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Editorial Article

Deletion of SHOX Gene Locus and a Derivative Chromosome der(22) of t(12;22) in a Child with Hypoplastic Left Heart Syndrome

Yenamandra A*, Hamid R, Gauthier J, Walsh W and Wheeler FC

Vanderbilt University Medical Center, Nashville TN, USA

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Hypoplastic left heart syndrome is a rare, complex, congenital heart defect in which the left side of the heart is critically underdeveloped. We report here a case of a one-month-old boy born with hypoplastic left heart syndrome consisting of mitral and aortic atresia, mild tricuspid insufficiency, acute respiratory failure, requiring mechanical ventilation, and acute myocardial failure requiring continuous inotropic support. The patient also had rhizomelia of all four limbs. Family history was significant for his mother having short stature (reported height 4'8") and one previous miscarriage.

SNP Chromosomal Microarray Analysis (CMA) of the peripheral blood sample revealed two copy number changes. The first is a single copy gain of 36,343 probes within the short arm of chromosome 12. This duplication includes the entire short arm of chromosome 12, and is approximately 34 Mb in size, extending from band 12p11.1 to band 12p13.33. The second change is a single copy loss of 800 probes; a terminal deletion of Xp22.33 is approximately 735 kb in size (Figures 1, 2 and 3). This deletion includes *SHOX* gene (OMIM# 400020).

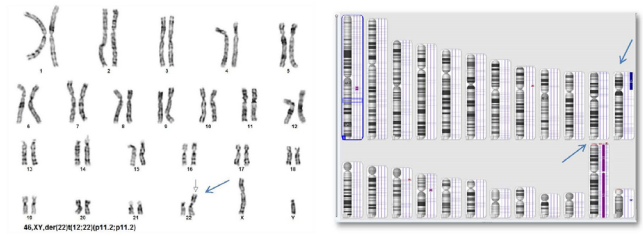
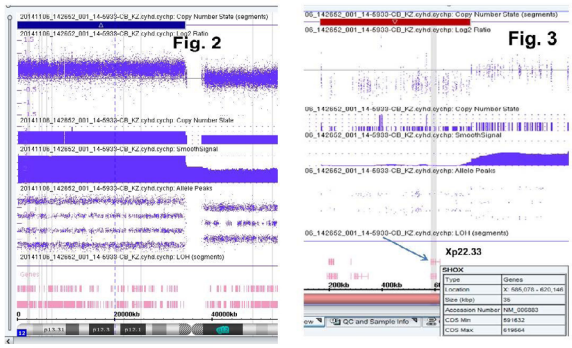


Figure 1: G banded and Digital Karyotype of the child with a der(22) of t(12;22) resulting in duplication of 12p and deletion of Xp (blue arrows).



Figures 2, 3: Genomic view of the duplication of 12p and deletion of XP that includes SHOX locus (arrow).

***Corresponding author:** Ashwini Yenamandra, Department of Pathology, Immunology and Microbiology, Vanderbilt University Medical Center @ 100 Oaks, 719, Thompson Lane, Nashville, TN 37204, USA, E-mail: ashwini.yenamandra@vanderbilt.edu

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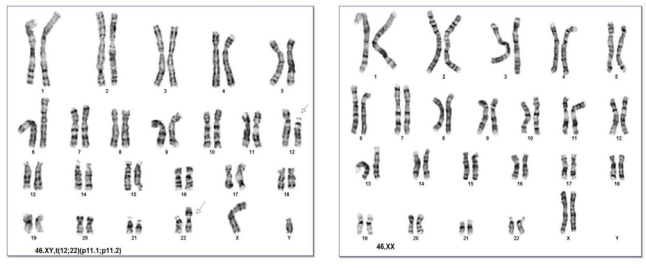
Metaphase chromosome analysis performed on the peripheral blood of the patient to characterize the abnormal array findings revealed a derivative chromosome 22 of t(12;22). Karyotype is described as 46,XY,der(22)t(12;22)(p11.2;p11.2) (Figure 1). The ISCN nomenclature describing this abnormal result is "arr Xp22.33(0-734,851)x1,12p13.33p11.1(173,786-34,521,804)x3".

Chromosome analysis of both parents revealed that the unbalanced der(22) is inherited from father. Father's karyotype was 46,XY,t(12;22)(p11.2;p11.2) and mother's karyotype was 46,XX (Figures 4 and 5). Fluorescence in Situ Hybridization (FISH)) with Xp22.33 region specific FISH probe for the *SHOX* gene revealed that the mother had the *SHOX* gene deletion and the child inherited the abnormal X chromosome from mother (Figure 6).



Figures 4, 5: karyotypes of father with t(12;22) translocation and karyotype of mother.

The *SHOX* gene is within the pseudoautosomal region of Xp and Yp, and the deletion of *SHOX* locus is associated with *SHOX*-related haploinsufficiency disorders including a spectrum of disorders ranging from Leri-Weill Dyschondrosteosis (LWD) to *SHOX*-related short stature [1,2].

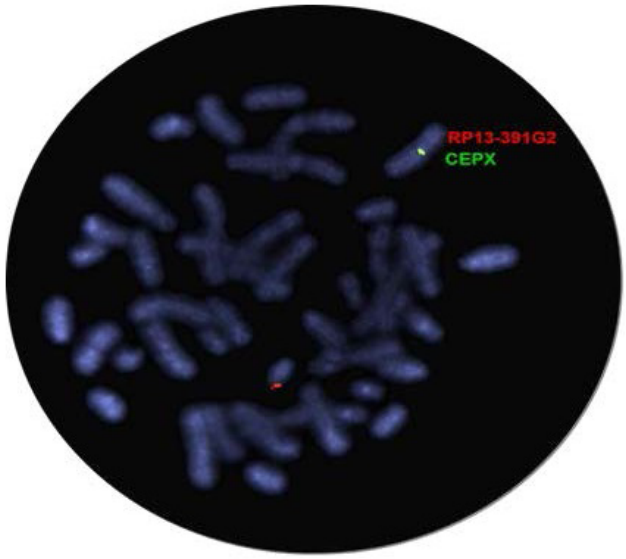


Figure 6: FISH with SHOX specific probe indicating a deletion of SHOX locus on Xp.

Our patient has inherited two genetic abnormalities, one from each parent: trisomy of 12p due to an unbalanced translocation inherited from the father, and a *SHOX* deletion from the mother. Clinical features of trisomy 12p include developmental delay, intellectual disability, dysmorphic features, and occasional seizures, behavioral problems and sleep disturbance [3]. Heart defects are not common, but have been reported. To our knowledge, this is the first case of hypoplastic left heart syndrome associated with trisomy 12p.

References

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