THE CHROMOSOME 18 REGISTRY & RESEARCH SOCIETY

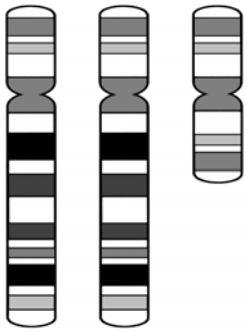
Tetrasomy 18p

Sixty-Second Summary

(Aliases: isochromosome 18p)

ICD-10 = Q93.2

UT Health San Antonio
The Chromosome 18 Clinical Research Center



Tetrasomy 18p

This condition is caused by an extra chromosome composed of 2 chromosome 18 p arms (i.e. an isochromosome). This results in a total of 4 copies of each of the genes on 18p. The p arm of chromosome 18 has 67 genes. Little is known about how the presence of four copies of these genes directly relates to the clinical features associated with Tetrasomy 18p. Therefore, we base our recommendations on descriptive studies of individuals with this condition

Key points on genotype

- Nearly all individuals with Tetrasomy 18p have the same genotype
- Definitive diagnosis requires:
    - A chromosome microarray to determine the precise region of net copy number change
    - A karyotype to demonstrate that the copy number change is due to an isochromosome
- Almost all are *de novo* events as opposed to inherited from a parent
- There have been a few case reports of parents with mosaicism or with a chromosome rearrangement
- Parents may consider chromosome analysis to better define risks for future pregnancies

Key Points on phenotype

- Most individuals are not medically fragile
- Developmental delay is very common
- The average full scale IQ score is 48, though there is a wide range of ability
- Behavioral concerns are common
- Life expectancy is believed to be near normal
- Congenital anomalies are possible. Specifically, individuals with Tetrasomy 18p have an increased likelihood of myelomeningocele, heart defects, hernias, palate abnormalities and orthopedic abnormalities

Follow-up

- Affected individuals do not appear to be at increased risk for adverse reactions to drugs or standard medical treatments
- Recommendations for specific evaluations and treatments are in the following sections

Enrollment

- The Chromosome 18 Clinical Research Center is enrolling anyone with any chromosome 18 abnormality in our longitudinal study of all aspects of the conditions
- Parents may contact Annice Hill at hilla3@uthscsa.edu or call (210) 567-5321
- Enrollment requires the diagnostic genetics report and any other informative medical records

Consultation

- Daniel Hale, MD, Medical Director of the Chromosome 18 Clinical Research Center can be reached through Annice Hill at hilla3@uthscsa.edu or call (210) 567-5321

Updated 2018

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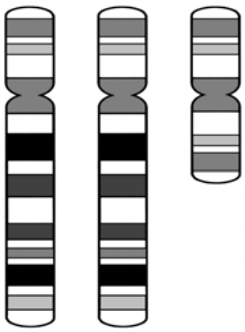
Tetrasomy 18p
Treatment and Surveillance

ICD-10 =Q93.2

These recommendations are inclusive of the entire population of people with Tetrasomy 18p. It should be noted that there is a great deal of variation among individuals with Tetrasomy 18p. Not all complications or concerns will be listed in this document. However, the recommendations contained here should be used as a baseline for monitoring and the health of individuals with Tetrasomy 18p



Potential conditions in a neonate:

- Structural
  - Palatal anomalies – 81%
  - Heart abnormalities – 47% by Echo/ECG
  - Congenital orthopedic abnormalities – 45%
  - Hernias – 12%
  - Myelomeningocele – 7%
- Functional
  - Feeding problems – 83%
  - Respiratory distress – 31%
- Biochemical
  - Jaundice – 57%

Initial evaluations after diagnosis:

- Ophthalmology
  - Strabismus – 75%
  - Refractive errors – 71%
- Audiology/Otolaryngology
  - Hearing loss – 32%
  - Recurrent otitis media – 57%
- Genitourinary
  - Cryptorchidism – 63%
  - Hypospadias – 7%
  - Urinary tract anomalies – 28%

Immediate Referrals to:

- Appropriate subspecialist as indicated by initial evaluations
- Genetics follow-up if not previous to diagnosis
- 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
  - Underweight (<3rd percentile)
- Endocrinology
  - Short stature (<25th percentile)
  - Growth hormone deficiency
- Otorhinolaryngology
  - Recurrent otitis media
  - Hearing loss
- Gastroenterology
  - Constipation
  - GE reflux
  - Hernias
  - Eosinophilic esophagitis
- Immunology/Rheumatology
  - Atopic disorders
  - IgA deficiency
  - Eosinophilic esophagitis
- Orthopedics
  - Congenital hip dysplasia
  - Foot abnormalities
  - Decreased bone mineral density
- Development
  - Milestones
  - School performance
- Dental
- Neurology
  - Seizures
  - Hypotonia
- Behavior/mood changes

Annual Screenings:

- Vision
- Hearing

Updated 2019

Potential conditions in a neonate:

- Structural
    - Palatal anomalies – 81%
        - High, arched or narrow
    - Cardiac abnormalities – 47% by Echo and ECG
        - Most common: PDA 17%, VSD 14%, PFO 7%, ASD 5%. None of these required surgery as most of these closed spontaneously
        - Other less occurred cardiac anomalies have included : hypoplastic transverse aortic arch; right ventricular hypertrophy; pulmonic stenosis; and valve abnormalities
    - Congenital orthopedic abnormalities – 45%
        - Club foot – 14%
        - Vertical talus – 5%
        - Metatarsus adductus – 5%
        - Rocker bottom foot – 5%
        - Hip dysplasia – 17%
    - Hernias (hiatal, inguinal, umbilical) – 12%
    - Myelomeningocele – 7%
- Functional
    - Feeding problems – 83%
        - Due to hypotonia, high arched palate or gastroesophageal reflux
    - Respiratory distress – 31%
- Biochemical
    - Jaundice – 57%

Initial evaluations after diagnosis:

- **Ophthalmology**
    - Strabismus – 75%
    - Esotropia – 17%
        - Accommodative – 30%
        - Infantile – 21%
        - Acquired non-accommodative – 8%
        - Intermittent – 8%
    - Esophoria – 4%
    - Intermittent exotropia – 4%
    - Refractive errors – 71%
        - Myopia – 17%
        - Hyperopia – 33%
        - Astigmatism – 25%
    - Anisometropia – 17%

- **Audiology / Otorhinolaryngology**
    - Hearing loss – 32%
        - Conductive, sensorineural, and mixed hearing loss have all been reported
    - Recurrent otitis media – 57%
    - Small or narrow ear canals – 42%
    - Laryngomalacia – 2%

- **Genitourinary**
    - Cryptorchidism – 63%
    - Hypospadias – 7%
    - Urinary tract anomalies – 28% (horseshoe kidney and bladder diverticuli, small kidney, renal cyst, hydronephrosis, vesicoureteral reflux varying degrees)
        - The actual incidence of kidney abnormalities may be higher than reported in the literature as abdominal ultrasounds have not performed on all individuals

Immediate Referrals to:

- **Genetics**
    - Referral to genetics is appropriate to review the condition, its management, and implications for other family members
    - A minority of parents of children with Tetrasomy 18p have a chromosome abnormality
    - There have been case reports of parents with mosaicism or with some type of chromosome rearrangement

- **Early intervention/developmental services**
    - All children with chromosome 18 abnormalities have a significant risk for developmental delay and intellectual disabilities. Prompt referral to a program the includes physical, occupational and speech therapy is important in order maximize their development
    - 100% with Tetrasomy 18p have developmental delay
    - 100% have muscle tone abnormalities that may benefit from physical therapy
    - 100% have intellectual disability, though the degree of severity varies

- **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)

- **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)

Closely monitor and manage:

- **Failure to thrive/ growth failure**
    - Underweight (<3rd%) – 19%
    - Weight gain

      Due to their hypotonia, feeding may be more difficult for an infant with Tetrasomy 18p. 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 should be evaluated for reflux and potentially for placement of a feeding tube. In addition, there have been a few individuals with Tetrasomy 18p that have been diagnosed with eosinophilic esophagitis

- **Endocrinology**
    - Short stature (<25%) – 52%
    - Failed two growth hormone provocative tests – 19%
    - IGF1 and IGFBP3 are not definitive tests for GH deficiency in these children
    - 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 typical performed by a pediatric endocrinologist
    - Thyroid and gonadotropin testing was normal in all participants but one individual (12 years old) is on thyroid medication because of hypothyroidism
    - Type 2 Diabetes – 1%

- **Otorhinolaryngology**
    - Recurrent otitis media – 57%
        - It is important to monitor hearing and treat ear infections quickly to avoid hearing loss and delayed speech development
    - Hearing loss – 32%
        - Conductive – 29%
        - Sensorineural – 12 %
        - Mixed hearing loss – 7%
        - Unspecified – 8%

- **Gastroenterology**
    - Chronic constipation – 76%
        - This is a chronic issue and failure to successfully manage bowel issues has resulted in failure to ever achieve bowel continence and has even resulted in the need for ileostomy. There are no data indicating neuogenic bowel disease but the serious and chronic nature of the constipation resembles such a condition
    - GE reflux – 36%
    - Hernias (hiatal, inguinal, umbilical) – 12%
    - Pyloric stenosis – 5%
    - Eosinophilic esophagitis – only a few individuals have been definitively diagnosed by endoscopy, however a significant proportion have some symptomology

- **Immunology/Rheumatology**
    - Atopic disorders
        - Food allergies – 33%
        - Asthma – 9%
        - Hay fever – 45%
        - Eczema – 21%
    - IgA deficiency – 18%
    - Arthritis – 5%
    - Celiac disease in one individual
    - Eosinophilic esophagitis – only 3 individuals have been definitively diagnosed by endoscopy

- **Orthopedics**
    - Orthopedic abnormalities – 69%
        - Scoliosis or kyphosis – 53%
        - Pes planus – 49%
        - Hip dysplasia –17%
        - Club foot – 14%
        - Metatarsus adductus 5%, Rocker bottom feet 5%, Vertical talus 5%
    - Low BMD (so far 100% of those assessed have low bone mineral density)

- **Development**
    - The average full scale IQ score is 48
    - Cognitive abilities vary significantly;
        - 37% in the mild range
        - 37% moderate
        - 26% in the severe to profound range
    - Mean age when: walking independently at 33 months, saying single words at 28 months and 2-3 word phrases at 66 months
    - Developmental milestones are delayed compare to a typical population (see O'Donnell et al., 2015)

- **Dental**
    - Dental crowding – 19%

- **Neurology**
    - Brain MRI variants – 58%
        - White matter changes (hyperintense /hypointense signal areas; low volume of white matter; hypomyelination) ~30%
        - Corpus callosum abnormalities (thin/hypoplastic)– 28%
        - Ventricular system enlargement – 23%
        - Choroid plexus cyst – 9%
        - Chiari malformation – 7%
        - Periventricular Leukomalacia – 7%
        - Iron deposition – 2%
        - Mastoiditis – 2%
        - There are other MRI changes in single individuals like: lipoma; extra fluid surrounding the brain; small pineal cyst
    - Seizures – 54% (most of the seizures were caused by fever/illness 33%, whereas 23% had no apparent trigger)
    - Microcephaly – 74%
    - Ptosis – 13%
    - Myelomeningocele – 7%
    - Abnormal muscle tone – 98%
        - Hypotonia – 50%
        - Hypertonia – 19%
        - Mixed tone – 28%
- **Behavior/mood changes:**
    - Children - Problems with functional communication (97%), activities of daily living (91%), attention problems (61%), hyperactivity (54%)
    - Adults – Problems with functional communication (62%), activities of daily living (62%), hyperactivity (54%)
- **Executive Function**:
    - Children – Problems with working memory (95%), task monitoring (90%), inhibiting (85%), initiating (70%), planning/organizing (70%), shifting (60%), emotional control (50%)
    - Adults – Problems with working memory (93%), initiating (71%), inhibiting (64%), shifting (64%), planning/organizing (64%), task monitoring (50%)
- **Social Impairment:**
    - Children and Adults – Problems with social cognition (91%), restricted interests and repetitive behaviors (91%), social awareness (82%), social communication (73%), social motivation (55%)
- **Early death**
    - In general, individuals with Tetrasomy 18p are not medically fragile. In our cohort of 76 individuals with Tetrasomy 18p, only one participant has died. Although the cohort is relatively young with an average age of about 17 years. The oldest participant is 51 years old. The one death was presumed to be from sudden cardiac arrest at age 13 years

- 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.

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