

# Proximal 18q- Treatment and Surveillance

ICD-10 = Q99.9 or Q93.89

*These recommendations are inclusive of the entire population of people with Proximal 18q deletions even though each person has a unique deletion. Therefore each person's deletion could have different genes that are hemizygous. The specific hemizygous genes for an individual patient will dictate the probability of particular phenotypes. Guidance for creating an individualized plan for evaluation and management based on the person's specific deletion can be found in the next section. However, the information in this document encompasses the global proximal 18q- evaluation and management plan.*



**Proximal 18q-** (18q11.2-q21.1)  
An interstitial deletion within the region between 20,000,000 and 45,700,000 bp;\* a region that includes 80 genes

\*hg 19 nucleotide scale

## Potential conditions in a neonate

- Structural
  - Palate abnormality
- Functional
  - Respiratory difficulties
  - Feeding difficulties
  - Central apnea
  - Hypotonia
- Biochemical
  - Jaundice

## Initial evaluations

- Cardiology evaluation -50% have cardiac defects
- Hearing evaluation - 30% with hearing deficits
- Renal ultrasound -43% with reflux
- Vision evaluation - 64% with optic problems
- MRI – 62% abnormal findings

## Referrals to

- Appropriate subspecialist as indicated by initial evaluations
- Genetics Follow-up
  - Parents genotyped for balanced rearrangements
- Early intervention/developmental services
- The Chromosome 18 Registry & Research Society
- The Chromosome 18 Clinical Research Center

## Closely monitor and manage

- Failure to thrive/ growth failure
  - Weight gain
  - Linear growth
- Sinus/ ear infections
- Genitourinary:
  - Reflux
- Gastrointestinal
- Immunology/Rheumatology:
  - Atopic disorders
- Orthopedics
  - Scoliosis
- Respiratory issues
- Neurology:
  - Seizure disorder
  - Tremors
  - hypononia
- Development:
  - Milestones
  - Psychometric data

## Annual Screenings

- Vision
- Hearing

## Current Adult Status

## Age and Cause of Death

## **Potential conditions in a neonate**

- **Structural**
  - Palate abnormality
    - 1 each; cleft palate, micrognathia
- **Functional**
  - Respiratory and feeding difficulties – 22%
  - Feeding difficulties
  - Central apnea – 10%
  - Hypotonia – 88%
- **Biochemical**
  - Jaundice – 20%

## **Initial evaluations**

- **Cardiac exam**
  - 50% had a cardiac abnormality and of those
    - 50% with heart murmur
    - 22% with VSD
    - 22% with patent foramen ovale
    - 11% with coarctation of the aorta
    - 11% with pulmonic stenosis
    - 11% with Tetralogy of Fallot
  - The actual incidence of heart defects may be higher as ultrasound and ECG evaluations have not been consistently been performed on all affected individuals.
- **Audiology**
  - 27% with hearing loss– Conductive, sensorineural or mixed
- **Renal ultrasound**
  - 50% with hydronephrosis
  - 30% with vesicoureteral reflux
- **Ophthalmology**
  - 40% with strabismus
  - 9% with nystagmus
  - 22% with myopia
  - 11% with Hyperopia
- **MRI**
  - 22% with delayed myelination
  - 37% with small corpus callosum
  - 37% with Virchow-Robin periventricular spaces
- There is no reason to think that they are at increased risk for surgical or anesthesia complications although they may need increased monitoring due to hypotonia.

## **Referrals to:**

### **• Genetics Follow-up**

- Genetics follow-up may be necessary if parental chromosomes have not been evaluated to rule out inherited rearrangement. 3% of the participants in our study have a parent with a balanced rearrangement. Even if no other children are planned, if one parent has a balanced rearrangement then their other children or the siblings of that parent are a risk for having the same rearrangement and consequently have a very high risk of passing on an unbalanced chromosome complement.
- A genetics follow-up may also be indicated if the original diagnosis was performed using cytogenetic techniques or low resolution microarray technology. A high resolution SNP or CGH microarray can determine exactly which genes are involved in the deletion. This information will become increasingly important over time as gene-specific interventions are developed.

### **• Early intervention/developmental services**

- All children with chromosome 18 abnormalities are at significant risk for developmental delay. Prompt referral to a program that includes physical, occupational and speech therapy is important in order to maximize their development.
- 100% with developmental delay
- 100% with intellectual disability
- 89% with speech delay
- 88% with hypotonia

### **• Referral to Chromosome 18 Registry & Research Society**

- The Chromosome 18 Registry is a parent support organization that provides family members with the opportunity to meet and learn from those who have gone before them. These are complex conditions to manage even in the least affected children making the establishment of a network of support a crucial component for maximizing the affected child's potential. The Registry has annual national and international conferences, regional get-togethers and social media outlets, all with programs for parents, siblings and affected adults. The Registry works closely with and financially supports the Chromosome 18 Clinical Research Center. ([www.chromosome18.org](http://www.chromosome18.org))

### **• Referral to the Chromosome 18 Clinical Research Center**

- The goal of the Chromosome 18 Clinical Research Center is to make the chromosome 18 abnormalities the first treatable chromosome abnormalities. Anyone with any chromosome 18 abnormality is eligible to enroll and encouraged to enroll. Once enrolled, participants have the opportunity to be involved in longitudinal studies of developmental progress, and when available, other studies that could include surveys or treatment trials. Families enrolled in the Research Center will also be the first to know new information about the conditions when it becomes available. Enrollment is a key part of proactive clinical management ([www.pediatrics.uthscsa.edu/centers/chromosome18](http://www.pediatrics.uthscsa.edu/centers/chromosome18))

## Closely monitor and manage

### • **Failure to thrive/ growth failure**

#### • Weight gain

Due to their hypotonia, suckling or feeding may be more difficult for the child. In addition, many affected children have gastroesophageal reflux, which increases not only their risk for aspiration, but also for pain, discomfort or emesis after feeding. Children <3 years who are failing to meet expected rates of weight gain, they should be evaluated for reflux and potentially for placement of a feeding tube

#### • Linear growth

- 14% are growth hormone deficient
- Children that are failing to grow linearly (length or height) at expected rates for age and sex should be tested using growth hormone stimulation (provocative) testing. This testing is typically done by a pediatric endocrinologist.
- All treated individuals responded to GH replacement therapy (0.3 mg/kg/week) with rates of growth comparable to children with classical isolated GH deficiency

### • **Sinus/ ear infections**

- 60% had chronic otitis media
- 30% had recurrent sinus infections
- American Academy of Otolaryngology recommends antibiotic treatment for 10 days for otitis media and 14 days for sinusitis

### • **Genitourinary**

- Renal anomalies and ureteral reflux are more frequent in children with proximal 18q. Affected children should have a renal ultrasound at the time of initial evaluation and referral to an pediatric nephrologist or urologist if abnormalities are noted. Affected children who have recurrent urinary track or kidney infections should have urodynamic studies.

### • **Gastrointestinal**

- 30% have GE reflux
- 20% have constipation
- 10% had a fundoplication

### • **Allergy/Immunology**

- 50% had Eczema

### • **Orthopedics**

- 12% have Scoliosis

### • **Pulmonology**

- 10% had asthma
- 20% obstructive sleep apnea
- 10% had tracheomalacia
- 10% has aspiration pneumonia

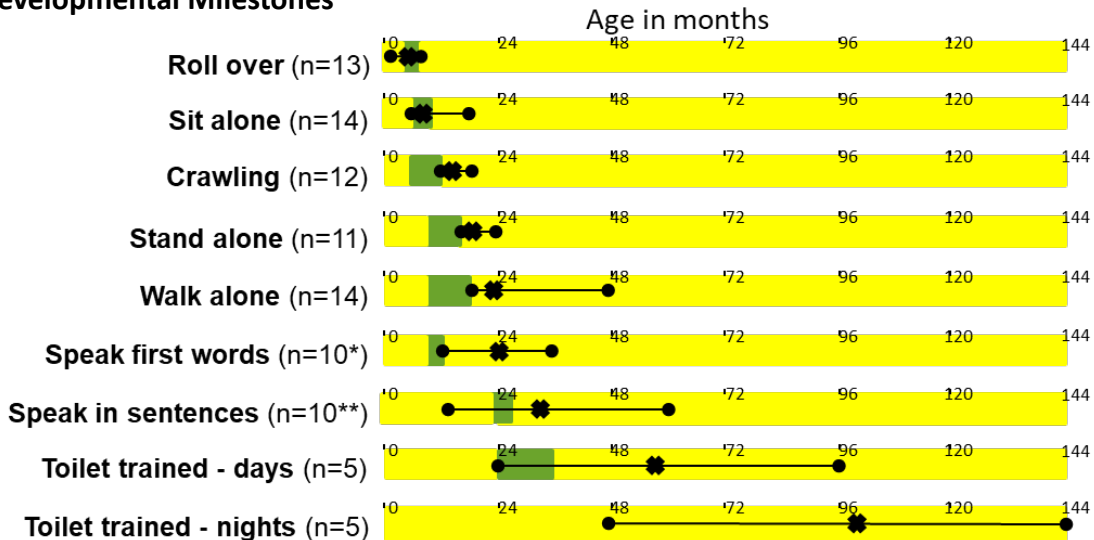
# Milestones

## Closely monitor and manage

### • Neurology

- 100% broad-based ataxic gait
- 88% hypotonia
- 71% seizure disorder. 1 participant with poorly controllable epilepsy died during a seizure at the age of 11.5 years of age.
- 44% tremors
- 10% sleep disordered breathing

### • Developmental Milestones



\*Not included are three do not speak (ages 2, 5, 5)

\*\* Included two who have not spoken in a sentence (ages 6, 9). They should have by now. This is in addition to the three who have not spoken first word.

Adaptive Behavior Assessment System (ABAS) – insufficient data to report at this time.

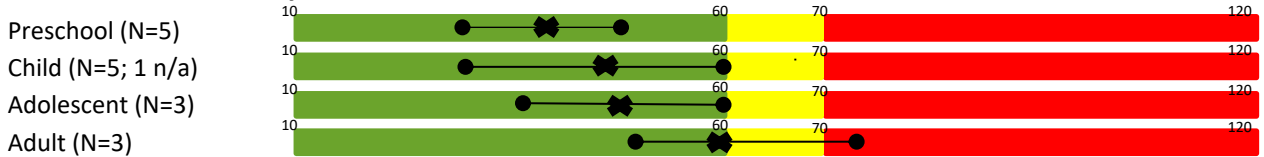
# Proximal 18q-

Within Normal Limits	At Risk	Clinically Significant	✖ = average score ●—● = the range of all the scores N= the number of participants
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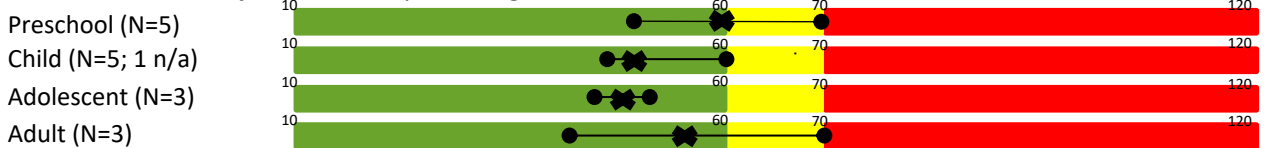
## Data from the Behavior Assessment System for Children and Adults (BASC)

### Internalizing Behaviors (problems that manifest internally)

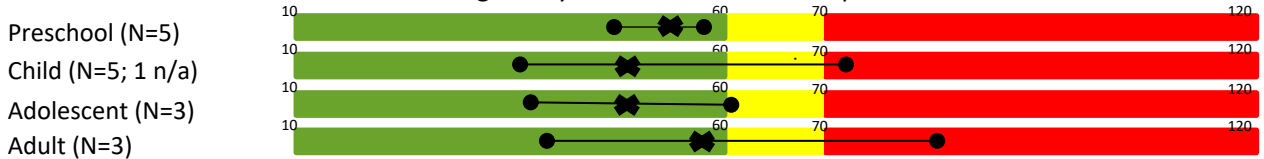
#### Anxiety: nervous, fearful and worrisome tendencies



#### Depression: incapacitating sadness or stress

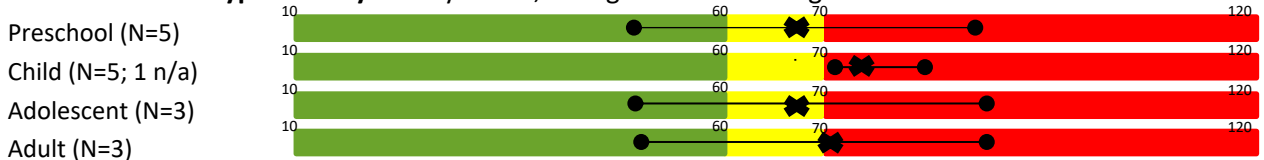


#### Somatization: behaving overly sensitive about minor problems

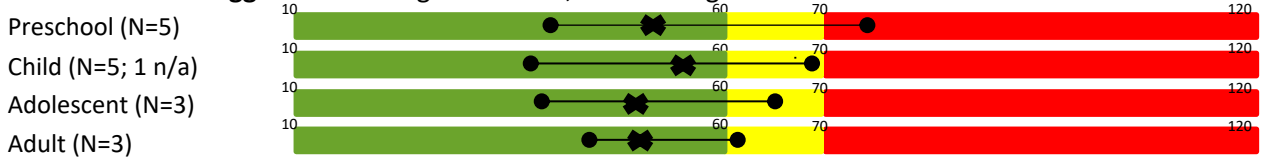


### Externalizing Behaviors (problems that manifest externally)

#### Hyperactivity: overly active, acting without thinking



#### Aggression: acting in a hostile, threatening manner



#### Conduct Problems: anti-social and rule-breaking behaviors



# Proximal 18q-

## Data from the Behavior Assessment System for Children and Adults (BASC) - continued

### Adaptive Skills: skills learned and used in daily life

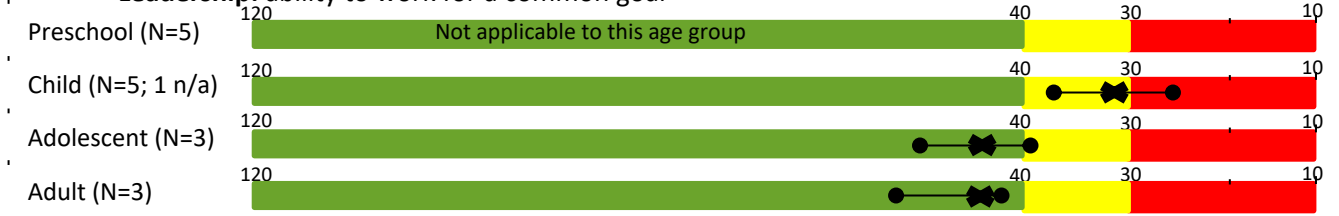
#### Adaptability: ability to adapt to change



#### Social Skills: interacting with peers



#### Leadership: ability to work for a common goal



#### Functional Communication: expressing ideas in a way understood by others



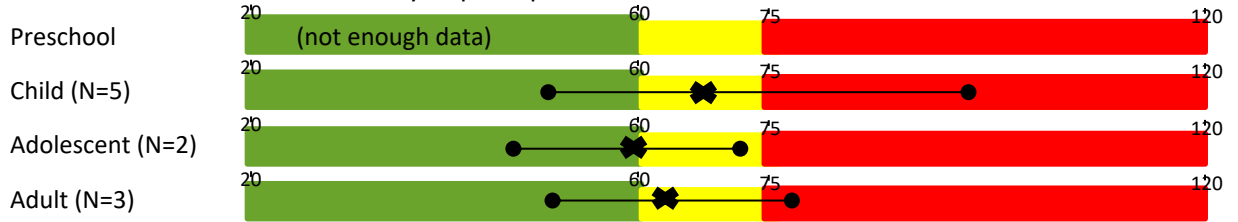
#### Activities of Daily Living: performing basic tasks safely



# Proximal 18q-

## Social Responsiveness Scale (SRS)

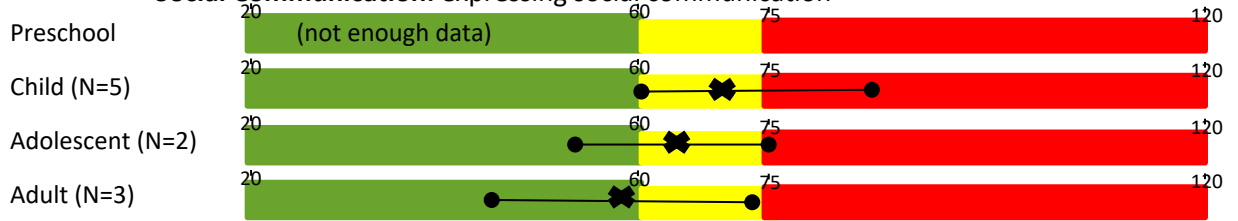
### Social Awareness: ability to pick up on social cues



### Social Cognition: interpreting social cues



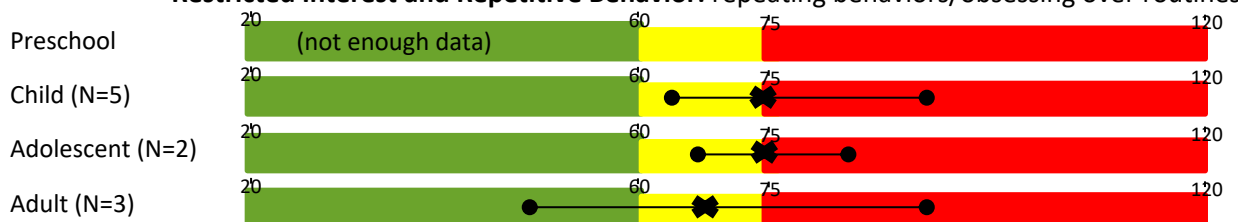
### Social Communication: expressing social communication



### Social Motivation: motivation to engage in social behavior



### Restricted Interest and Repetitive Behavior: repeating behaviors/obsessing over routines





# Proximal 18q- Behavior Rating Inventory of Executive Function (BRIEF)

**Behavioral Regulation:** ability to regulate and monitor behavior effectively

**Inhibit:** inhibiting behavior or not acting on an impulse



**Self-Monitor:** understand the effect of behaviors on others



**Emotional Regulation:** ability to regulate emotional responses

**Shift:** move from one situation to another



**Emotional Control:** modulating emotional response

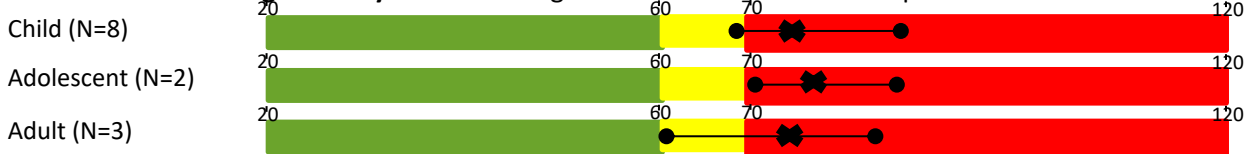


**Cognitive Regulation:** ability to control and manage cognitive processes and problem solve effectively

**Initiate:** beginning tasks



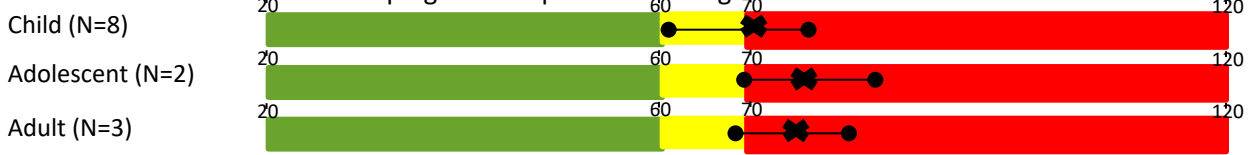
**Working Memory:** remembering information in order to complete a task



**Plan / Organize:** managing current and future orientated tasks



**Task Monitor:** keeping track of problem solving successes or failures



**Organization of Materials:** keeping work and living spaces orderly



- **Adult Status**
  - **(>18 years of age)**

Total N=8

Received Responses: N=4

No Contact or No Response: N=3

Deceased: N=1

LIVING ARRANGEMENTS

Lives with parents/guardians	3
Lives away from parents in a residence as part of a supervised independent living program	1

HIGHEST EDUCATION LEVEL

Did not complete high school	1
Completed high school (certificate)	1
Currently attends centers based/transitional program post high school	2

MARITAL STATUS

Married (Yes)	0
Married (Never)	4

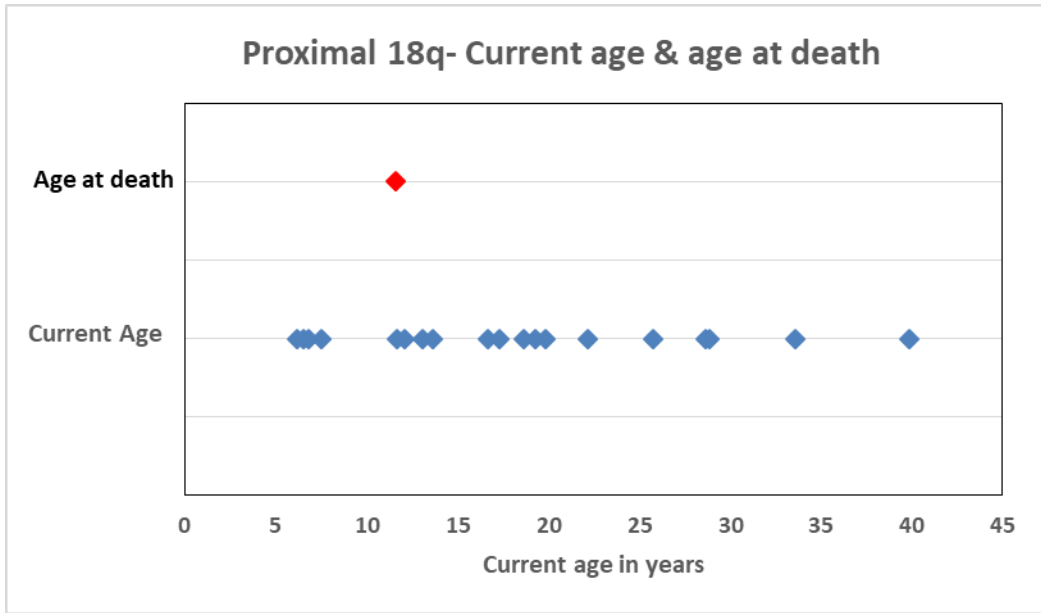
CHILDREN

Children (Yes)	0
Children (No)	4

WORK POSITIONS

Part Time PAID and Volunteer	1
Part Time UNPAID	1
Through school (work study, etc...)	1
Attends day habilitation program	1

- **Annual screenings**
  - Vision
  - Hearing
    - 27% have hearing loss –  
Conductive, sensorineural or  
mixed



Proximal Interstitial			
Age deceased	Gender	Cause of death	Past medical history
11 years 7 months	M	Seizure complications	At 5 months parents report that he has never breathed normally; plagiocephaly; spastic cerebral palsy; dysphagia-G-tube; nissen fundoplication; epilepsy; pneumonia several times-aspirating; feeding studies-aspirating; obstructive apnea; allergic to mold, morphine and codeine; hiatal hernia.; heart murmur

## **References**

Cody JD, Sebold C, Malik A, Heard P, Carter E, Crandall A, Soileau B, Semrud-Clikeman M, Cody CM, Hardies LJ, Li J, Lancaster J, Fox PT, Stratton RF, Perry B, Hale DE. (2007) Recurrent interstitial deletions of proximal 18q: a new syndrome involving expressive speech delay. Am J Med Genet 143A:1181–1190, doi: 10.1002/ajmg.a.32557.

Cody JD, Carter EM, Sebold C, Heard PL, Hale DE. (2009) A gene dosage map of chromosome 18: a map with clinical utility. Genet Med 11:778–782, doi:10.1097/GIM.0b013e3181b6573d.

Heard PL, Carter EM, Crandall AC, Sebold C, Hale DE, Cody JD. (2009) High resolution genomic analysis of 18q– using oligo-microarray comparative genomic hybridization (aCGH). Am J Med Genet 149A:1431–1437, doi:10.1002/ajmg.a.32900.

Perry B, Sebold C, Hasi M, Heard P, Carter E, Gelfond J, Hale DE, Cody JD. (2013) Sensorineural hearing loss in people with deletions of 18q. Otol Neurotol. 2014 Jun;35(5):782-6. doi: 10.1097/MAO.0000000000000363. PubMed PMID: 24662633; PubMed Central PMCID: PMC4170734.

Soileau B, Hasi M, Sebold C, Hill A, O'Donnell L, Hale DE, Cody JD. (2014) Adults with Chromosome 18 Abnormalities. J Genet Couns. 24:663-674