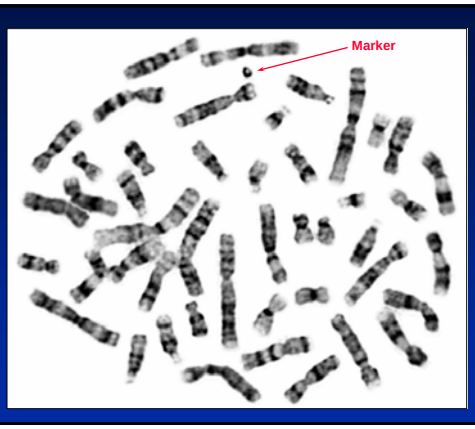
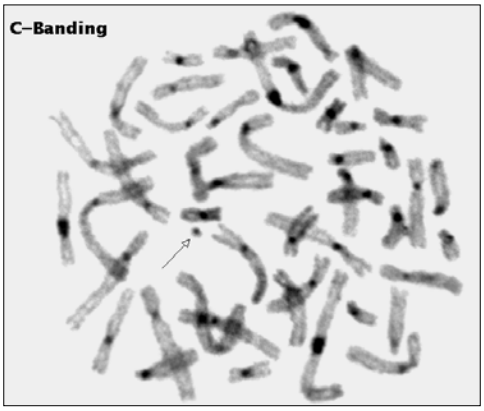
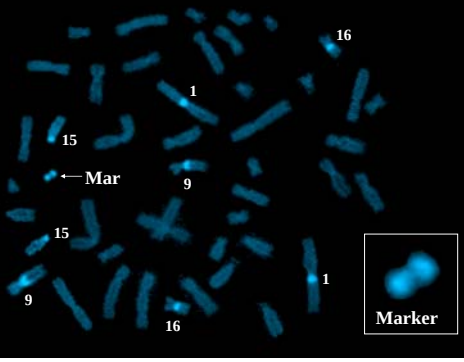
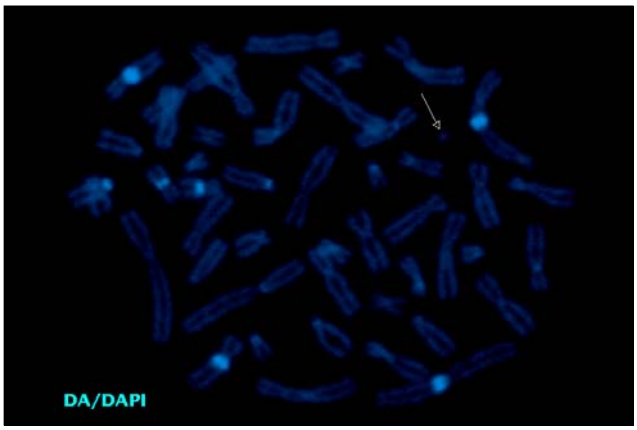
FIRST PRENATAL

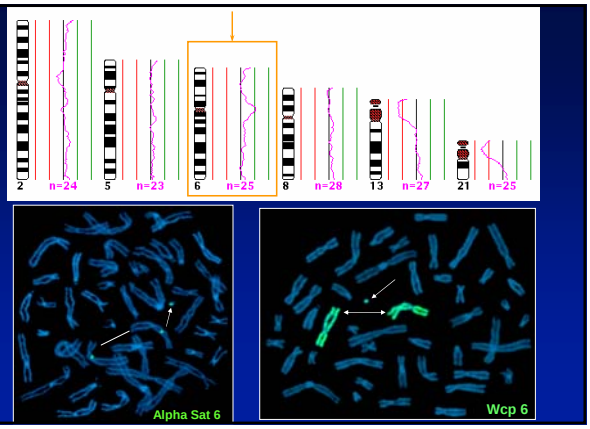




DA-DAPI Staining







Chromosome 6 Marker – Counseling Issues

Only 2 other cases reported

Chromosome 6 Marker – Case 1

35 yr Male

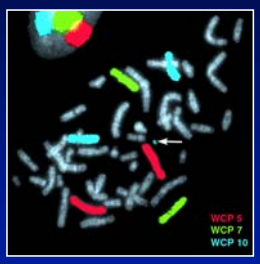
- Severe MR & Seizures
- Unusual facies, thick lips w/ lower lip everted
- Scoliosis
- Truncal obesity
- Soft skin, lax joints
- Thick tapering fingers
- Marker CEP 6 + / wcp +

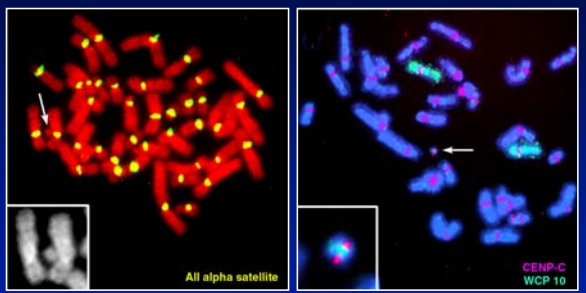
Chromosome 6 Marker – Case 2

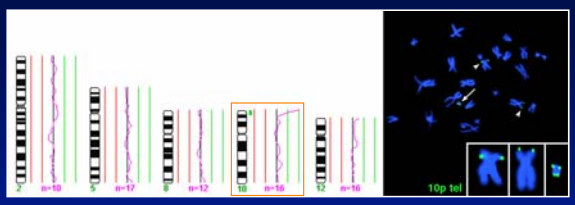
Infant

- 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

47,XY,+mar







First report of partial tetrasomy 10p resulting from an analphoid 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-equinovarus
- 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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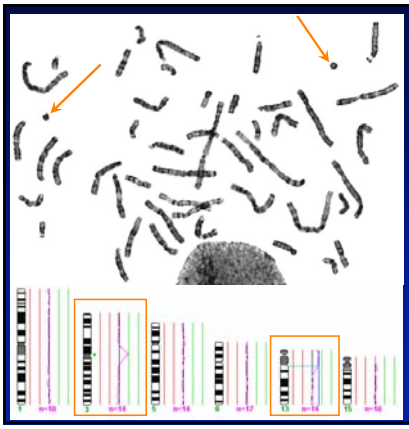
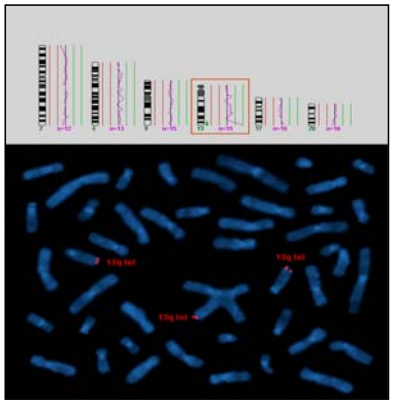
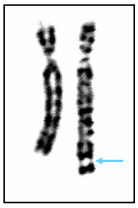


4 Cell Lines:

46,XY
47,XY,+mar1 (3)
47,XY,+mar2 (13)
48,XY,+mar1,+mar



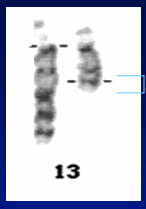


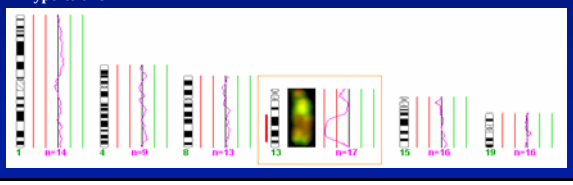
Original Karyotype
46,XX,dup(4)(?q33q34)

Revised Karyotype
46,XX,add(4)(q35),rev ish der(4)t(4;13)(q35;q32) enh(13)(q32qter)

Patient Details:

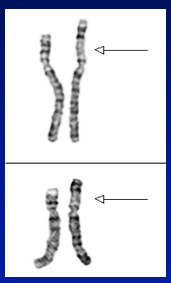
- Developmental Delay
- Microcephaly
- Bilateral Colobomas (w/ eye size discrepancy)
- VSD
- Hydronephrosis
- Bilateral undescended testes
- Bilateral hip dysplasia
- 5th finger clinodactyly
- Low set ears
- Hypertelorism

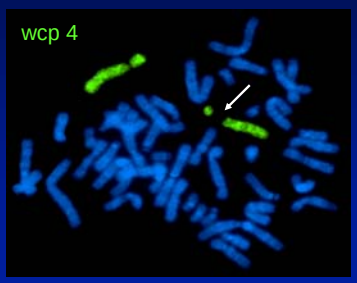




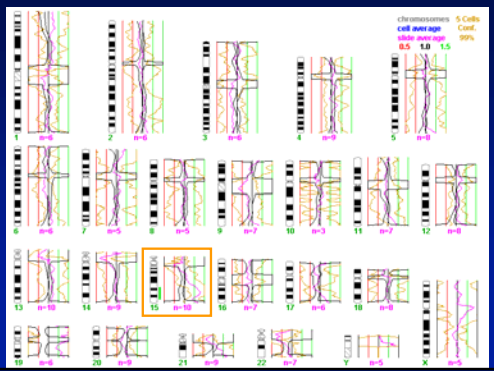
38

Chromosomal Insertion

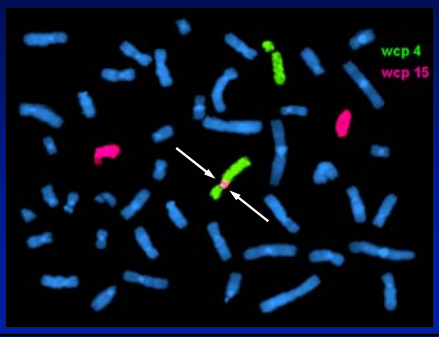




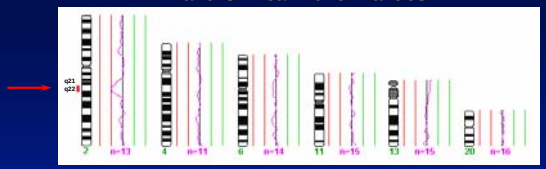
CGH Workup of Insertion 4

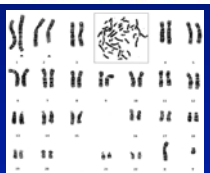


Validation of CGH Findings in Insertion 4 Case



CGH in a patient with an "Apparently Balanced Translocation" and Clinical Abnormalities

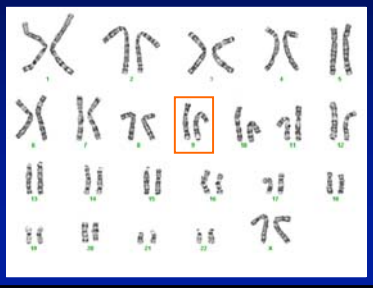


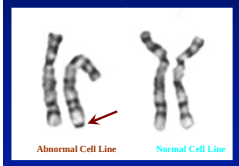


Initial Karyotypic Designation
46,XY,t(1;2)(p22;q14.1)

Distal Trisomy 4q syndrome Inherited from a Phenotypically Normal Mother with Mosaicism

Distal Trisomy 4q syndrome Inherited from a Phenotypically Normal Mother with Mosaicism





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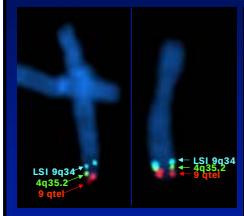
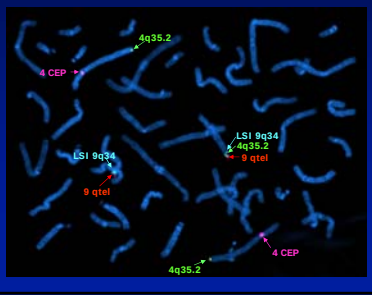


Metaphase showing 3 signals of 4q35.2, with the 3rd signal inserted into the long arm of chromosome 9 between 9q34 and 9q telomere.



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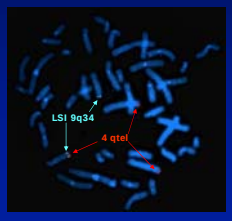


Centromeres & Neocentromeres

- 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 tri-or terasomy 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

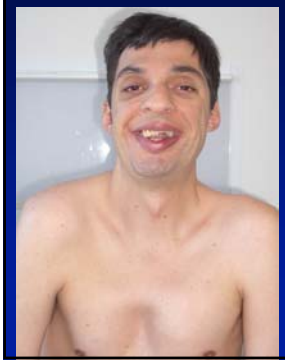
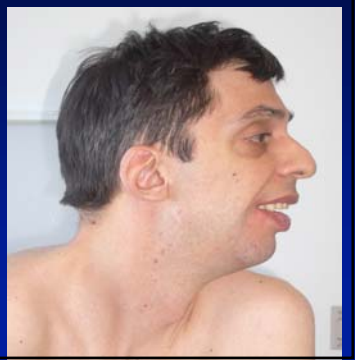
At Birth:

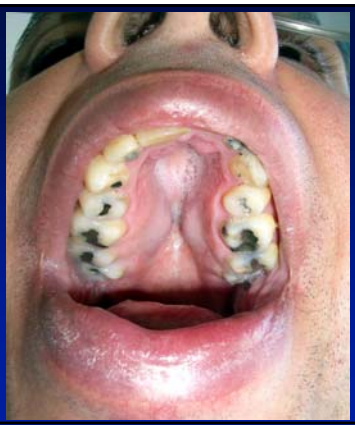
- 2317g product of a 37 week IVF pregnancy in a 37 year old gravida 5, para 1031 mother
- She was 47 cm long with a head circumference of 32 cm
- Dysmorphic skull
- Horseshoe kidney with hydronephrosis, metopic and bilateral coronal craniosynostoses (craniotomy at 5 months)

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

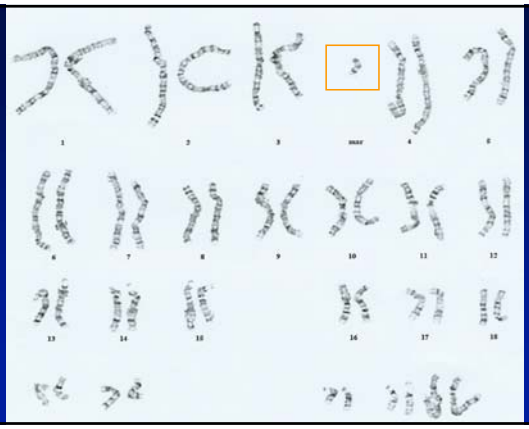





Case 1- Cytogenetic Findings

Amniocentesis:

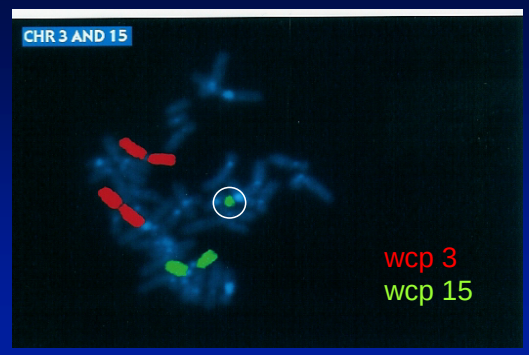
- Revealed mosaicsm for a small marker chromosome

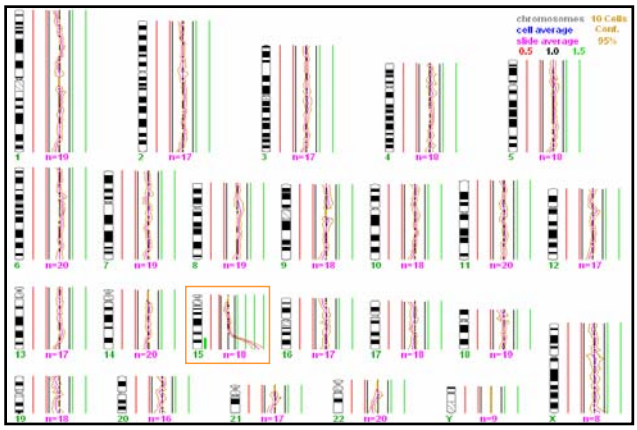


Case 1- Molecular Cytogenetic Findings

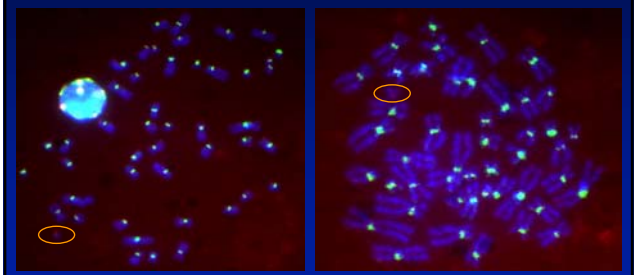
Postnatal:

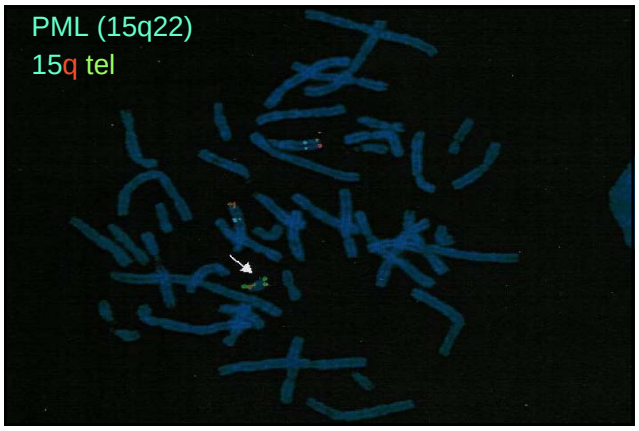
- Painting with multiple whole chromosome paints (wcp) revealed the marker to be derived from chr. 15
- PW/AS probe negative
  - Marker lacks 15 centromeric alpha satellite
  - Marker does not contain 15q11-q13 region (PW/AS)
  - Marker does not contain 15q22 region (PML)
- Molecular cytogenetic analysis 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





Neo 15q – CENP C & Alpha Satellite





Case 2- Cytogenetic Findings

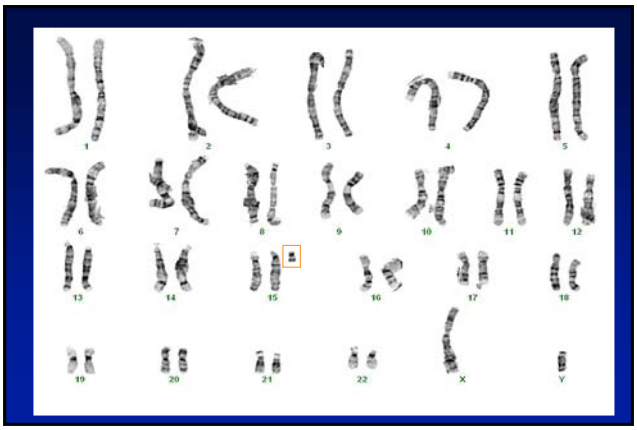
Peripheral Blood:

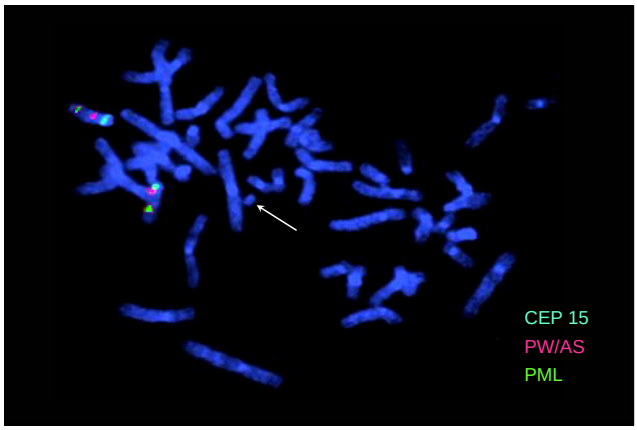
- Revealed small marker chromosome
- NOR negative
- C-band negative

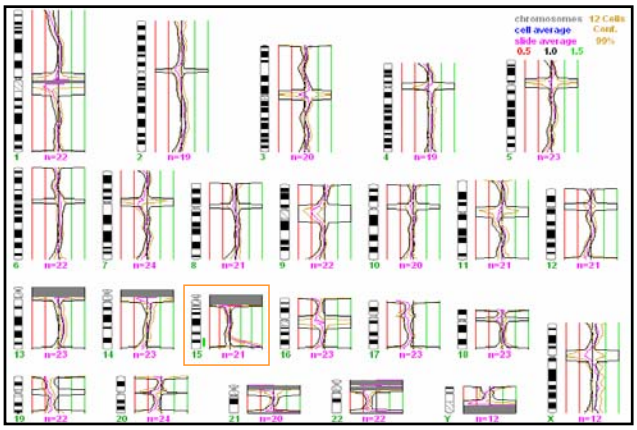
Case 1- Molecular Cytogenetic Findings

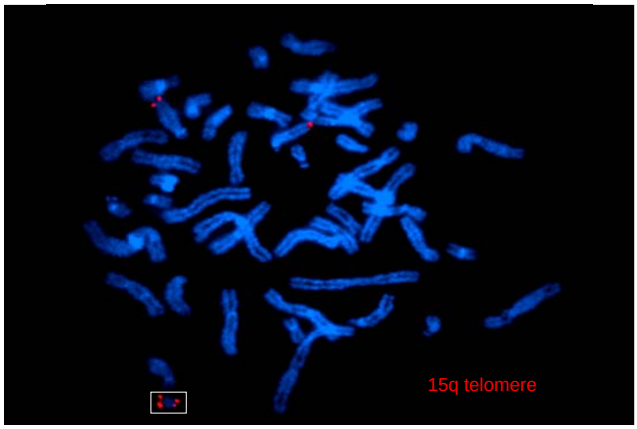
Postnatal:

- Molecular cytogenetic analysis using Comparative Genomic Hybridization (CGH) showed an overrepresentation of 15q24-qter, consistent with tetrasomy of this region
- 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)
- 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 ?