

18p-

Treatment and Surveillance

ICD-10 = Q99.9 or Q93.89

These recommendations are inclusive of the entire population of people with 18p deletions. Even though about half of this group have deletions of the entire short arm of the chromosome and the other half have individually unique deletion of only a portion of the chromosome arm. Consequently, not everyone with 18p- has exactly the same genes that are hemizygous. The specific hemizygous genes for an individual patient will dictate the probability of particular phenotypes. However, the information in this document includes the global 18p- evaluation and management plan.

Potential conditions in a neonate:

- Structural
 - Hernias (inguinal, umbilical)
 - Heart abnormalities
 - Cryptorchidism
 - Sacral agenesis / myelomeningocele
- Functional
 - Respiratory distress
 - Feeding problems
 - Hypotonia
- Biochemical
 - Jaundice
 - Hypoglycemia

Initial evaluations after diagnosis

- Cerebral MRI - abnormalities - >70%
- Ophthalmology exam – ptosis – 47%
vision and optic problems - >38%
- Audiology evaluation - hearing deficits - >22%
- Thyroid evaluation - thyroid problems – 17%
- Cardiology exam - cardiac defects - 45%
- Orthopedic exam - orthopedic problems 47%
- Renal ultrasound- hydronephrosis or malformations – 14%

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



18p-

An interstitial or terminal deletion of any region of chromosome 18p between the end of the chromosome (at 1Mb) and the centromere (at 15.6 Mb). 18p has 67 genes, only 12 of which are thought to either lead to haploinsufficiency or are conditionally dosage sensitive.

*hg 19 nucleotide scale

Closely monitor and manage:

- Failure to thrive/ growth failure
 - Weight gain
 - Linear growth
- Ear infections
- Immunology/Rheumatology:
 - Atopic disorders
 - Arthritis
 - Other autoimmune conditions
- Orthopedics
 - Scoliosis or kyphosis
 - Sacral agenesis
- Development:
 - Milestones
 - School performance
- Neurology:
 - Seizure disorder
 - Balance problems
 - Muscle weakness
 - Hypotonia
- Behavioral/ mood changes

Annual screenings

- Thyroid
- Vision
- Hearing

Potential conditions in a neonate:

- **Structural**
 - Hernias (inguinal, umbilical) – 22%
 - Cardiac abnormalities – 56%
 - Cryptorchidism in 14%
 - Sacral agenesis - 6%
 - Myelomeningocele - 3%
- **Functional**
 - Respiratory distress and feeding difficulties
 - Feeding problems
 - Hypotonia
- **Biochemical**
 - Jaundice
 - Hypoglycemia in 8% and 5% were diagnosed with panhypopituitarism.

Initial evaluations after diagnosis:

- **Cerebral MRI/ Neurology**
 - Holoprosencephaly or HPE microform – 13%
 - Other MRI abnormalities – 66%
 - Seizures – 13%
 - Myelomeningocele – 3%
- **Ophthalmology**
 - Ptosis – 47%
 - Strabismus – 38% . The exact gene responsible has not been identified but it is known to be within a small region between 1 and 1,192,031Mb. Only persons with a deletion including this region have this risk for this condition.
 - Myopia – 17%
 - Nystagmus – 9%
 - Congenital cataract – 6%
 - Optic nerve hypoplasia – 6%
- **Audiology and Otolaryngology**
 - Within the total population of people with 18p deletions:
 - Conductive hearing loss – 22%. The exact gene responsible has not been identified but it is known to be within a small region between 1 and 2,931,532 Mb. Only persons with a deletion including this region have this risk for this condition.
 - Sensorineural hearing loss – 8%. The exact gene responsible has not been identified but it is known to be within a small region between 1 and 1,192,031Mb. Only persons with a deletion including this region have this risk for this condition.
 - Narrow ear canals – 2%
- **Thyroid levels**
 - thyroid dysfunction – 17%
 - Secondary hypothyroidism is the most common
 - Antibody positive hypothyroidism is less common
 - Hyperthyroidism has been reported

- **Cardiology**

- cardiac abnormality – 56% of those who had ECG
 - ASD or VSD – 40%
 - Tetralogy of Fallot – 15%
 - The exact gene responsible has not been identified but it is known to be within a region between 1 and 9,148,02Mb. Only persons with a deletion including this region have this risk for this condition.
- The actual incidence of heart defects may be higher as ultrasound and ECG evaluations have not been consistently been performed on all affected individuals.

- **Orthopedic**

- Orthopedics problems – 47%:
 - Scoliosis or kyphosis – 33%. The exact gene responsible has not been identified but it is known to be within a small region between 1 and 2,931,532 Mb. Only persons with a deletion including this region have this risk for this condition.
 - Pectus excavatum – 29%
 - Pes planus – 15%
 - Sacral agenesis - 3%
 - Hip dysplasia – 3%

- **Renal ultrasound**

- Kidney abnormality - 14% - hydronephrosis or malformations
- The actual incidence of kidney abnormalities may be different as abdominal ultrasound was not performed on all individuals.

Referrals to:

- **Genetics follow-up**

- Genetics follow-up may be necessary if parental chromosomes have not been evaluated to rule out inherited rearrangement. ~12% 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**
 - Developmental delay – 100%. Prompt referral to a program that includes physical, occupational and speech therapy is important in order to maximize their development.
 - Speech delay – 100%
 - Articulation problems – 49%
 - Delayed speech development – 30%
 - Apraxia – 12%
 - Non-verbal – 9%
 - Motor delay – 96%
 - Hypotonia / mixed tone abnormality – 84%
- **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**
 - Weight gain
 - Due to their hypotonia, suckling or feeding may be more difficult for the child. Children <3 years who are failing to meet expected rates of weight gain should be evaluated for placement of a feeding tube.
 - 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.

- Linear growth
 - Short (<2SD) - ~40%
 - Growth hormone deficient - ~30%
 - 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 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
- **Ear infections**
 - Recurrent otitis media – 63%
- **Immunology/Rheumatology:**
 - Autoimmune disorders – 62%
 - Atopic disorders /Hypersensitivity – 30%
 - IgA, IgG or IgM deficiency – 13%
 - Arthritis – 3%
- **Orthopedics**
 - Scoliosis or kyphosis – 33%
 - Sacral agenesis – 6%
- **Development:**
 - For those with deletions of the entire p arm, the average full scale IQ score was 69 with a range from 51 to 99.
 - For those with smaller deletions, the average full scale IQ score was 76 with a range from 50 to 111.
 - Developmental milestones are delayed compare to a typical population ([see Sebold et al., 2015](#)).
 - School performance – assure appropriate special educational services and support.
- **Neurology:**
 - Structural
 - Cerebral MRI findings – >70%
 - White matter abnormalities – ~50% (delayed myelination; subtle thinning of white matter; white matter signal abnormalities; white matter changes due to ischemic insult; T2 hyperintensities and dysmyelinationm).
 - Pituitary abnormalities – 13% and hypothyroidism -7% (secondary or panhypopituitarism)
 - One individual had lobar holoprosencephaly and one had septo-optic dysplasia.
 - Sacral agenesis – 6%
 - Myelomeningocele – 3%

- Functional
 - Hypotonia – 74%
 - Speech disturbance/dysarthria – 68%
 - Facial weakness – 13%
 - Seizure disorder – 13%. The average age at onset is 6 years old. Age at onset between ~1 year old to 15 years old.
 - Scapular winging – 8%
 - Movement disorder – 6% (dystonia, tics, or myoclonic events)

- **Behavioral/ mood changes**

- At least some autistic features >19%

- **Annual screenings**

- Thyroid hormone and TSH
- Vision
- Hearing
 - Hearing loss – ~34%- conductive, sensorineural or mixed

- 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.

References

- Cody JD, Hasi M, Soileau B, Heard P, Carter E, Sebold C, O'Donnell L, Perry B, Stratton RF, Hale DE. (2014) Establishing a reference group for distal 18q-: Clinical description and molecular basis. *Hum Genet* 133:199-209, doi: 10.1007/s00439-013-1364-6.
- Cody JD, Heard PL, Crandall AC, Carter EM, Li J, Hardies LJ, Lancaster J, Perry B, Stratton RF, Sebold C, Schaub RL, Soileau B, Hill A, Hasi M, Fox PT, Dale DE. (2009) Narrowing critical regions and determining penetrance for selected 18q- phenotypes. *Am J Med Genet* 149A:1421-1430, doi:10.1002/ajmg.a.32899.
- 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.
- Daviss WB, O'Donnell L, Soileau BT, Heard P, Carter E, Pliszka S, Gelfond JAL, Hale DE, Cody JD. (2013) Mood disorders in individuals with distal 18q deletions. *Am J Med Genet Part B* 162B:879-888, doi: 10.1002/ajmg.b.32197.
- Dharmaraj, P. and Grueters, A. (2006) The management of thyrotoxicosis in a pre-pubertal child with 18p deletion syndrome. *European journal of endocrinology*, 155(suppl 1), pp.S145-S147.
- Hasi-Zogaj M, Sebold C, Heard P, Carter E, Soileau B, Hill A, Rupert D, Perry B, Atkinson S, O'Donnell L, Gelfond J, Lancaster J, Fox PT, Hale DE, Cody JD. (2015) A review of 18 p deletions. In *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* (Vol. 169, No. 3, pp. 251-264).
- Schaub RL, Reveles XT, Baillargeon J, Leach RJ, Cody JD. (2002) Molecular characterization of 18p deletions: Evidence for a breakpoint cluster. *Genet Med* 4:15
- 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
- Sebold C, Soileau B, Heard P, Carter E, O'Donnell L, Hale DE, Cody JD. (2015) Whole Arm Deletions of 18p: Medical and Developmental Effects