

The Contribution of Aneusomy 15q25-qter to the Etiology of the Shprintzen-Goldberg Syndrome

David Tegay¹, Peter Papenhausen², James Tepperberg², Odelia Nahum³, Peter Warburton⁴, Beth Pletcher⁵, Alan Shanske⁶ and Brynn Levy³

¹NY Col Osteopathic Med at NYIT, Old Westbury, NY; ²LabCorp Inc. Cytogenetics, RTP, NC; ³College of Physicians and Surgeons of Columbia University, New York, NY; ⁴Department of Human Genetics, Mount Sinai school of Medicine; ⁵Newark, NJ; ⁶Center for Craniofacial Disorders, Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY.



INTRODUCTION

The hallmark of the Shprintzen-Goldberg syndrome (SGS) is craniosynostosis & marfanoid habitus. Additional clinical features include: scaphocephaly, ocular proptosis, strabismus, micrognathia, pectus excavatum, camptodactyly of 5th fingers and enlargement of the palatal shelves. The etiology of SGS is uncertain & a single case report links SGS to a mutation in the fibrillin-1 gene (15q21.1).

Centromeres are functionally defined as the chromosomal regions responsible for ensuring the proper segregation of replicated sister chromatids during mitosis and meiosis. All normal human chromosomes contain alpha satellite DNA at their centromeres. Neocentromeres are new centromeres that have formed on low or single copy DNA and do not contain satellite DNA, yet they have fully formed kinetochores containing all the normal functional kinetochore proteins thus far examined. Neocentromeres provide mitotic stability to rearranged or marker chromosomes that have separated from endogenous centromeres and would normally be acentric and lost. The formation of neocentromeres often results in partial tetrasomy.

We report 3 cases of partial tetrasomy of the distal segment of the long arm of chromosome 15, all in the form of a neocentric marker chromosome. All patients have a distinctive phenotype that strongly resembles the Shprintzen-Goldberg syndrome.

CLINICAL REPORT

CASE 1

The proband (Fig.1) was the 2317g product of a 37 week IVF pregnancy in a 37 year old gravida 5, para 1031 mother. She was 47 cm long with a head circumference of 32 cm. She had a dysmorphic skull. Clinical examination showed a horseshoe kidney with hydronephrosis, metopic and bilateral coronal craniosynostoses. She underwent a craniotomy at 5 months of age. When first seen at 4½ years she was noted to have turriccephaly, thoracodorsal scoliosis, absence of digital flexion creases and contractures of fingers 2, 3 and 4 bilaterally, and clinodactyly of both fifth fingers. She was non-verbal and severely developmentally delayed.



Figure 1. Patient at age 4½

CASE 2

The proband (Fig.2) was first evaluated at 32 years of age for overgrowth, marfanoid habitus and mild mental retardation. He was delivered full-term via C-section to a 25 year old gravida 2 para 1001 mother weighing 5900 grams at 63 centimeters in length. He underwent surgery for craniosynostosis at 8 months of age and scoliosis at 29 years of age. Global developmental delay was present with a full-scale WAIS-R IQ of 57. At 32 years old he was 193.5 cm tall with a head circumference of 57cm & dysmorphic features including dolicocephaly, malar flattening, low-set ears, a pseudo-cleft palate, retrognathia, pectus deformity and large hands.

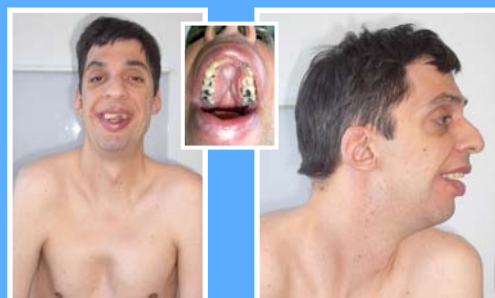


Figure 2. Patient at age 32

CASE 3

The proband (Fig.3) was the 3239 gm product of a full term uneventful pregnancy, born by NSVD to a 30 year old gravida 9 para 6026 mother. In the neonatal period, he had mild respiratory distress requiring CPAP as well as feeding difficulties. At age six years, the patient was noted to have significant postnatal growth retardation with macrocephaly, turriccephaly, a broad nasal root, an extremely high vaulted and narrow palate with a bifid uvula, kyphoscoliosis and an asymmetric thorax with a prominent tail-like coccyx. Extremities were long and thin with fifth finger clinodactyly and flexion contractures of the digits, as well as long overlapping toes. He was non-verbal and severely developmentally delayed, although he was able to communicate needs with gestures.



Figure 3. Patient at age 6

RESULTS

Conventional and Molecular Cytogenetic Studies: Chromosome analysis in all 3 patients revealed a small non-mosaic supernumerary marker chromosome (Figure 4). Conventional CGH analysis was performed on DNA from cases 1 and 2 and SOMA was performed on all three cases using the Affymetrix 500k array. In cases 1 and 2, the CGH ratio profile observed for chromosome 15 appeared significantly over-represented in the 15q24 → qter region suggesting the marker to be disomic for this region resulting in tetrasomy (Figure 5). FISH using a 15q sub-telomeric probe revealed two distinct pairs of signals at each end of the marker, consistent with an inversion duplication of the distal 15q sequences (Figure 6). The 15q probe also hybridized to the telomeric region of each normal chromosome 15, confirming partial tetrasomy for 15q (Figure 6). The absence of alpha satellite DNA on the marker was confirmed by using an "all human centromere" alpha satellite probe which hybridized to all normal human centromeres but did not hybridize to the marker chromosome (Figure 7). The presence of a functional centromere on the marker chromosome was confirmed by immunofluorescence with antibodies to CENP-C, which showed the characteristic double-dot CENP-C kinetochore pattern at the centromeres of all chromosomes including the marker (Figure 7). SOMA confirmed that the neocentric markers were derived from the distal region of chromosome 15 and showed the breakpoints in cases 1-3 to be 15q25.2-qter (17.3Mb) (Figure 8), 15q26.1-q26.3 (11.3Mb) and 15q26.1-qter (16Mb) respectively.

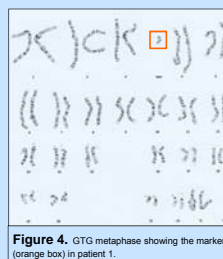


Figure 4. GTG metaphase showing the marker (orange box) in patient 1.

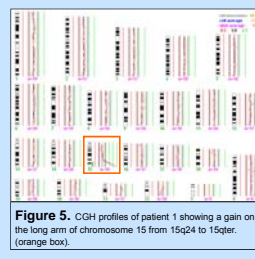


Figure 5. CGH profiles of patient 1 showing a gain on the long arm of chromosome 15 from 15q24 to 15qter. (orange box).

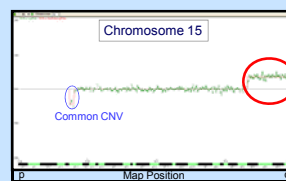


Figure 8. SOMA results for patient 1. Graphic representation of copy number changes for chromosome 15 using CNAT 4.0.1. Log₂ ratios values are plotted in green. Median Log₂ ratio values of all contiguous SNPs in the given Hidden Markov Model (HMM) copy number state segments are plotted in red. The gain of 17.3 Mb in the patient from 15q25.2-qter is circled in red. All other chromosomes showed normal copy number profiles. The deletion at proximal 15q is a commonly observed copy number variant (cnv).

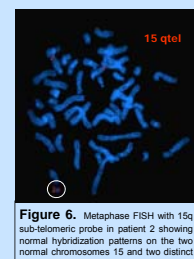


Figure 6. Metaphase FISH with 15q sub-telomeric probe in patient 2 showing normal hybridization patterns on the two normal chromosomes 15 and two distinct pairs of signals at each end of the marker (white circle).

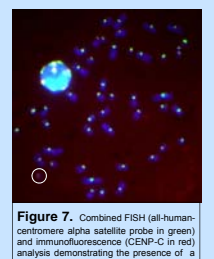


Figure 7. Combined FISH (all-human-centromere alpha satellite probe in green) and immunofluorescence (CENP-C in red) analysis demonstrating the presence of a functional centromere (CENP-C) but absence of alpha satellite sequences on the neocentric marker (white circle).

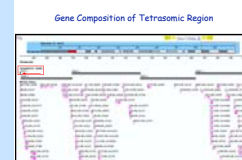


Figure 9. Gene composition of the Tetrasomic Region in Patient 1: Screen shot from the Database of Genomic Variants showing the gene composition of the tetrasomic region.

CONCLUSION

These 3 cases of neocentromeric marker chromosome derived distal 15q tetrasomy sharing classical features of SGS (including intellectual disability, evidence of craniosynostosis, characteristic facial dysmorphism, scoliosis, arachnodactyly and/or finger contractures) add to a small number of similar cases in the medical literature (Hu et al, 2002; Rowe et al, 2000; Blennow et al, 1994), though only 1 was classified as SGS. Despite initial case reports of occasional Fibrillin1 gene mutations in SGS cases, further studies attest to its rarity (Robinson et al, 2005) while the SGS diagnosis has been questioned in TGFB2 mutation cases (Kosaki et al, 2006; Van Steensel et al, 2007; Stheneur et al, 2008), leaving some to consider the etiology of SGS unknown. Growing numbers of distal tetrasomy 15q and trisomy 15q (q25-qter) cases with rather classical SGS-like phenotypes, without direct Fibrillin/TGFB2 involvement, suggest alternative molecular mechanisms for SGS. The 15q25-26 region is rich in segmental duplications which may promote rearrangements of this area. Future studies must explain how gene dosage effects or dysregulation of genes in 15q25-qter contribute to the SGS phenotype.