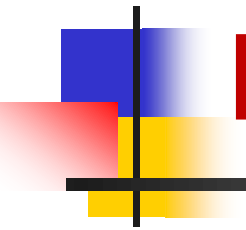


Malan Syndrome

Sotos -2

NFIX-related condition(s)

Sotos-like syndrome

- Patients with many features of Sotos syndrome but not classic
- About 8% will have an NSD1 mutation
- (?) Atypical cases of Weaver and Beckwith-Wiedeman syndromes
- Maybe 5% will have a change in a gene called NFIX (sometimes called Sotos-2 or Malan syndrome)
- Other reported genes: APC2 (Sotos-3) and SETD2 (Luscan-Lumish Syndrome)
- Several others TBA
  - Dr. Fahrner's research

Malan Syndrome (Clinical Features)

- GROWTH
  - Height
    - Birth height above centile 95
    - Postnatal height above centile 98
  - Weight
    - Birth weight above centile 95
  - Other
    - Height-weight ratio below centile 25

Malan Syndrome (Clinical Features)

- Cardinal facial characteristics include
  - long, narrow, triangular face
  - macrocephaly
  - prominent forehead
  - everted lower lip
  - prominent chin

Malan Syndrome (Clinical Features)

- HEAD & NECK
  - Head
    - Macrocephaly
    - High forehead
  - Eyes
    - Hypermetropia
    - Strabismus
    - Nystagmus
    - Astigmatism
    - Downslanting palpebral fissures
  - Mouth
    - Small mouth
    - Everted lower lip
    - Prognathism
  - Teeth
    - Premature eruption of teeth

Malan Syndrome (Clinical Features)

- SKELETAL
  - Advanced bone age
  - Chest
    - Pectus excavatum
  - Back
    - Scoliosis
  - Limbs
    - Coxa valga
  - Hands
    - Long fingers

Malan Syndrome (Clinical Features)

- ABDOMEN / GI
  - Abdominal wall hypotonia
  - Vomiting,
  - Chronic diarrhea, constipation
- SKIN, NAILS, & HAIR
  - Livedo reticularis, generalized
- Nails
  - Malformed nails

Malan Syndrome (Clinical Features)

- NEUROLOGIC
  - Seizures
- NEURO-DEVELOPMENT
  - Cognitive impairment
  - Motor delay
  - Hypotonia
- NEURO-SENSORY
  - Speech delay / apraxia
  - Vision changes
    - Strabismus, nystagmus
    - Optic nerve hypoplasia
- NEURO-IMAGING
  - Ventricular dilatation
  - Hypoplasia corpus callosum
  - Ventricular dilatation

Malan Syndrome (Clinical Features)

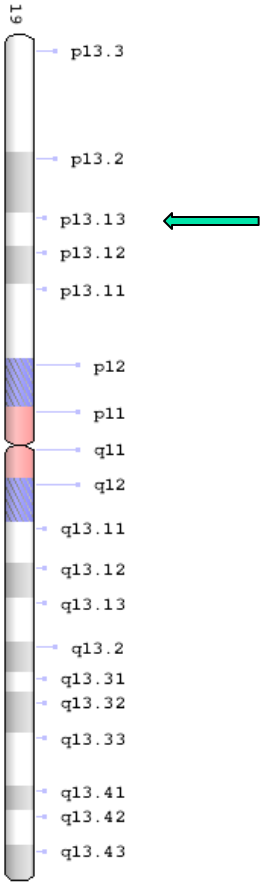
- BEHAVIORAL / PSYCHIATRIC MANIFESTATIONS
  - Autistic traits
  - Behavioral anomalies especially anxiety

observed in both our patients are marked in bold).

		NM Deletion of 19p13.2	AB *NFIX* mutation
Development	**Motor retardation**	+	+
	Hypotonia		+
	Speech delay	+	+
	Mental deficiency	+	+
	Behavioral anomalies	+	+
	Autistic traits		
Craniofacial features	Long / narrow face		+
	Downslanting palpebral fissures	+	+
	Hypertelorism	+	
	Proptosis		
	Epicanthal folds		
	Small mouth	+	
	Thin upper lip		+
	Everted lower lip		
	Prognathia		
	Small nose		
	Short nose		
	Anteverted nares		
	Low nasal bridge		
	High forehead	+	+
	Frontal bossing		
	Complex craniosynostosis		
	Flat occiput		
Eyes	Hypermetropia		
	Strabismus	+	+
	Nystagmus		
	Astigmatism		
	Optic nerve hypoplasia		
Musculo-skeletal abnormalities	Abdominal wall hypotonia		+
	Pectus excavatum		
	Coxa valga		
	Scoliosis		
	Advanced bone age	+	
Hand / foot abnormalities	**Long fingers**	+	+
	Clinodactyly of the 5th finger		
	Overlapping toes	+	
Brain MRI	Ventricular dilatation		+
	Hypoplasia of the corpus callosum		
	Mild atrophy		
	Chiari I malformation		
Seizures / EEG anomalies	**Abnormal EEG**	+	+
	Seizures	+	
Gastrointestinal abnormalities	Chronic diarrhea		
	Abdominal pain		
	Constipation	+	
	Vomiting		
	Poor feeding		
	Celiac disease		
	FTT (G-tube)		
Other abnormalities	**Malformed nails**	+	+
	Premature eruption of teeth		
	Generalized livedo		
	Hearing loss		

Malan Syndrome (GENETICS)

- NFIX gene
  - 19p13.13
- May be caused by a microdeletion or gene mutation
- Pathogenesis = haploinsufficiency
- Autosomal dominant inheritance



NFIX gene

- NFIX gene encodes a protein that functions as a transcription factor
  - Transcription factors turn specific genes "on" or "off" by binding to nearby DNA sequences.
- Very little is known about the genes regulated by NFIX and the role they play in causing Malan syndrome
- Different changes in the NFIX gene cause a different condition known as Marshall-Smith syndrome

Deletion Cases

- Involves genes other than NFIX
  - Ataxia
  - Migraines
    - One case had cyclical vomiting responsive to pizotifen (migraine medication)

Genotype does not define phenotype !!!!

That is, you can not predict what a particular person with NF1X gene changes is going to experience or not experience based on the genetic test results.

Pleiotropy

- Multiple clinical features all due to changes in the same gene
- For example people with NF1X gene changes can have:
  - Overgrowth
  - Macrocephaly
  - Vision problems
  - Hearing loss
  - Skeletal changes
  - Neurologic changes
    - Neurodevelopmental
    - Seizures
    - Structural brain changes (seen on MRI)

Important Clinical Genetic Concept

- Each person with Malan syndrome will not exhibit every reported trait.
- They have an increased threshold for developing certain problems, but everyone's baseline threshold is different.
- It is sort of like a buffet line ….

What's on the buffet line?

- Common features
  - Overgrowth
  - Macrocephaly
  - Low muscle tone
  - Speech /language problems
  - Facial changes
  - Developmental delays
  - Behavioral changes
- Less common features
  - Seizures
  - Skeletal changes
  - Gastrointestinal problems
  - Vision / hearing problems

Expanded Phenotype

- Often described as a spectrum
  - i.e. the spectrum of NF1X related features
- It has been suggested that at a minimum 100 cases of a condition need to be described before it can be assumed that the major part of the phenotypic spectrum has been identified
  - (2015) 20
  - (2018) 80
  - (2019) ~ 82

Important Clinical Genetic Concepts

- The NF1X is only one of 19,000 genes that a person has.
  - Even if it has a change, this does not 'trump' the way the other genes work.
- A person with Malan syndrome will still have all of the other genetic traits and predispositions that are inherited from the parents.
  - Malan syndrome does not define the child!

CLINICAL MANAGEMENT

1. Hypotonia

Hypotonia

- Common in Malan syndrome
- Low muscle tone
  - Not the same as strength

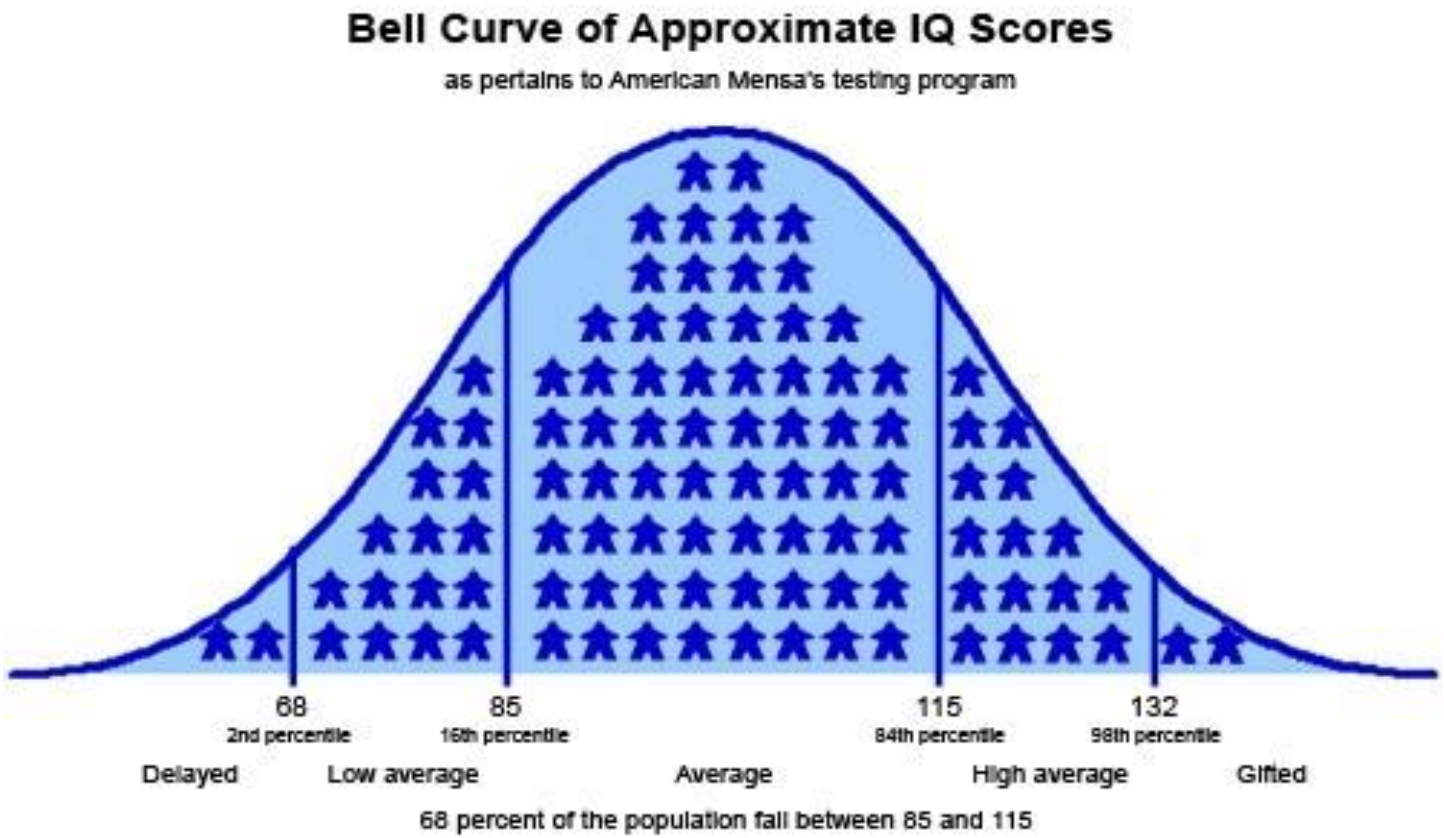
Consequences of hypotonia

- 'Floppy baby'
- Delayed motor development
  - Problems over-coming gravity
- Loose (hyperflexible) joints
  - Not a CTD
- Oro-motor problems
  - Protruding tongue
  - Drooling
  - Problems with feeding / swallowing
- Frequent infections (not immune deficiency)
  - Ear infections
  - Colds, bronchitis

Hypotonia

- Generally improves with time
- Probably never completely goes away
- Therapies (don’t have to know anything about Malan syndrome)
  - Physical therapy
  - Occupational / speech therapy
  - Orthotics
  - Surgeries

2. Neuro-developmental delays



Key Principles of Development

- Development is not a foot race
- Few predictive tools
  - Neuropsychologic testing

Pediatric Neuropsychology

What is assessed?

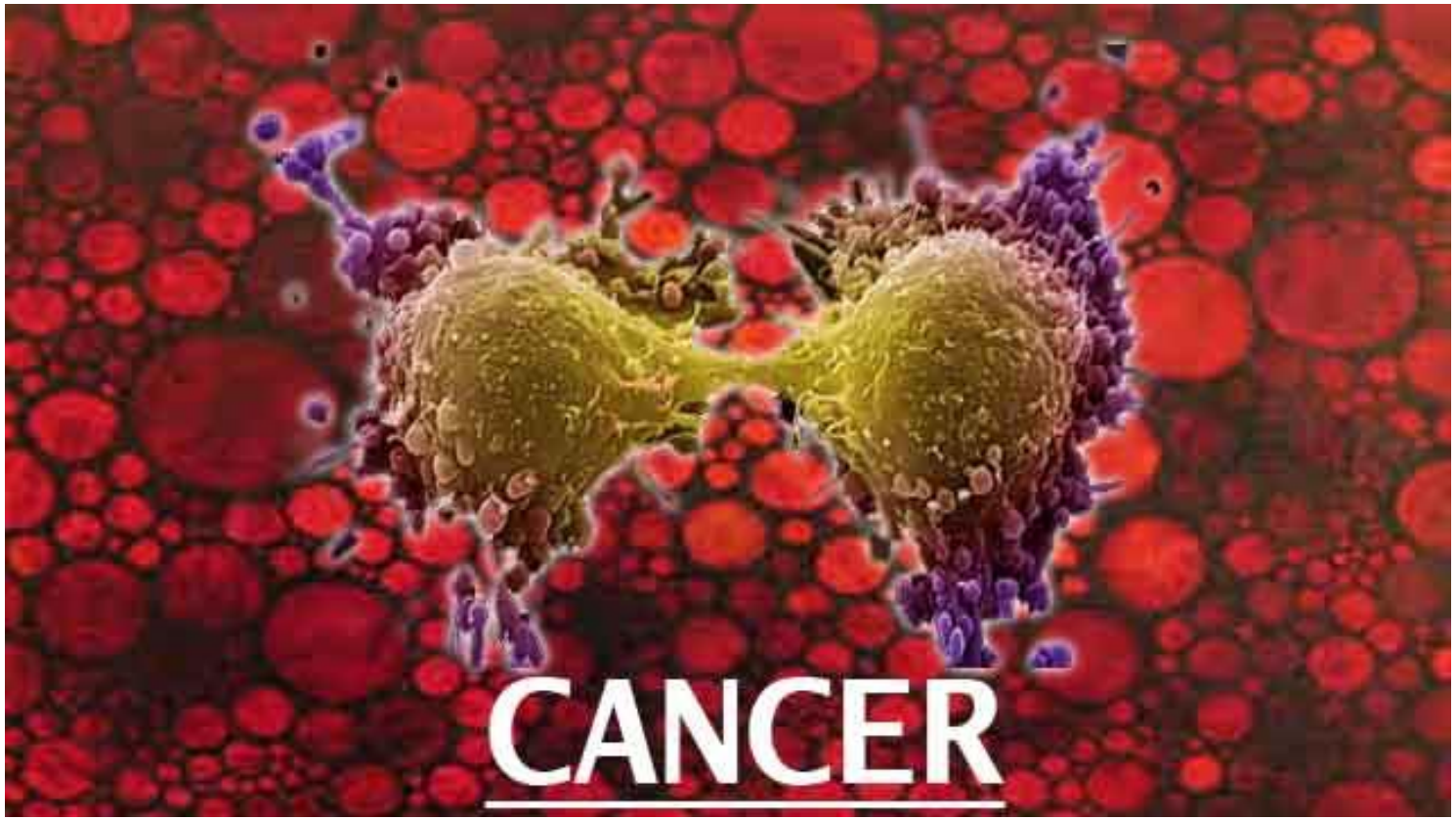
- Intelligence
- Achievement skills
- Attention / Executive Functioning
- Learning & Memory
- Language
- Sensory & Sensory Motor
- Motor
- Behavioral, Emotional, & Social Functioning

3. Behavioral changes

Which therapies to use?

- Consider risks / side effects
- Look for reputable documentation of efficacy
- Seek input from trusted health care professionals
- Talk to other families
- If it isn’t working stop it
- Customize for your child

4. What about cancer?



Cancer and Malan syndrome

- Nothing reported to date

Secretory Carcinoma of the Skin: Report of 6 Cases, Including a Case With a Novel NFIX-PKN1 Translocation.

5. Seizures

- Seizures
  - can appear in many forms
- Some forms are subtle
  - e.g. absence seizures
- Temperature control problems may exacerbate seizures
  - “febrile seizures” (actually seizures associated with fevers)

Watch for 'stuff'
If it ain't broke, don't fix it

- The following are appropriate at times of clinical evaluations:
  - Thorough history to identify known clinical sequelae of Malan syndrome
  - Examination / monitoring for curvature of the spine
  - Audiologic assessment
  - Referral to a pediatric ophthalmologist. May want pediatric neuro-ophthalmologist Referral to the appropriate clinical specialist if problems are identified.