

Distal Trisomy 10p and 4q Monosomy: Associated with Marfanoid Features, Syndromic Aortic Root Dilatation and Intellectual Disability

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Case Report

A 35 year old man presented in childhood with global developmental delay, hypotonia and a Marfanoid phenotype with dolichocephaly, long narrow face with malar hypoplasia and retrognathia, high-arched palate and dental crowding, chest asymmetry, severe scoliosis and pes planus (Figure 1A). There were no ocular findings of Marfan syndrome (MS) and no known relevant family history. Investigations revealed normal plasma amino acids and urine organic acids, normal total plasma homocysteine and normal fragile X syndrome results.

At this visit, there was progressive shortness of breath, moderate aortic regurgitation and progressive dilatation of aortic root dimensions (3cm at 8 years, 4.6 cm by 20 years and 5.6 cm at 35 years on serial transthoracic echocardiography confirmed by computed tomography. The latter also showed dilated pulmonary artery sinuses to 4.1cm (Figure 1B). During his work up for aortic root surgery, a coronary angiogram via transfemoral access revealed a “string of beads” appearance of the femoral artery (Figure 1C) typical of the medial fibroplasia type of fibromuscular dysplasia [1].

Cytogenetic microarray (Combimatrix, Irvine CA) analysis revealed a de novo unbalanced karyotype 46, XY, der(4)t(4;10)(q34.3;p12.1)dn.arr [gh19] 4q34.3q35.2(179,589,516-191,154,276)x1,10p15.3p12.1(0-29,304,999)x3.

The derivative chromosome 4 resulted from an unbalanced translocation between the long arm of chromosome 4 and the short arm of chromosome 10, at bands 4q34.3 and 10p12.1, respectively. The resulting net genetic imbalance of the der(4) is monosomy for the distal region of chromosome 4 from 4q34.3 ≥ q35 and trisomy for the region of chromosome 10 from 10p12.1 ≥ p15 (Figure 2). These findings were confirmed by fluorescent in situ hybridization (FISH) analysis (data not shown). Both parents had normal microarray and FISH analyses.

Therefore, our provisional diagnosis was an adult male with severe intellectual disability, aortic root dilatation and other vascular anomalies, and a Marfanoid habitus resulting from an unbalanced karyotype. DNA

Received date: 9 Dec 2015; Accepted date: 24 Dec 2015; Published date: 5 Jan 2016.

Citation: Shah P, Dawson A, Tam J, Semaniuk N, Hovanes K, et al. (2016) Distal Trisomy 10p and 4q Monosomy: Associated with Marfanoid Features, Syndromic Aortic Root Dilatation and Intellectual Disability. J Clin Case Stu 1(1): doi <http://dx.doi.org/10.16966/2471-4925.103>

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sequencing of the ACTA2, FBN1, TGFBR 1 and 2, TGFB2, COL3A1 and SMAD3 genes in a core vascular aneurysm panel revealed no known disease-causing mutations (Collagen Diagnostic Laboratory, University of Washington and Seattle).

The patient successfully underwent a tricuspid aortic valve sparing procedure (David's reimplantation). Intraoperatively, his aortic root and pulmonary artery dilatations appeared very similar to the dilatation seen in MS or Loeys-Dietz syndrome (Figure 1D). Histologically cystic medial necrosis was observed in the resected specimen. Some features of both these disorders were lacking. The patient did not meet the 2010 Ghent criteria for MS [4] and DNA studies of known candidate genes proved negative.

Global developmental delay, hypotonia and craniofacial features seen in our patient have been described in patients with 10p trisomy [2], whereas distal 4q monosomy has been associated with milder phenotypes [3]. We believe that this derivative chromosome is, to our knowledge, unique. Detailed review of the many genes known to be mapped to the unbalanced segments of 10p and 4q using OMIM and other databases (Decipher, UCSC Genome Browser) revealed no candidate genes, and no genetic disorders associated with a Marfanoid phenotype [4], fibromuscular dysplasia, or syndromic aortic root dilatation. However many genes mapped to the 10p and 4q regions of interest have no known phenotype as yet. This would suggest either a new syndrome involving a candidate gene mapped to 10p or 4q with a new function or, there may be a gene mutation in a chromosome region elsewhere in the genome associated with aortopathy and developmental disability as previously described [5].

In conclusion, patients with chromosome aneuploidy associated with syndromic features and /or Marfanoid phenotype should be monitored for aortic root dilatation and should be surgically treated between 4.2 cm (Loeys-Dietz) to 5cm (MS), depending upon rate of growth. Parents and siblings of affected individuals should be screened with echocardiography and microarray analysis.



Figure 1: Phenotypic Features (A) With permission, photograph of patient demonstrating Marfanoid habitus. (B) Fluoroscopy image of the femoral artery demonstrating a “beaded” appearance. (C) Computed tomography image (coronal plane) demonstrating dilated aortic root and pulmonary artery. (D) Intraoperative photograph demonstrating syndromic aneurysmal aortic root. Cranial is to the left and caudal to the right.

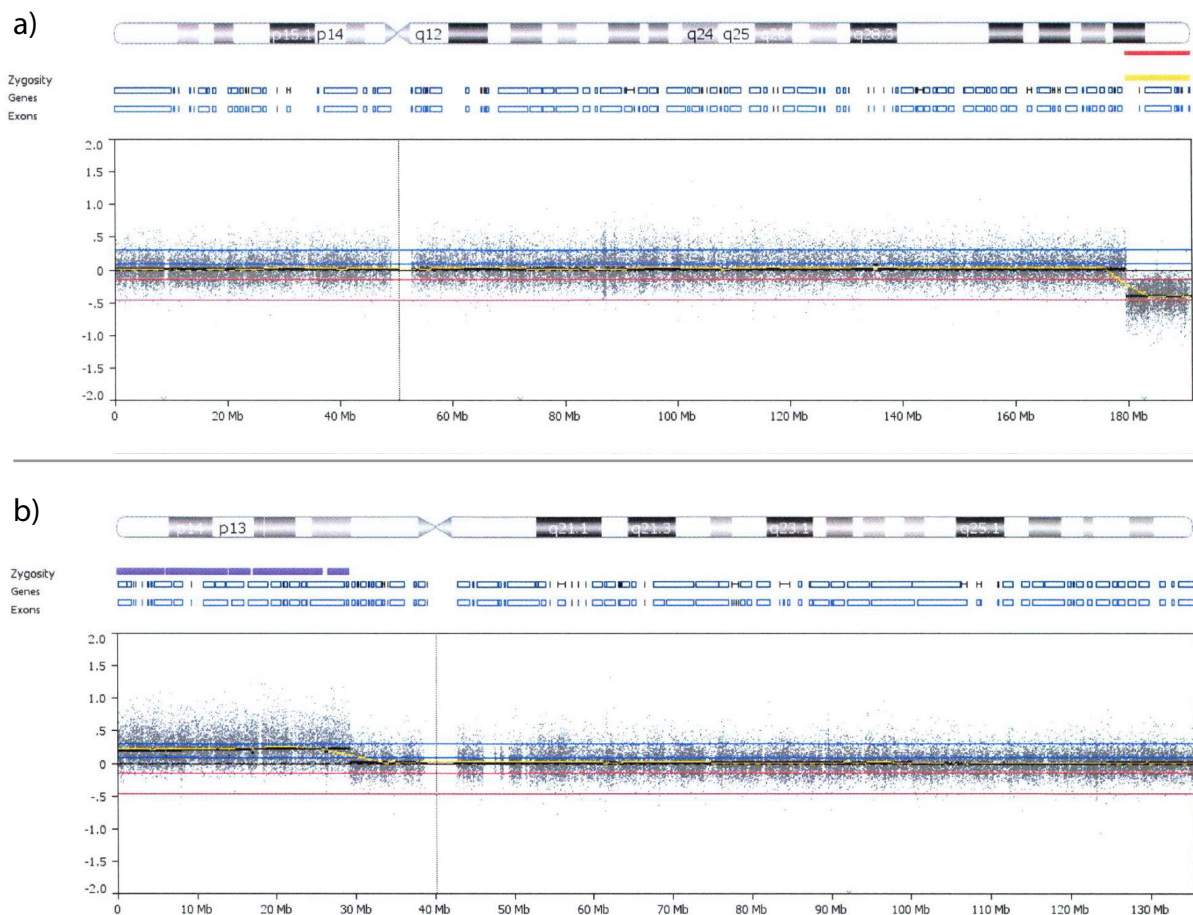


Figure 2: Cytogenetic microarray of **a)** Chromosome 4, showing the deletion of 4q34.3 ≥ qter, **b)** Chromosome 10, showing the duplication of 10p12.1 ≥ pter

References

1. Poloskey SL, Kim ESh, Sanghani R, Al-Quthami AH, Arscott P, et al. (2012) Low yield of genetic testing for known vascular connective tissue disorder in patients with fibromuscular dysplasia. *Vascular Medicine* 17: 371-378.
2. Kohannim O, Peredo J, Dipple KM, Quintero-Rivera F (2011) Clinical findings associated with De Novo Partial Trisomy 10p11.22p15.3 and Monosomy 7p22.3 Detected by Chromosomal Microarray Analysis. *Case Rep Genet.* 2011: 131768.
3. Bateman MS1, Mehta SG, Willatt L, Selkirk E, Bedwell C, et al. (2010) A de novo 4q34 interstitial deletion of at least 9.3 Mb with no discernible phenotypic effect. *Am J Med Genet A.* 152A: 1764–1769.
4. Bart L Loeyts, Harry C Dietz, Alan C Braverman, Bert L Callewaert, Julie De Backer, et al. (2010) The revised Ghent nosology for Marfan Syndrome. *J Med Genet* 47: 476-485.
5. Parrott A, James J, Goldenberg P, Hinton RB, Miller E, et al. (2015) Aortopathy in the 7q11.23 microduplication syndrome. *Am J Med Genet A* 167A : 363-370.