**DA-DAPI Staining**

Only 2 other cases reported

**Chromosome 6 Marker – Counseling Issues**
Chromosome 6 Marker – Case 1

35 yr Male
- Severe MR & Seizures
- Unusual facies, thick lips w/ lower lip everted
- Scoliosis
- Truncal obesity
- Soft skin, lax joints
- Thick tapering fingers
- Marker CEP 6 + / wcp +

Chromosome 6 Marker – Case 2

Infant
- Ascertained b/c of IUGR @ 35wks – Delivery @ 38wks
- Severe Transient Neonatal Diabetes
- No other significant clinical features
- Marker CEP 6 + / wcp +
- rev. ish – 6p21.2-6q10
- UPD of normal chr 6 homologues

First report of partial tetrasomy 10p resulting from an anaiphoid marker chromosome with a neocentromere.
Trisomy 10p Syndrome - Clinical Features

- Distinct craniofacial anomalies
- Various organ malformations
- Skeletal abnormalities
- Bilateral foot deformities
- Flexion abnormalities, especially talipes-equinovalus
- Severe mental and psychomotor retardation
- Developmental delay
- Seizures
- Hypotonia

Tetrasomy 10p – Clinical Features

- No major structural abnormalities were apparent on a high resolution ultrasound or on a fetal echocardiogram.
- Detailed examination of the POC revealed a relatively normal phenotype with development appropriate for that stage of gestation.
- The absence of any major anatomical anomalies suggests that many of the clinical findings of trisomy 10p may be due to partial aneuploidy of regions more proximal than 10p15/14.
- It is also possible that partial aneuploidy, in the form of an analphoid SMC with a neocentromere, may give rise to an entirely different phenotype due to the chromatin remodeling of endogenous chromosomal material to facilitate the formation of the neocentromere. In such a case, the creation of a neocentromere may effectively inactivated certain genes which, in the aneuploid state, contribute to the features observed in the trisomy 10p syndrome.

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In any event, the absence of major structural anomalies does not eliminate the risk of other features such as mental/psychomotor retardation, developmental delay and seizures.

47,XY,+mar (is it ???)
Steps Taken to Work up Marker

• SKY – Positive for chromosome 13
• CEP 13 – Negative
  – Conclusion: Neocentromere 13
  – Plan: Define using CGH

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4 Cell Lines:
- 46,XY
- 47,XY,+mar1 (3)
- 47,XY,+mar2 (13)
- 48,XY,+mar1,+mar2

Original Karyotype
- 46,XX,dup(4)(q33q34)

Revised Karyotype
- 46,XX,add(4)(q35).rev ish der(4)t(4;13)(q35;q32) enh(13)(q32qter)
**Patient Details:**
- Developmental Delay
- Microcephaly
- Bilateral Colobomas (w/eye size discrepancy)
- VSD
- Hydronephrosis
- Bilateral undescended testes
- Bilateral hip dysplasia
- 5th finger clinodactyly
- Low set ears
- Hypertelorism

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**Chromosomal Insertion**

**CGH Workup of Insertion 4**

**Validation of CGH Findings in Insertion 4 Case**

**CGH in a patient with an “Apparently Balanced Translocation” and Clinical Abnormalities**
Distal Trisomy 4q syndrome Inherited from a Phenotypically Normal Mother with Mosaicism

A Normal Cell Line

B Abnormal Cell Line

- Metaphase showing 3 signals of 4q35.2, with the 3rd signal inserted into the long arm of chromosome 9 between 9q34 and 9q telomere.

Centromeres & Neocentromeres

- 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.
- Neocentromeres often result in partial trisomy or tetrasomy because their formation confers mitotic stability to acentric chromosome fragments that would normally be lost.
Clinical Features of the Shprintzen-Goldberg Syndrome

- Scaphocephaly
- Ocular proptosis
- Strabismus
- Micrognathia
- Pectus excavatum
- Arachnodactyly
- Camptodactyly of 5th fingers
- Enlargement of palatal shelves

Case 1- Clinical Features

At Birth:
- 2317g product of a 37 week IVF pregnancy in a 37 year old gravida 5, para 10 mother
- She was 47 cm long with a head circumference of 32 cm
- Dysmorphic skull
- Horseshoe kidney with hydronephrosis, metopic and bilateral coronal craniosynostoses (craniotomy at 5 months)

At 4.5 years:
- Turricephaly
- Thoracodorsal scoliosis
- Absence of digital flexion creases and contractures of fingers 2, 3 and 4 bilaterally
- Clinodactyly of both fifth fingers
- Non-verbal and severely developmentally delayed

Case 2- Clinical Features
**Case 1- Cytogenetic Findings**

**Amniocentesis:**
- Revealed mosaicism for a small marker chromosome

**Case 1- Molecular Cytogenetic Findings**

**Postnatal:**
- Painting with multiple whole chromosome paints (wcp) revealed the marker to be derived from chr. 15
- PW/AS probe negative
  - Marker lacks 15 centromeric alpha satellite
  - Marker does not contain 15q11-q13 region (PW/AS)
  - Marker does not contain 15q22 region (PML)
- Molecular cytogenetic analysis using Comparative Genomic Hybridization (CGH) showed an overrepresentation of 15q24-qter, consistent with tetrasomy of this region
- Tetrasomy confirmed using a subtelomeric probe for 15q
- The marker was positive for CENP-C indicating the presence of a functional centromere and thus confirming the presence of a neocentromere
PML (15q22)
15q tel

Case 2- Cytogenetic Findings

Peripheral Blood:
- Revealed small marker chromosome
- NOR negative
- C-band negative

Case 1- Molecular Cytogenetic Findings

Postnatal:
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  - Marker does not contain 15q22 region (PML)
- Tetrasomy confirmed using a subtelomeric probe for 15q
- CENP-C studies pending
Mechanism Leading to SGS

- Dietz et al. (1995) found that SGS is associated with mutation in the fibrillin-1 gene (15q21.1), the same gene that is mutant in the Marfan syndrome.
  - One of their patients was a 7-year-old girl with typical ocular, skeletal, and cardiovascular features of Marfan syndrome.
  - Hypotonia, scaphocephaly with craniosynostosis, low-set anomalous ears, hyperelastic skin, diastasis recti, and mental retardation.
  - She was found to have a 3668G-A transition in the FBN1 gene, resulting in a cys1223-to-tyr substitution within one of the repetitive EGF-like domains.
  - The mutation was heterozygous and was a de novo event.

Distal 15q Neocentromeres & SGS

- Gene regulation of FBN1 gene (15q21.1) by genes in 15q24-qter region.
- Gene dosage versus actual presence of neocentromere?
  - Trisomy vs tetrasomy.
- FBN1 gene is not etiology of SGS.
  - SGS due to dysregulation of genes in 15q24-qter?