THE CHROMOSOME 18 REGISTRY & RESEARCH SOCIETY

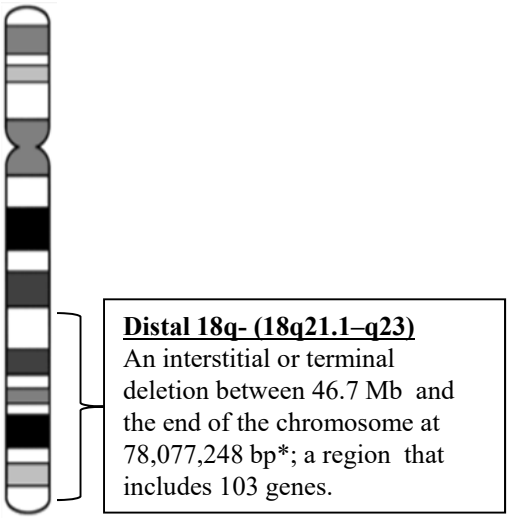
SCHOOL OF MEDICINE UT HEALTH SCIENCE CENTER THE CHROMOSOME 18 CLINICAL RESEARCH CENTER

Ring 18

Distal 18q-: Treatment and Surveillance

ICD-10 = Q99.9 or Q93.89

These recommendations are inclusive of the entire population of people with Distal 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 distal 18q- evaluation and management plan.



Distal 18q- (18q21.1–q23)
An interstitial or terminal deletion between 46.7 Mb and the end of the chromosome at 78,077,248 bp*; a region that includes 103 genes.

*hg 19 nucleotide scale

Potential conditions in a neonate

- Structural
  - Hernias (inguinal, umbilical)
  - Cryptorchidism, chordee, and hypospadias in >50% of males
  - Palate abnormality
- Functional
  - Respiratory and feeding difficulties
  - Hypotonia
- Biochemical
  - Jaundice

Initial evaluations after diagnosis

- Cardiology evaluation -29% have cardiac defects
- Orthopedic exam -74% with foot defects
- Otolaryngology including audiology evaluation - >50% with hearing loss
- Thyroid levels - 15% with hypothyroidism
- Renal ultrasound -18% with reflux or malformations
- Ophthalmology exam- 72% with optic problems
- Genitourinary
- Neurology / cerebral MRI evaluation
- Pediatric anesthesiology if surgery is indicated

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
- Immunology/Rheumatology
  - IgA deficiency
  - Atopic disorders
  - Arthritis
  - Other autoimmune conditions
- Neurology
  - Seizure disorder
  - Intention tremors
  - Hypotonia
- Orthopedics
  - Scoliosis or kyphosis
- Development
  - Milestones
  - Psychometric data
- Behavioral/ mood changes

Annual Screenings

- Thyroid
- Vision
- Hearing

Current Adult Status

Age and Cause of Death

Updated 2020

Potential conditions in a neonate:

- Structural
    - Hernias (inguinal, umbilical)
    - Cryptorchidism, chordee, and hypospadias in >50% of males
    - Palate abnormality
        - >40% with abnormalities, including: high, narrow, wide, bifid uvula, submucus cleft, cleft palate alone or cleft lip and palate.
- Functional
    - Respiratory and feeding difficulties
    - Hypotonia
- Biochemical
    - Jaundice

Initial Evaluations:

- **Cardiology**
    - 29% had a cardiac abnormality and of those
        - 43% has an ASD or VSD
        - 38% had pulmonic stenosis.
        - No definitive region of the chromosome is associated with CHD implying there is more than one gene on 18q impacting the development of the heart.
    - The actual incidence of heart defects may be higher as ultrasound and ECG evaluations have not been consistently been performed on all affected individuals.
- **Orthopedics**
    - 74% have a foot deformation:
        - Clubfoot, vertical talus, metatarsus adductus, pes planus or pes cavus.
    - The critical region for vertical talus is between 73 and 75.5 Mb
    - Scoliosis or kyphosis –possibly related to hypotonia
- **Audiology**
    - Within the total population of people with 18q deletions:
        - 49.5% had conductive hearing loss
        - 28% had sensorineural hearing loss
    - 78% of individuals whose deletion includes the TSHZ1 gene at 73 Mb have ear canal stenosis/atresia often leading to conductive hearing loss.
- **Otolaryngology**
    - Aural atresia/stenosis common
    - Middle ear effusion common
    - Normal pinnae
- **Thyroid levels**
    - 15% have developed thyroid dysfunction, often at <10 years of age
        - Antibody positive hypothyroidism is the most common, by far
        - Hyperthyroidism has been reported

- **Renal ultrasound**
    - 25% with a deletion including the region from 73.1 – 75.1 Mb have a renal malformation
- **Ophthalmology**
    - Strabismus 40%, nystagmus 29 % , myopia 35%
    - Nystagmus critical region is from 72.6-75.1 Mb
- **Genitourinary**
    - Infants with genital abnormalities should be evaluated by a pediatric urologist in the first month of life. Treatment should be initiated on the same timetable as would be used for typical infants
- **Neurology**
    - MRI findings:
        - 97% have CNS dysmyelination (i.e. delayed myelination), although 100 % of those individuals missing a region between 74.3 and 73.5 Mb have dysmyelination, it is not a progressive degenerative condition.
        - 47% Paranasal Sinus Disease (Maxillary or Ethmoid sinusitis)
        - 26% Mastoiditis
        - 34% Enlargement of Ventricular System (possibly related to brain hypoplasia; corpus callosum hypoplasia or white matter loss)
        - 32% Delayed maturation of Occipital lobes
        - 14% Brain abnormal signals
        - 14% Corpus Callosum abnormalities (thinner, smaller, partial or total agenesis)
        - 14% Iron deposition
        - 6% Pituitary gland abnormalities
        - 3%Virchow-Robin Perivascular spaces
        - 2.5% Deep white matter ischemia
        - 1.7% Periventricular Leukomalacia
        - 1.7% Dandy-Walker variant
        - 1.7% Chiari I malformation

    - 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 compliment.

    - 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 the includes physical, occupational and speech therapy is important in order maximize their development.
    - 100% have developmental delay
        - 91% have speech problems
        - 32% articulation
        - 17% non-verbal
        - 18% delayed speech development
        - 7% apraxia
        - 26% not-specified
    - 79% have hypotonia
    - 68% have an intellectual disability

- **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. In addition, many affected children have gastroesophogeal 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
        - 64% are short (<2SD) and the majority are growth hormone deficient
        - 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

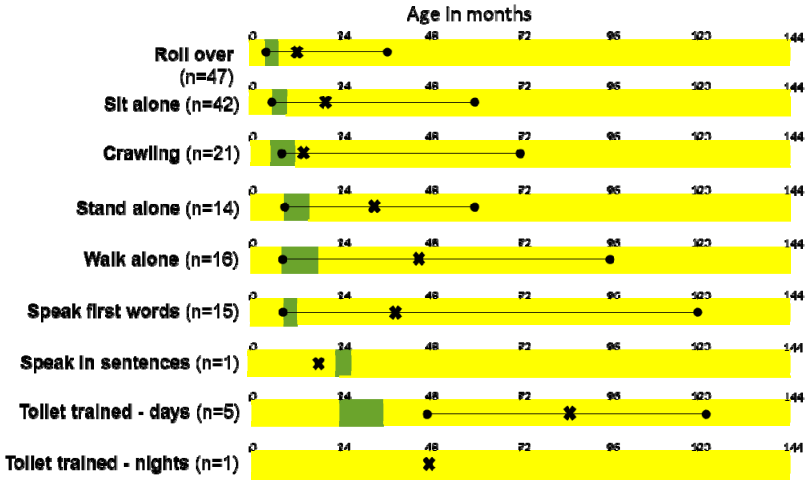
- **Sinus/ ear infections**
    - Due to abnormal midface architecture, affected children are at increased risk of otitis media and sinusitis. Many have atretic or stenotic ear canals, making visual inspection difficult. In addition, they often do not present with the typical signs of a sinus or ear infection. Therefore there should be a high index of suspicion of sinus infections when there are behavioral changes which then dictate a longer duration of antibiotic treatment; recommendations are 10 days for otitis media, and 14 days for sinusitis.

- **Genitourinary:**
    - Renal anomalies and ureteral reflux are more frequent in children with distal 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

- **Immunology/Rheumatology:**
    - Immunodeficiency – 18%
        - IgA deficiency – most common
            - The exact gene responsible has not been identified but it is known to be within a region between 62.5 and 76.9 Mb (Linnankivi et al., 2006). Only persons with a deletion including this region have this risk for this condition.
    - Hypersensitivity
        - Asthma, Allergic rhinitis, Food Allergy, Atopic Dermatitis (Eczema) – 41%
    - Autoimmune conditions – 41%
        - Tyroid disease -16%
        - Skin /hair condiotns -12%
        - Arthritis – 4%
        - Other conditions – Lupus, Sjogren's, Diabetes

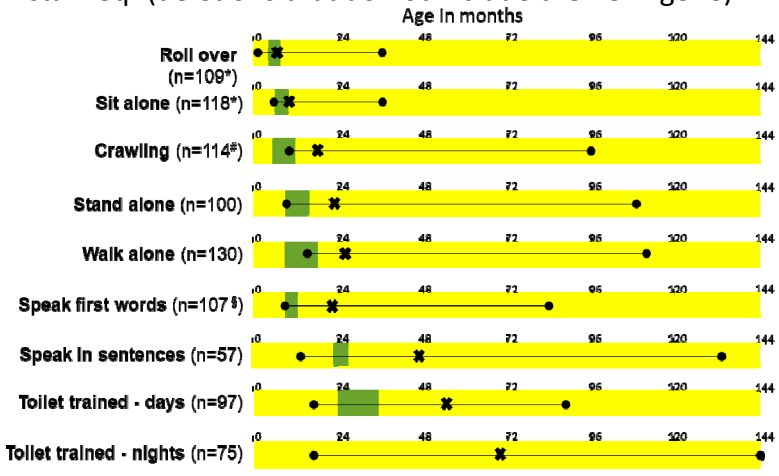
Closely monitor and manage

- **Neurology**
  - 96% have decreased reflexes
  - 79% have hypotonia
  - 68% have gait abnormalities
  - 62% have tremors
  - 38% have a seizure disorder. Average age at onset = 5 yrs., range = neonate to 27 yrs.
    - The seizures are treated with anticonvulsants medications. Sometimes more than one medication is needed to control seizures. Usually , but not always, the seizures are under control while on medications. 34 (67%) out of 51 diagnosed with seizures had no seizure relapse for >12 month. The most common medication used was Valproic acid (Depakene or Depakote) followed by Carbamazepine (Tegretol); Levatiracetam (Keppra); Oxcarbazepine (Trileptal).
- **Orthopedics**
  - 7% develop Scoliosis or kyphosis
- **Development**
  - There are two broad groups of people with distal 18q deletions; those with deletions that include the *TCF4* gene and those whose deletion does not include *TCF4*. People whose distal 18q deletion does not include *TCF4* have IQ scores from above normal to mild intellectual disability. Those whose deletion includes *TCF4* generally do not develop skills beyond that of a typical 18 month old.
  - Milestones
    - Distal 18q- (deletions that include the *TCF4* gene)



We only have data on those who achieved each milestone. We do not know the number who have not yet or never achieved the milestone because most continue work to achieve them.

    - Distal 18q- (deletions that do not include the TCF4 gene)



*Includes one (age 2) who cannot sit alone
20 skipped crawling and are included in the N
§ 4 cannot speak (ages 2, 2, 4, 8)

Updated 2020

- Psychometic data

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

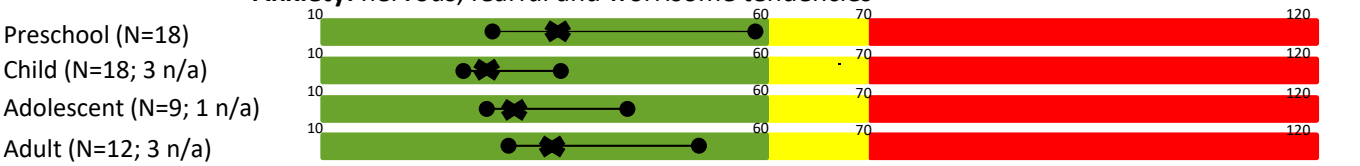
Distal18q-: with deletions that include the *TCF4* gene

Within Normal Limits | At Risk | Clinically Significant

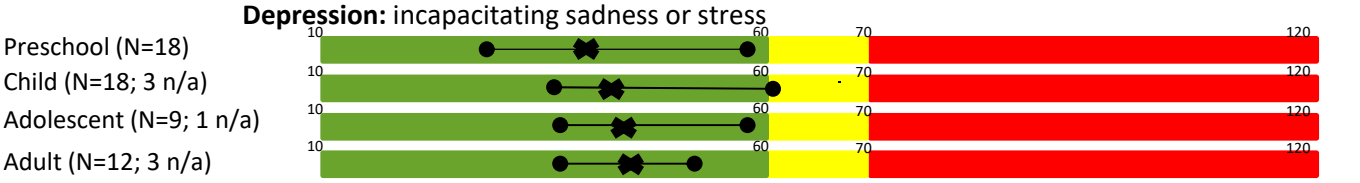
✖ = average score
●——● = the range of all the scores
N= the number of participants

Internalizing Behaviors (problems that manifest internally

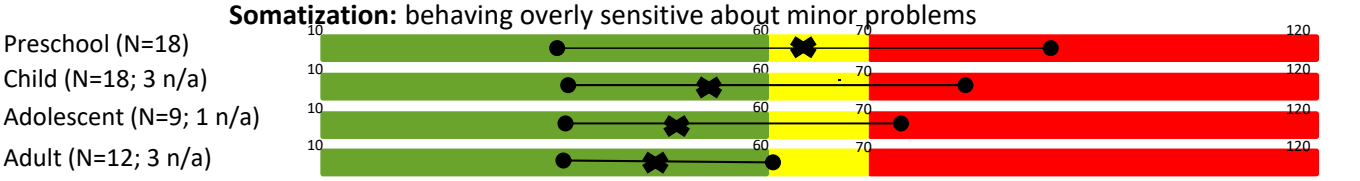
Anxiety: nervous, fearful and worrisome tendencies



Depression: incapacitating sadness or stress

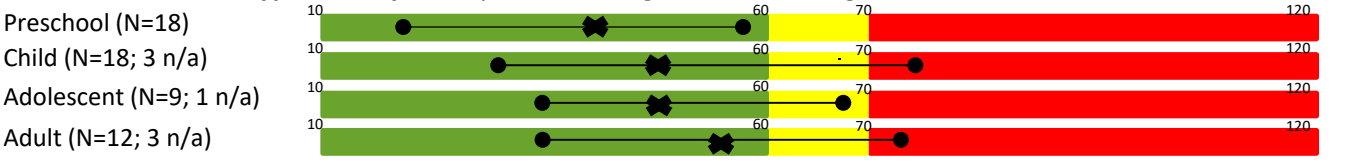


Somatization: behaving overly sensitive about minor problems

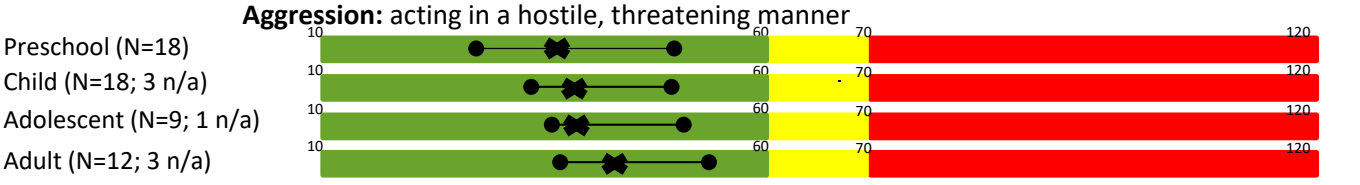


Externalizing Behaviors (problems that manifest externally)

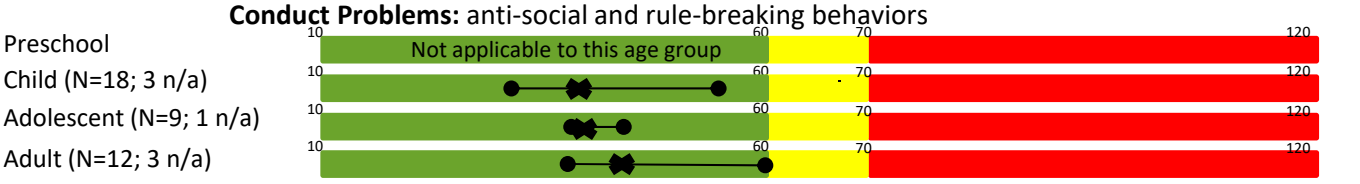
Hyperactivity: overly active, acting without thinking



Aggression: acting in a hostile, threatening manner



Conduct Problems: anti-social and rule-breaking behaviors

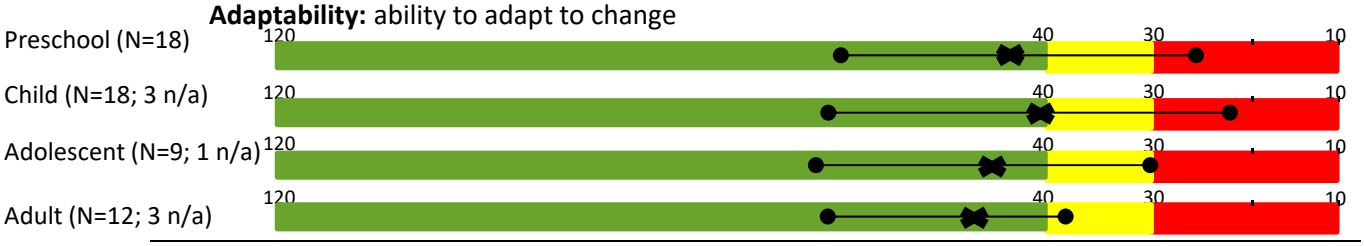


Distal18q-: with deletions that include the *TCF4* gene

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

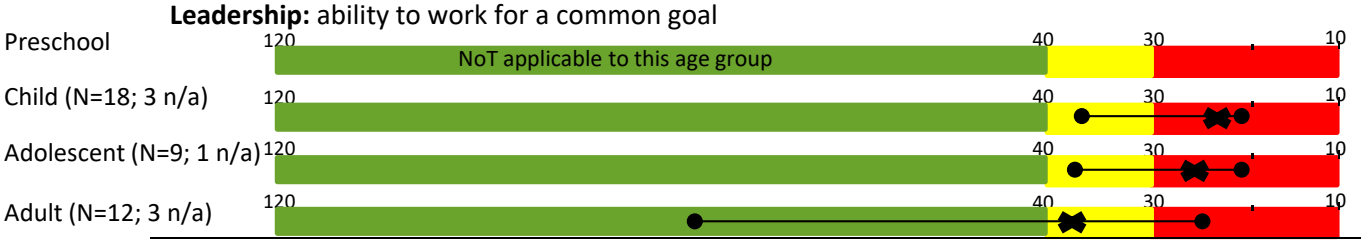
Adaptive Skills: skills learned and used in daily life

Adaptability: ability to adapt to change



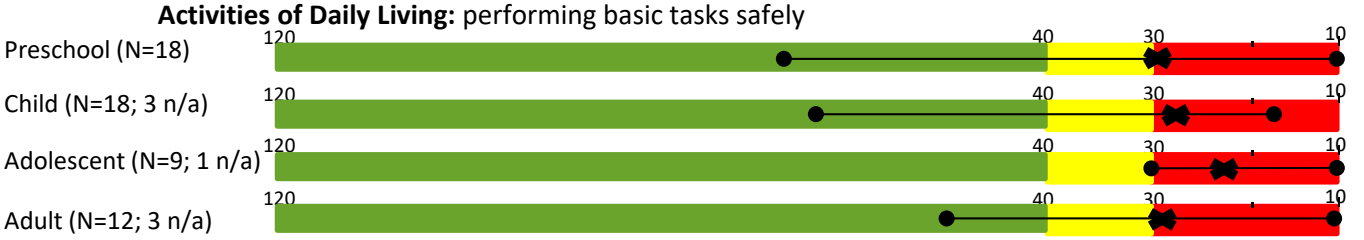
Social Skills: interacting with peers

Leadership: ability to work for a common goal



Functional Communication: expressing ideas in a way understood by others

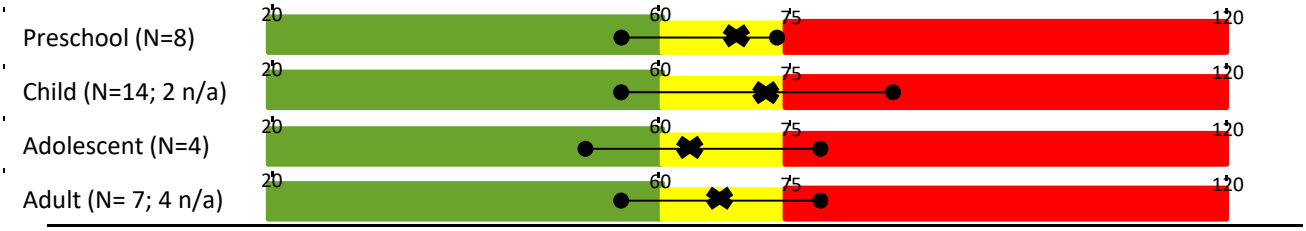
Activities of Daily Living: performing basic tasks safely



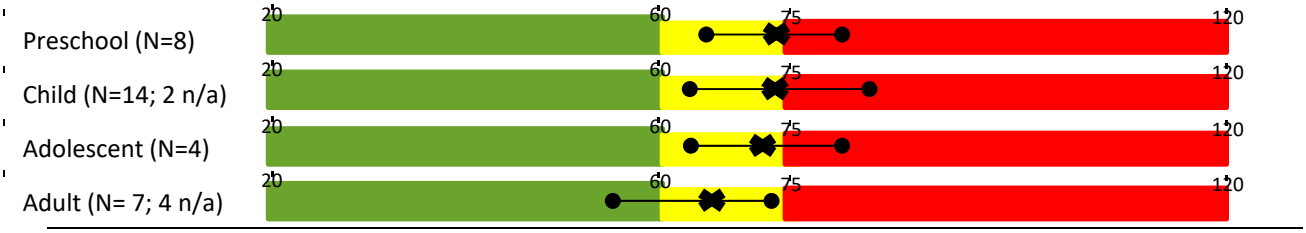
Distal18q-: with deletions that include the *TCF4* gene

Social Responsiveness Scale (SRS)

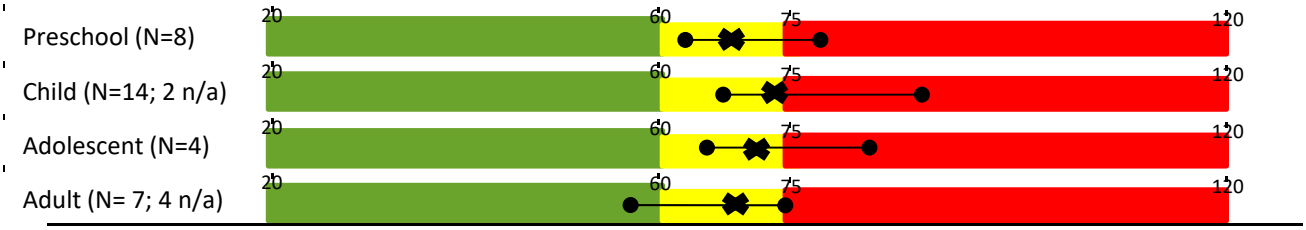
Social Awareness: ability to pick up on social cues



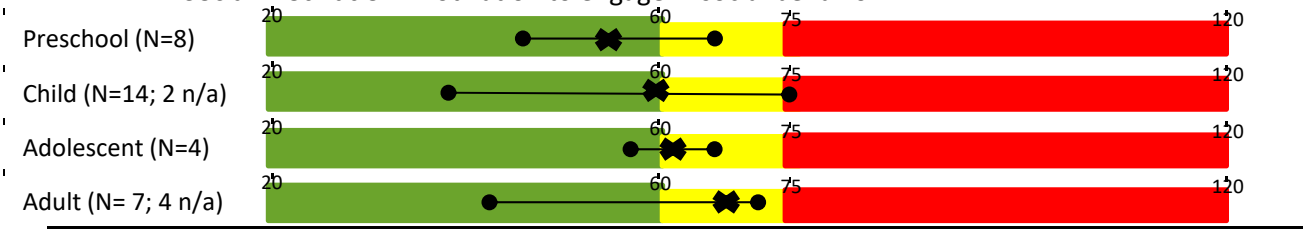
Social Cognition: interpreting social cues



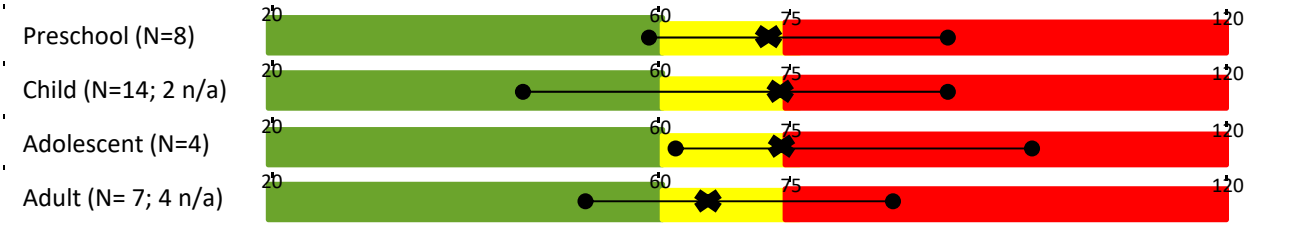
Social Communication: expressing social communication



Social Motivation: motivation to engage in social behavior



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

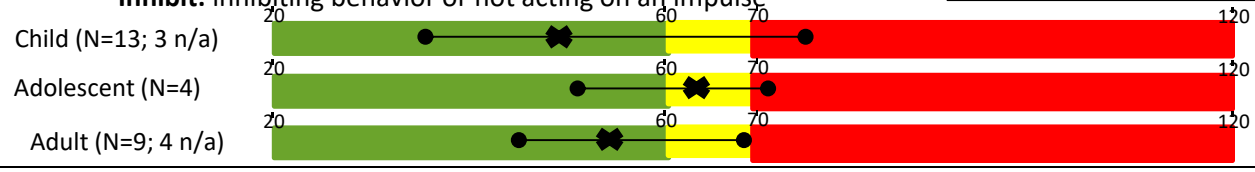


Distal18q-: with deletions that include the *TCF4* gene

Behavior Rating Inventory of Executive Function (BRIEF)

Behavioral Regulation: ability to regulate and monitor behavior effectively

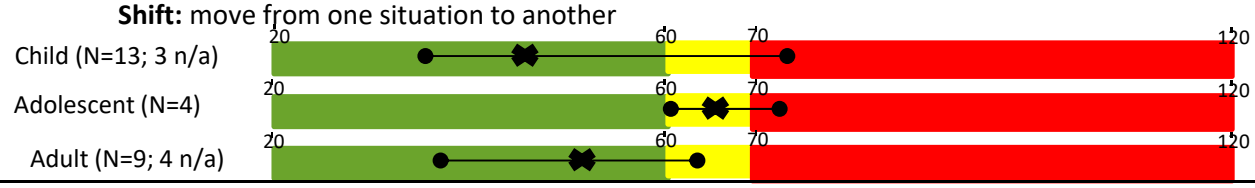
Inhibit: inhibiting behavior or not acting on an impulse



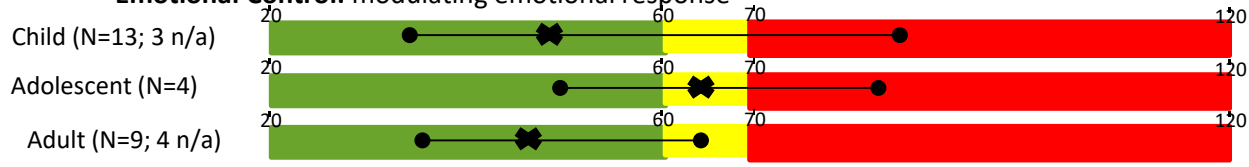
Self-Monitor: understand the effect of behaviors on others

Emotional Regulation: ability to regulate emotional responses

Shift: move from one situation to another

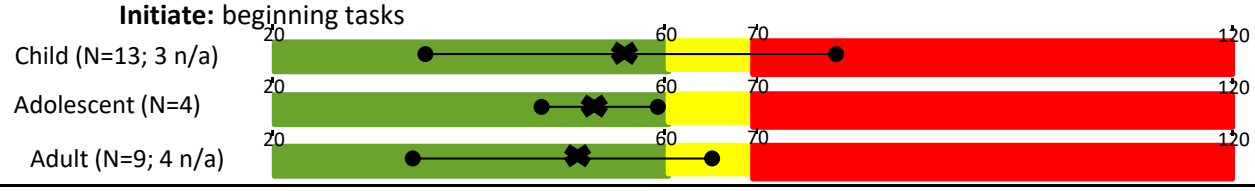


Emotional Control: modulating emotional response

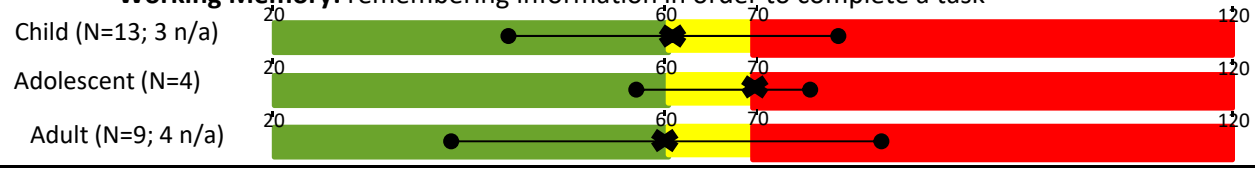


Cognitive Regulation: ability to control and manage cognitive processes and problem solve effectively

Initiate: beginning tasks

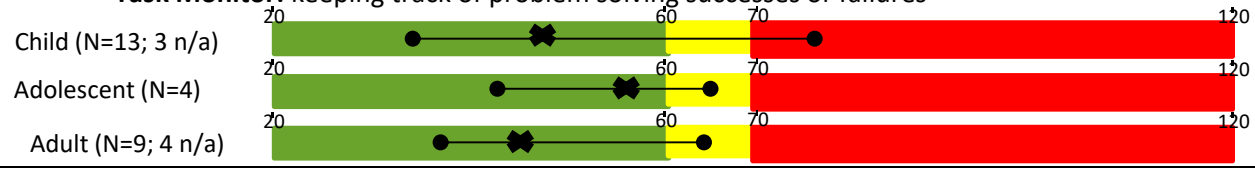


Working Memory: remembering information in order to complete a task



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

June 2020

Distal18q- (including the Reference Group, not including the TCF4 deletion group)

June 2020

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

Within Normal Limits | At Risk | Clinically Significant

✖ = average score
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Internalizing Behaviors (problems that manifest internally

Anxiety: nervous, fearful and worrisome tendencies

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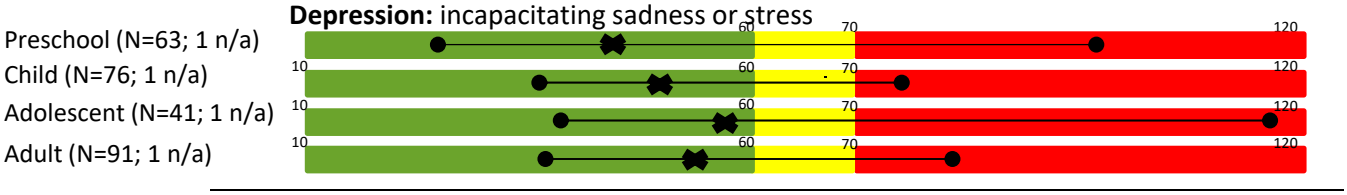

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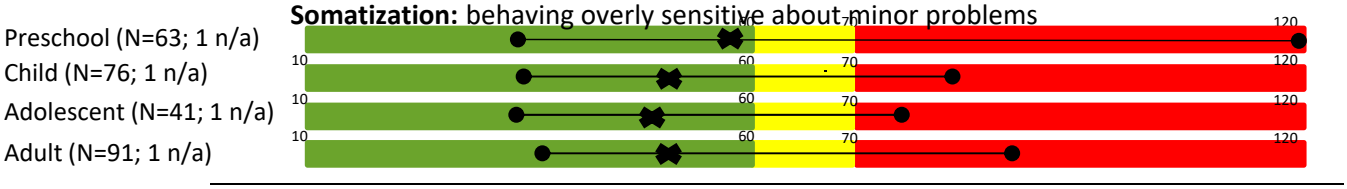

Externalizing Behaviors (problems that manifest externally)

Hyperactivity: overly active, acting without thinking

Aggression: acting in a hostile, threatening manner

Conduct Problems: anti-social and rule-breaking behaviors

Distal18q-

(including the Reference Group, not including the TCF4 deletion group)

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Adaptive Skills: skills learned and used in daily life

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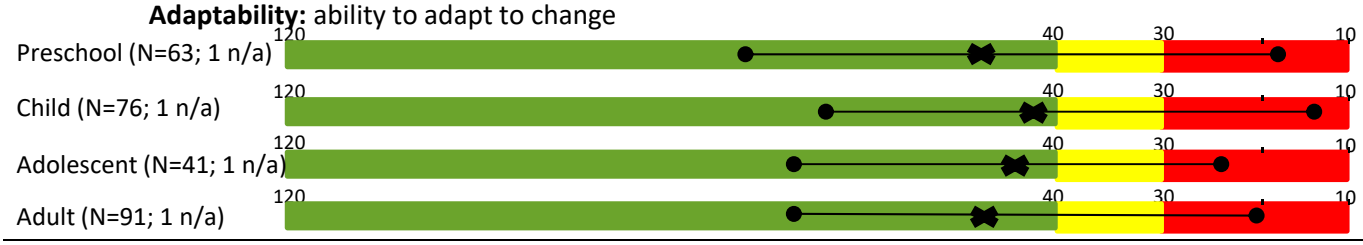

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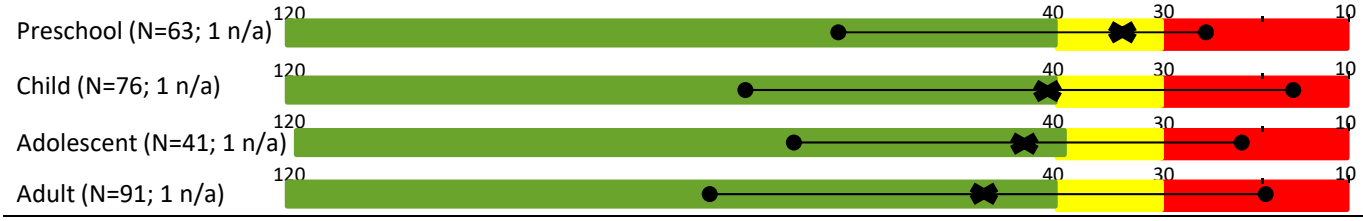
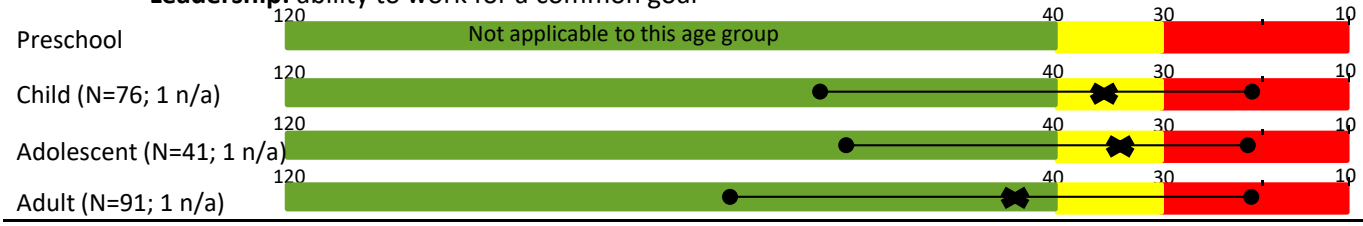


Leadership: ability to work for a common goal



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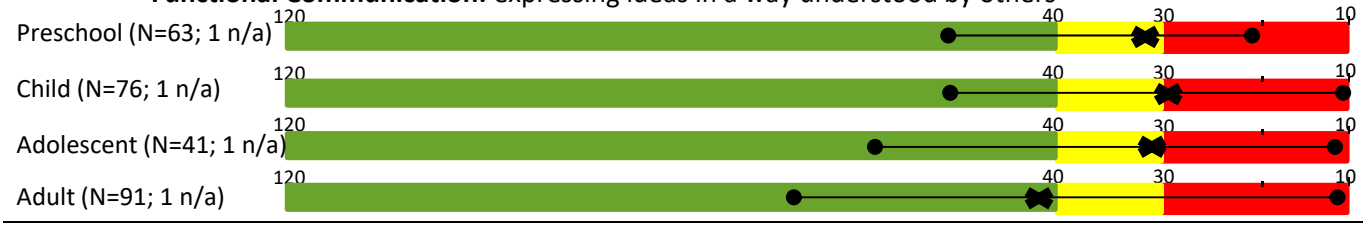

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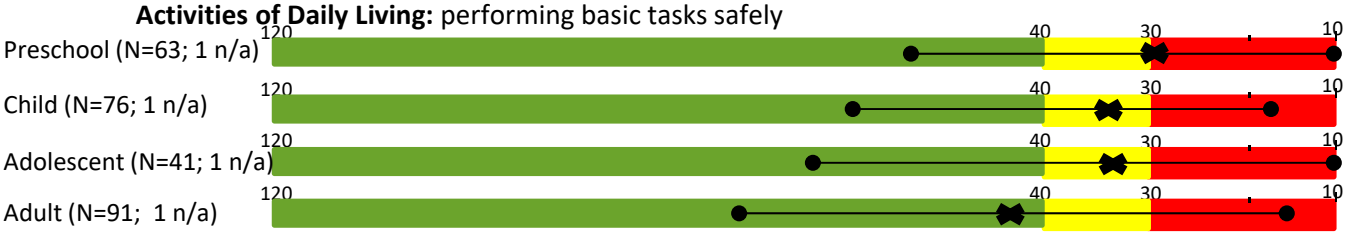

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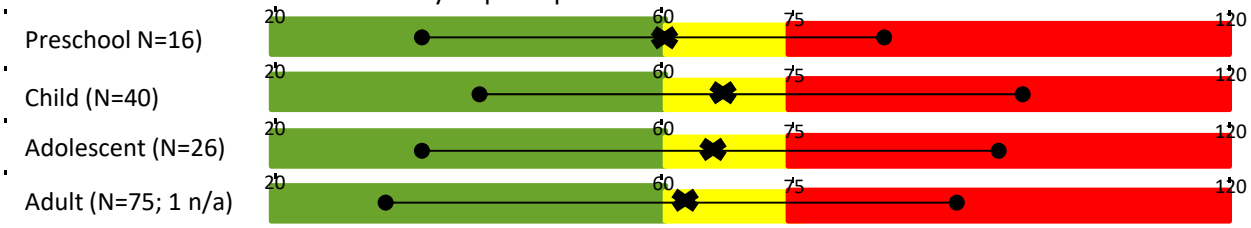
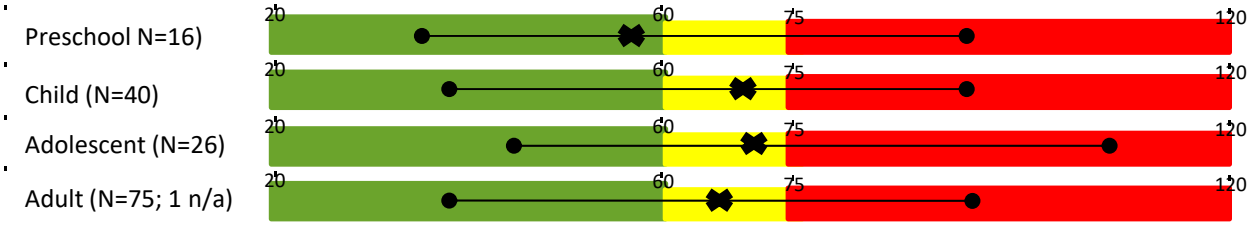
Social Responsiveness Scale (SRS)

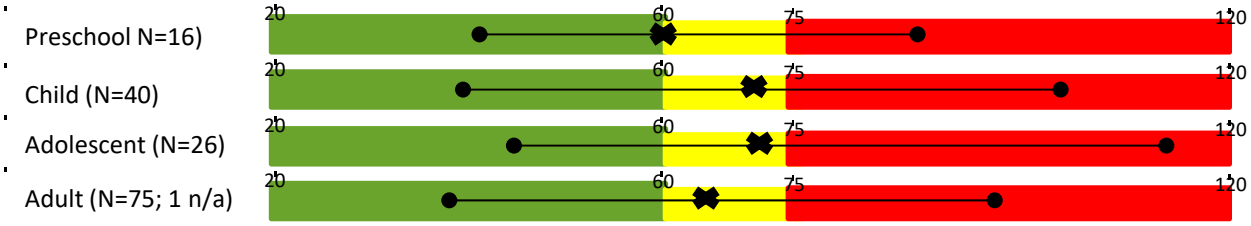
Social Awareness: ability to pick up on social cues



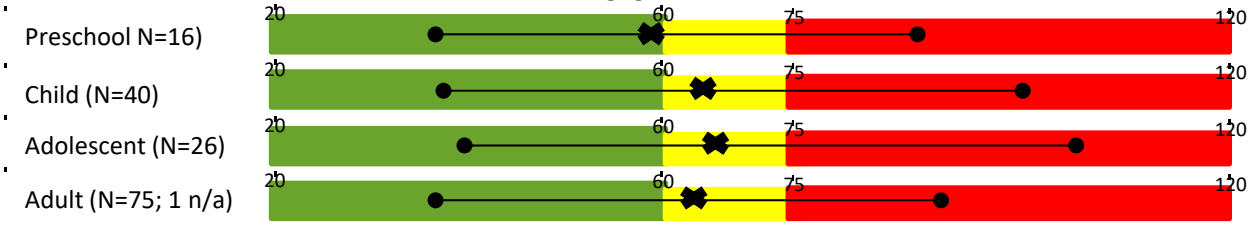
Social Cognition: interpreting social cues



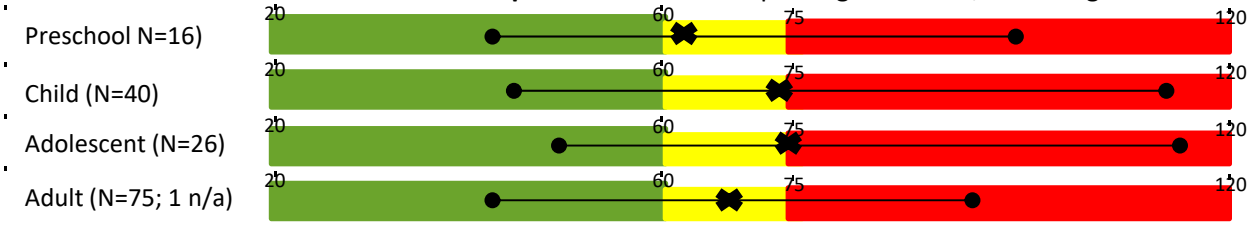
Social Communication: expressing social communication



Social Motivation: motivation to engage in social behavior



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



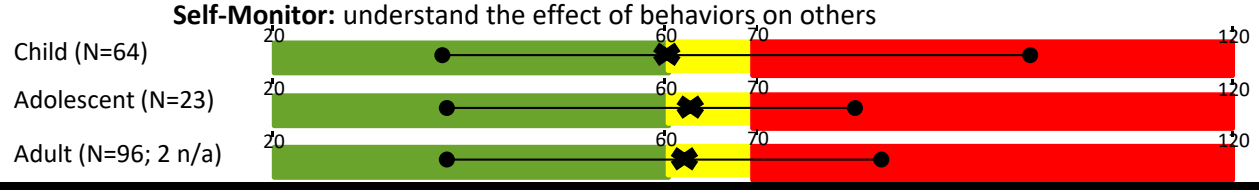
Distal18q- (including the Reference Group, not including the TCF4 deletion group)

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



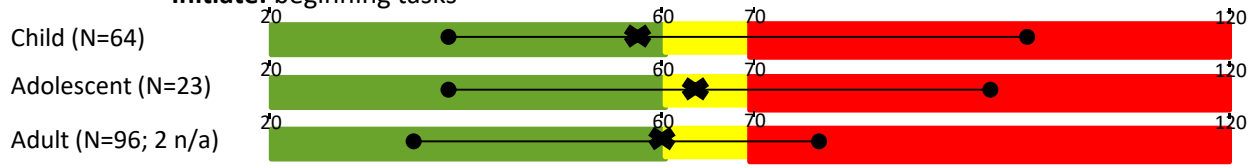
Emotional Regulation: ability to regulate emotional responses

Shift: move from one situation to another

Emotional Control: modulating emotional response

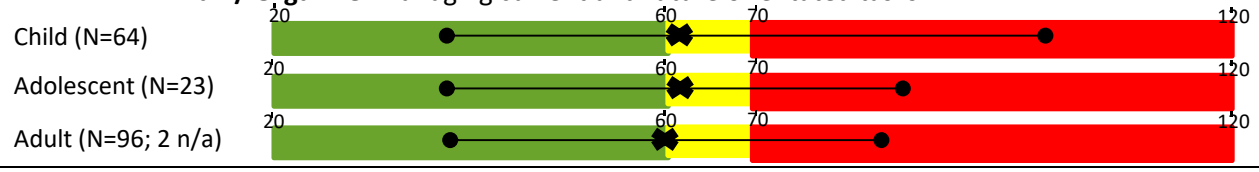
Cognitive Regulation: ability to control and manage cognitive processes and problem solve effectively

Initiate: beginning tasks

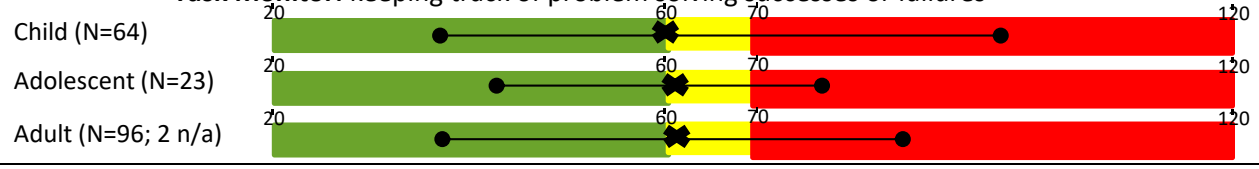


Working Memory: remembering information in order to complete a task

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

June 2020

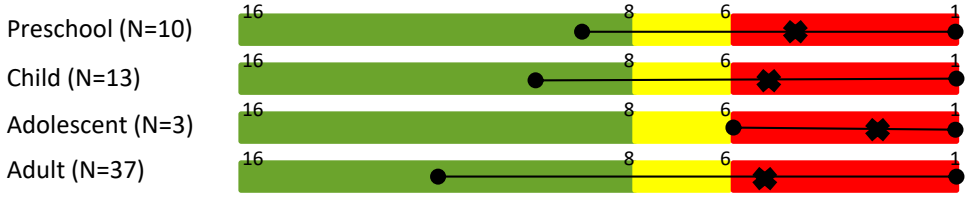
Distal18q-

(including the Reference Group, not including the *TCF4* deletion group)

Adaptive Behavior Assessment System (ABAS)

Conceptual Composite (ideas that occur in the mind, speech or in thought)

Communication (speech, language, and listening skills needed for communication with other people)

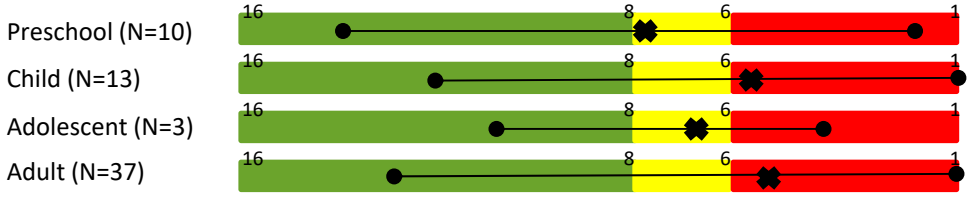


Functional Academics (basic academic skills needed for daily, independent functioning)

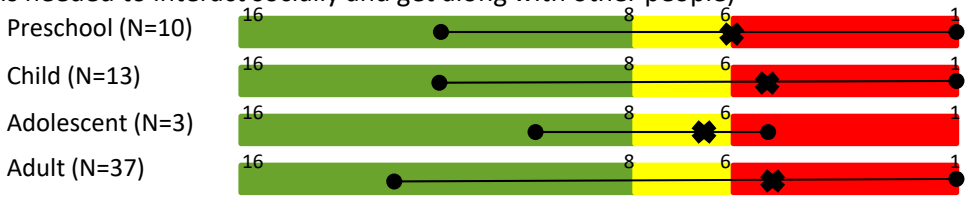
Self-Direction (skills needed for independence, responsibility and self-control)

Social Composite (skills needed to interact with others)

Leisure (skills needed for engaging in and planning leisure and recreational activities)



Social (skills needed to interact socially and get along with other people)



Distal18q-

(including the Reference Group, not including the TCF4 deletion group)

Adaptive Behavior Assessment System (ABAS - continued)

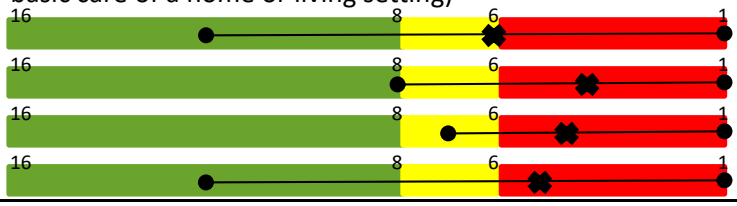
Practical Composite (skills needed for independent living)

Community Use (skills needed for functioning in the community)

Preschool (N=10)
Child (N=13)
Adolescent (N=3)
Adult (N=37)

Home Living (skills needed for basic care of a home or living setting)

Preschool (N=10)
Child (N=13)
Adolescent (N=3)
Adult (N=37)

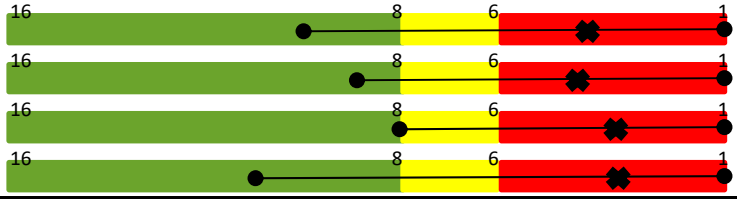


Health and Safety (skills needed for protection of health and to respond to illness and injury)

Preschool (N=10)
Child (N=13)
Adolescent (N=3)
Adult (N=37)

Self-Care (skills needed for personal care)

Preschool (N=10)
Child (N=13)
Adolescent (N=3)
Adult (N=37)



Work (skills needed for successful functioning and holding a part/full time job)

Adult (N=24)

Not in a composite

Motor (skills needed to perform fine and gross motor activities)

Preschool (N=10)

- **Behavioral/ mood changes**
    - 73% have a lifetime risk of a mood disorder
    - 64% have an anxiety disorder
    - 63% have at least some autistic features
    - 37% with an ADHD diagnosis
    - 36% with other externalizing disorders

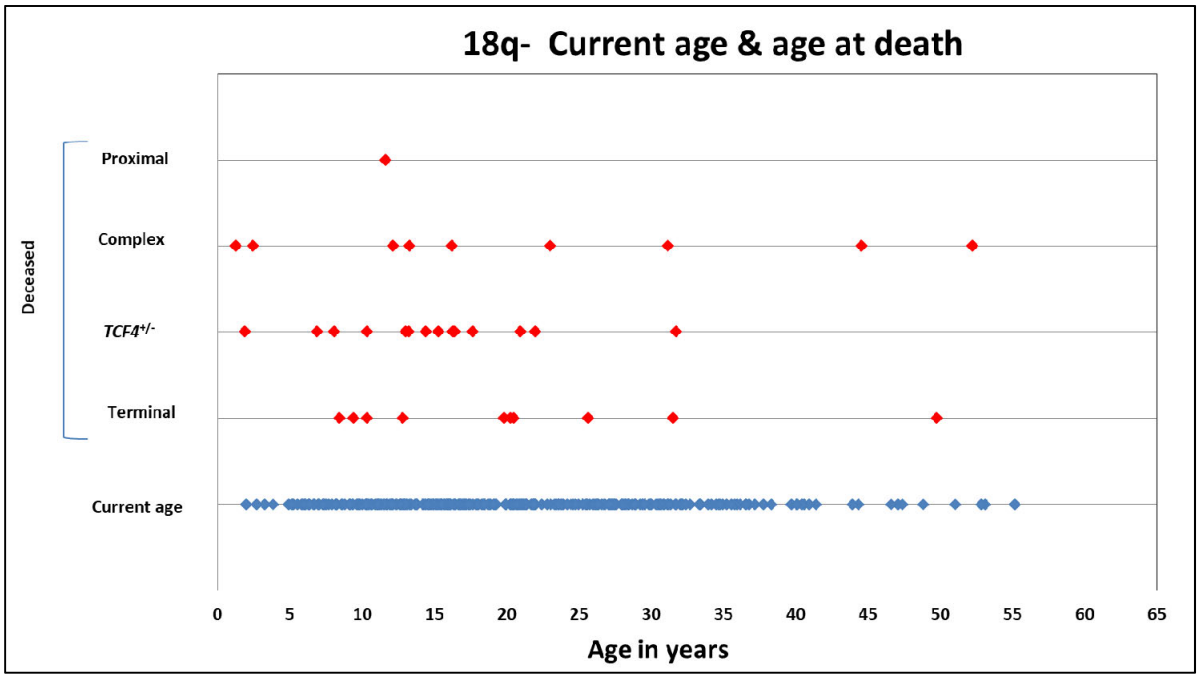
- **<u>Annual Screenings</u>**
    - Thyroid hormone and TSH
    - Vision
    - Hearing
        - 70% have hearing loss – Conductive, sensorineural or mixed
- **<u>Current Adult Status</u>**

Distal 18q- (deletions including the *TCF4* gene)	
Total N=34 Received Responses: N=15 No Contact or No Response: N=9 Deceased: N=10	
LIVING ARRANGEMENTS	
Lives with parents/guardians	13
Lives away from parents (alone or with roommate) and receives assistance from support staff	1
Lives in group, foster or respite home	1
HIGHEST EDUCATION LEVEL	
Did not complete high school	7
Currently a high school student	3
Completed high school (certificate)	4
Completed transitional program post high school	1
MARITAL STATUS	
Married (Yes)	0
Married (Never)	15
CHILDREN	
Children (Yes)	0
Children (No)	15
WORK POSITIONS	
Part Time UNPAID	1
Through school (work study, etc…)	1
Attends day habilitation program	6
Does not work	7

Adult Status (>18 years of age)

Distal 18q- deletions that do not include the *TCF4* gene	
Total N=157	
Received Responses: N=111	
No Contact or No Response: N=35	
Deceased: N=11	
LIVING ARRANGEMENTS	
Lives with parents/guardians	74
Lives with parents (independent part of home)	5
Lives with spouse/partner	5
Lives away from parents in a residence as part of a supervised independent living program	3
Lives away from parents (alone or with roommate) and receives assistance from support staff	8
Lives away from parents (alone or with roommate) without assistance from support staff	5
Lives in a dormitory	2
Lives in group, foster or respite home	7
Lives with extended family	2
HIGHEST EDUCATION LEVEL	
Did not complete high school	4
Currently a high school student	8
Completed high school (certificate)	25
High School Graduate (received diploma)	32
Currently attends college/university	4
Currently attends vocational school	1
Currently attends centers based/transitional progam post high school	5
Working towards continuing education/correspondence course certificate	1
Completed some college, but no longer attends (no degree)	9
Completed some vocational school, but no longer attends (no certificate/degree)	1
Completed transitional program post high school	5
Received continuning education/correspondence course certificate	3
Vocational School Certificate/Degree	5
Associates Degree	2
Bachelors Degree	5
Masters Degree	1
MARITAL STATUS	
Engaged	1
Married (Yes)	4
Married (Never)	106
CHILDREN	
Children (Yes)	6
Children (No)	105
WORK POSITIONS	
Full-Time PAID	5
Part Time PAID	37
Part Time PAID and Volunteer	7
Part Time PAID and Day Habilitation Program	2
Part Time UNPAID	2
Volunteer	9
Through school (work study, etc…)	4
Attends day habilitation program	18
Does not work	27

- **Age and Cause of Death**



18q- & complex rearrangements			
Age deceased	**Gender**	**Cause of death**	**Past medical history**
15 months	F	N/A	Multiple congenital heart defects; G-tube; hernia repair; intestine malrotations; hydrocephalus; pallor optic nerves; severe sleep apnea
2 years 6 months	M	Heart complications after heart surgery	Multiple heart surgeries; malrotated bowel; hypothyroidism; reactive airway disease
12 years 1 month	F	Had been sick and throwing up. Went to cardiac arrest. Then complications from lack of O2 and kidney failure after resuscitation was initially succesful.	Multiple food allergies; cleft palate (cleft of the hard and soft palate (palatal prosthesis)); vertical talus; pulmonary valve stenosis; hip dysplasia, congenital; bilatareal varus osteotomies and blade plate fixation; asthma; accommodative esotropia;mild hearing loss;had some words; non-ambulatory
13 years 3 months	M	N/A	Central hypotonia; 2 yrs 4 months: hypertonia; bilateral hearing loss; severe developmental delay; renal reflux; feeding difficulties; G-tube; aspiration
16 yrs 3 months	M	Kidney and heart failure	Profound developmental delay; sleep disorder; staring spells; mitral and aortic valve insufficiency; bilateral hypoplastic kidneys; chronic renal insufficiency
23 years	M	Medical records: Unspecified intestinal obstruction; volvulus; unspecified septicemia; acute kidney failure; acute cardiopulmonary arrest secondary to sepsis stemming from ileocecal volvulus, status post bowel resection ; likely cerebral hemorrhage ; disseminated intravascular coagulopathy with marked thrombocytopenia; Surgical procedures: right hemicolectomy ; partial resection of small intestine;	Neonatal complications; ASD; tricuspid insufficiency ; pulmonary valve stenosis; pulmonary hypertension; Hypertension; pneumonia several times; seizures; kidney stone; pyloric stenosis; urinary reflux; tracheomalacia; significant pulmonary disease;dysphagia by reduced tongue movement; chronic kidney disease; Diabetes insipidus; disorders of magnesium metabolism (hypomagnesemia) hypothyroidism; history of intracranial hemorrhage; hypoglicemia; MRI 2013: smaller hypothalamus, generalized tortuosity of his intracranial arterial structures, diffuse cerebral white matter volume loss; Large right hepatic venous malformation ; posterior staphylomas in both eyes
31 years 2 months	F	N/A	No medical records available
44 years 6 months	F	Choking due to a recurrent habit of retaining food in her cheeks	No medical records available
52 years 2 months	F	N/A	Chronic otitis media, status post myringotomy; hypoplastic external ear canals; Dental caries and periodontal disease ; St post repair of congenital hip dysplasia; Impulse control disorder; profound intellectual disability; hypothyroidism

Updated 2020

Distal 18q- (with a *TCF4* deletion)			
Age deceased	**Gender**	**Cause of death**	**Past medical history**
22 months	F	Admitted to the Hospital for central apnea. Developed tachycardia	Respiratory distress;central apnea; respiratory tract infections very often; silent aspirations; failure to thrive; oropharyngeal dysphagia; staring spells
6 years 10 months	M	Aspiration (at the time of death pt had cold/congestion). Admitted to the Hospital for not breathing. Cause of death : aspiration	Reactive airway disease; pneumonia; dehydration; diarrhea; ASD which was closed spontaneously
8 years	M	Sepsis	Never walked, talked or sit; poor immune system; developed interstitial lung disease and asthma; apnea; obstructed bowels; aspiration secondary to GERD; ASD; seizures; corneal staphyloma (Right);
10 years 4 months	F	Complications from rhabdomyosarcoma	Initially dg at 3 yrs old with mandibuilar mass which was later dg to be rhabdomyosarcoma; metastasis in lungs, chemotherapy; febrile seizures
13 years	M	Sepsis (developed an infection on his liver which was not able to to be controlled and spread to other organs)	Immature lung development as a newborn; cortical blindness; pneumonia very often; silent aspirations; central apnea
13 years 3 months	F	Very unexpectedly and suddenly. Fell ill what appeared a cold, got antibiotics, After two days, when mother went to check on her in the morning found her struggling to breath, Emergency help, but she passed away. Post mortem findings: Intussusception.	Only few medical records available: often respiratory infections; hypoplastic corpus callosum;
14 years 3 months	M	N/A	Pyloric stenosis;PFO and mitral valve prolapse (per parent); tremors; seizures; nonverbal, nonambulatory at 4 yrs old; history of G-tube; constipation; cryptorchidism; pharyngeal dysphagia; history of pneumonia; history of mild to moderate hearing loss; cortical visual impairment;mild macular hypoplasia; nystagmus
15 years 3 months	F	Her passing was very sudden. She had already had two bowel malrotations that had been repaired. This time the doctors believed it malrotated and tore causing internal bleeding and sepsis. It was really too late to fix it surgically when they finally figured out the cause of the sepsis. Autopsy n/a	Partial agenesis of corpus callosum; Intestinal malrotation; G-tube; GERD;meningitis
16 years 3 months	F	N/A	Scoliosis; bronchitis always turned into bronchial pneumonia', at about 3 x a year; one lung functions only at 10% due to scarred tissues from pneumonia; asthma; history of seizures.
16 yrs 5 months	M	Sudden death (Had his breakfast. Brushed his teeth and he was gone just like that). Autopsy n/a.	Pneumonia many times; history of asthma; glaucoma in the left eye, transplant surgery in the left eye; seizures
17 years 8 months	M	Was taking a nap and did not wake up. The cause of death was considered "natural causes". Death certificate:" cardiac arrest".	Leaking amniotic fluid in the fourth month; had fluid in his lungs at birth, and required O2 for 4 days; abnormal tone and meconium stained amniotic fluid; IUGR; profound conductive HL and mild sensorineural HL; hypospadias and chordee; no medical records available after 3 months of age.
20 years 11 months	F	Vomiting; poor feeding tolerance; Worsening apneic episodes; Adynamic illeus	Recurrent aspiration pneumonia; central apnea; Irregular breathing cycles; history of cyclical vomiting; GE reflux; constipation; malrotation of intestine; pulmonary stenosis
22 years	F	N/A	Pneumonia in multiple times; asthma; alopecia totalis; fused kidneys; trouble with swallowing and controlling secretions; severe developmental delay
31 years 8 months	M	N/A	Seizures; pyloric stenosis; salivary gland surgery; tetses removal; multitude of foods and environmental allergies; has had 3 pancreatitis/vomiting attacs. versy sensitive skin; nonverbal, on wheelchair, basically non-ambulatory

Distal 18q- (without a *TCF4* deletion)			
Age deceased	**Gender**	**Cause of death**	**Past medical history**
8 years 4 months	F	N/A	Pneumonia newborn; PDA (patent ductus arteriosus); PFO (patent foramen ovale); failure to thrive; congenital hypothyroidism; cleft palate; bifid thumb; club feet; slightly alrotated right kidney; records only as an infant.
9 years 4 months	M	Pulmonary hemorrhage per grandmother	Nonverbal; nonambulatory; G-J tube for svere GERD; severe encephalopathy; seizure disorder; severe hypertonicity; spastic quadriparesis
10 years 3 months	F	N/A	idiopathic pulmonary hemosiderosis; frequent pneumonias; respiratory distress; sinus arrythmia; minimal mitral regurgitation; severeal hospitalizations for pulmonary bleeding
12 years 9 months	M	N/A	Records only at a very young age (2 yrs old): neonate: periodic breathing; episodes of apnea; pyloric stenosis; cleft palate; silent aspirations; jejunostomy tube; oropharyngeal dysmotility
19 years 9 months	M	Sudden death	History of heart murmur-resolved; pulmonary valve stenosis-resolved ? ; dysarthria; MRI: Chiari I malformation
20 years 3 months	F	Death Certificate:Part 1: Hypoxic brain injury: Cardiopulmonary arrest; Bilateral Pulmonary Embolus; Part 2: Other significant condistions contributing to death: aspiration pneumonia; DIC; 18q deletion. ICU admission: CT chest: Bilateral pulmonary emboli; ultrasound: DVT in lower extremity; It appeared that she was going into DIC (disseminated intravascular coagulation). Brain flow study: brain dead. Mom stated that she had been having a few days with URI, with cough and some shortness of breath	Acquired hypothyroidism; Growth hormone deficiency; hearing loss; bilateral grade II-III vesicoureteral reflux;dysmenorrhea; mild hip dysplasia
20 years 6 months	F	N/A	History of gastroenteritis; failure to thrive (records available only as a toddler)
25 years 6 months	F	N/A	Failure to thrive; bilateral aural atresia; cleft palate; significant developmental delay; records availbale only until 7 years old
31 years 6 months	F	Sudden, unstoppable epileptic event	Meningitis at 9 months old; asthma at 12 yrs old and lasted for about 8 yrs; mitral insufficiency; history of seizures as a young adult: onset at 5 yrs old; periventricular leukomalacia (MRI)
49 years 8 months	F	N/A	Torticollis; probable scoliosis; tremors starting at the age of 4 years old, and getting worse over the years; hearing loss; cerebral atrophy (MRI)

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