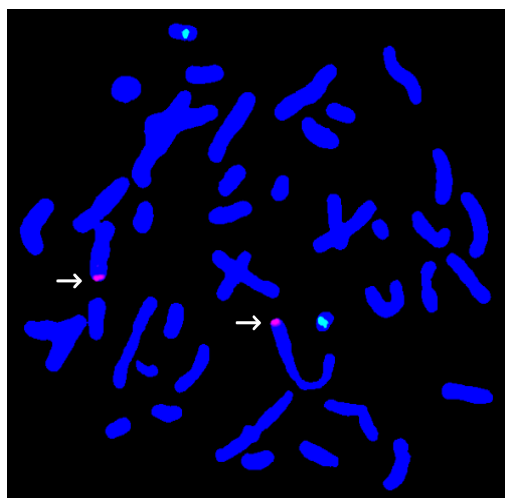


Fig. 2. FISH analysis using Vysis LSI *bcr/abl* es probe on a metaphase obtained from 72-hours lymphocyte culture revealing translocation of long arm of chromosome 9 (harbouring *abl* gene) onto chromosome 2

DISCUSSION

Short stature in females has usually been linked to Turner syndrome (45,X) wherein one of the two X chromosomes is missing. Apart from 45,X, variants of Turner syndrome (like 45,X/46,XX), some sex chromosomal anomalies (for example, t(X;Y)) (Kant et al. 2003; Kuznetsova et al. 1994) and translocations between X chromosome and autosomes [e.g. t(X;1), t(X;9)] (Gardner et al. 1983; Kuznetsova et al. 1994) have also been reported in females with short stature. However, there are very few instances of short females revealing translocations between autosomes on cytogenetic analysis. We present the first case, to the best of our knowledge, of a female with short stature revealing t(2;9) (p23;q13).

Translocation between chromosome 2 and 9 has earlier been reported as a congenital abnormality in autism spectrum disorder (ASD), microcephaly with features of 9q subtelomeric deletion syndrome and a case of bilateral retinoblastoma (Roohi et al. 2008; Busche et al. 2008; Balestrazzi et al. 1984). However, the breakpoints in these cases reported with t(2;9) varied amongst each other and were also different from the ones observed in the present case. In the former 2 cases, the breakpoint was in the short

arm of chromosome 2 (that is, p13 and p25.2) while in the case with retinoblastoma, it was in the long arm (that is, q11). The breakpoint in the chromosome 9 also varied and was in the short arm in cases with ASD and retinoblastoma (p24 and p11 respectively) while in the case with microcephaly with features of 9q subtelomeric deletion syndrome, it was in the long arm (that is, q34.3). In contrast to these, breakpoints in the present case were p23 and q13 in chromosomes 2 and 9 respectively that was also confirmed by FISH analysis that have not been reported. Further, none of these reported cases presented with short stature like the present one.

The participation of chromosome 2 in translocations has, however, been reported earlier in a few cases of females with short stature although these females had other congenital anomalies as well. A translocation between chromosomes 2 and 7 was reported in a 6-years old girl with short stature, peculiar facies, slight mental retardation and microcephaly (Vivarelli et al. 1988). Similar anomaly was also reported in her mother and grandmother. The region of chromosome 2 involved in the translocation was terminal part of short arm to q23.

In another case with mesomelic dysplasia, a balanced translocation, t(2;8)(q31;p21) was reported in four members of a family with short stature and shortening of middle segments of the limbs (Sugawara et al. 2002). A cryptic translocation, t(2;8)(q37.3;q24.3) was also reported in five members of a family with Albright hereditary osteodystrophy (AHO)-like phenotype with short stature as one of the observed features (Bijlsma et al. 1999). In the present case, however, the parents and younger sibling of the proband were not available for cytogenetic analysis.

Similar to above cases with part of chromosome 2 being translocated to another autosome, chromosome 9 has also been reported to be partially translocated to X chromosome and chromosome 4 (Liu et al. 2006; Striano et al. 2005; Zhao et al. 2008). However, the breakpoints in all these cases with short stature were in the short arm of chromosome 9 unlike in the present case.

Liu et al. (2006) identified the q22 region on chromosome 9 as being genetically linked to human height in Caucasians. This region on chromosome 9 harbors the ROR2 gene that is

required for growth plate development. In the present case, this region was translocated onto the short arm of chromosome 2. However, it is not clear whether the promoter of the gene got interrupted due to the translocation thereby changing the functional aspect or some other gene on chromosome 9 is linked to human height.

The region of chromosome 2 translocated to chromosome 9 was the terminal region of short arm which may also harbour gene for human height or development. This region (2pter→2p23) is known to harbour few genes like ALK (anaplastic lymphoma kinase), SRC-1 (steroid receptor coactivator-1) and so on among highly repetitive DNA sequences (Deloukas et al. 1998).

Human height is a typical and important complex trait, which is determined by both actions and interactions of multiple genes. Although an increasing number of genes or genomic regions have been discovered for their independent effects on height variation, no study has been performed to identify genes or loci that interact to control the trait. To the best of our knowledge, t(2;9)(p23;q13) has never been reported in literature in a case with short stature, revealing no development of secondary sexual characters and with slightly elevated FSH. The reporting of individuals with similar translocation (or translocations involving same regions) and extensive study of such cases at the molecular level may help further delineate the genetic basis of human height, as well as genes involved in development of female reproductive organs and secondary sexual characters.

ACKNOWLEDGEMENT

The authors would like to acknowledge the support of Dr. Aparna Jha Ahuja, Lab Director, Clinical reference Lab, SRL, Gurgaon.

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