Malan Syndrome: A distinct disorder of overgrowth and neurodevelopment

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No Disclosures
Objectives

• To introduce concepts of Genetics
• To understand Malan syndrome as a genetic disease
• To provide an update on current knowledge of molecular changes in Malan syndrome
• To review clinical features of Malan syndrome
• To understand connection between Malan syndrome and Sotos syndrome
DNA, Genes, and the Genetic Code

- Our bodies are made up of billions of cells
- Each cell contains genetic material in the form of DNA
- DNA contains 22,000 genes
- Genes determine traits
- Each gene is a set of instructions (code) to make a protein with a specific function
- DNA sequence (code) is made up of 4 bases
- “Genetics” refers to the DNA code

Adapted from http://elcaminogmi.dnadirect.com
Adapted from http://rachelscsusm511.blogspot.com/2012/11/unit-4-lesson-4-chromosomes-dna.html
Genetic mutations are mistakes in the DNA code that cause disease

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Mutation

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Mutations in the *Nuclear Factor one X (NFIX)* gene cause Malan syndrome.
Summary 1

• DNA is the genetic material and contains genes

• Mutations are mistakes in genes that alter the DNA sequence or code

• Mutations in genes \((NFIX)\) cause disease (Malan syndrome)
How do mutations in \textit{NFIX} cause Malan syndrome?
**NFX** encodes a transcription factor that turns many genes (with many functions) on and off.

When **NFX** is not fully functional, these genes are not turned on and off correctly.
Malan syndrome results from mutations in the *NFIX* gene

- Affected individuals typically have *de novo* and unique mutations
- Inherited in an autosomal dominant manner
- Most mutations that cause Malan syndrome occur in exon 2
- Other mutations in *NFIX* can cause a distinct condition, Marshall-Smith syndrome
- A smaller number of individuals with Malan syndrome have a 19p13 deletion that includes *NFIX* and other genes

Modified, Priolo, Fahrner et al. *Hum Mut* 2017
Facial characteristic in Malan syndrome

Priolo et al. Hum Mutation 2018
Clinical features in individuals with Malan syndrome

- Overgrowth
  - Macrocephaly
  - Tall stature
- Intellectual disability (ID)/global developmental delay
  - Moderate-severe with some mild
- Neurobehavioral features
  - Hypotonia
  - Anxiety
  - Autistic features
  - Seizures/EEG abnormalities*
  - Brain MRI findings
- Eye findings
  - Small optic nerves
  - Low vision
  - Poor depth perception
  - Reduced peripheral vision
  - Strabismus
  - Cortical vision impairment
- Musculoskeletal findings
  - Scoliosis +/- kyphosis
  - Pectus deformity of chest
  - Slender body habitus
- Highly arched palate
- Aortic, PA dilation/aneurysms
Work-up for individuals with Malan syndrome

- Echocardiogram to evaluate for cardiac structural anomalies

- Abdominal ultrasound to evaluate for organ enlargement or structural anomalies

- Ophthalmologic exam to evaluate for eye findings

- Consider brain MRI to evaluate for structural anomalies
Clinical Genetic Testing for Malan syndrome

- Sequencing and deletion/duplication of *NFIX* (gene panel preferred over single gene testing)
- Exome sequencing-most/all protein coding genes (trio preferred over proband only)
- SNP microarray/Array CGH to evaluate for the deletion
- Parental testing
NFX is involved in multiple organs systems

Craniofacial development
Eyes
Blood vessels
<table>
<thead>
<tr>
<th>Organ system or disease</th>
<th>Evidence for role of NFIX</th>
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<tbody>
<tr>
<td>CNS (brain size)</td>
<td>$Nfix^{-/-}$ mice have significantly larger brains</td>
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<td>Reduced symmetric neural stem cell divisions in $Nfix^{-/-}$ mice</td>
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<td>Bias towards oligodendrogenesis in $Nfix^{-/-}$ hippocampal NSCs</td>
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<td>$Nfix^{-/-}$ mice have defects in learning and memory</td>
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<tr>
<td>CNS (cortex and ventricles)</td>
<td>Aberrant neuroblast progenitor proliferation in SVZ and neuroblast migration in RMS of $Nfix^{-/-}$ mice</td>
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<td>Delayed radial glial differentiation in $Nfix^{-/-}$ mice</td>
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<td></td>
<td>Bias towards oligodendrogenesis in $Nfix^{-/-}$ NSCs</td>
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<td>$Nfix$ implicated in regulation of quiescence of NSCs</td>
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<td>$Nfix$ required for normal ependymal cell structure and function</td>
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<tr>
<td>CNS (cerebellum)</td>
<td>$Nfix$ is expressed in multiple cell populations in cerebellum</td>
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<td>Delay in development of cerebellar granule neurons, Purkinje cells, and Bergmann glia in $Nfix^{-/-}$ cerebella</td>
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<td>PNS (spinal cord)</td>
<td>Delayed astrocyte differentiation in $Nfix^{-/-}$ spinal cord</td>
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<td>Hematopoiesis</td>
<td>Reduced colony-forming ability in $Nfix$-deficient HSPCs</td>
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<td>$Nfix$ promotes $Mpl$ expression and HSPC survival</td>
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<td>$Nfix$ can promote conversion of B cells to myeloid cells</td>
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<td>Loss of $Nfix$ promotes myeloid and lymphoid differentiation</td>
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<td>Musculature</td>
<td>NFIX regulates embryonic-to-fetal muscle transition</td>
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<td>NFIX interacts with PKCθ and Mef2A, activating MCK expression</td>
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<td>NFIX represses $MyHC$-$I$ expression by inhibiting NFATc4</td>
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<td>$Nfix$ modulates myostatin expression</td>
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<td>$Nfix$ mediates Sox6 inhibition of $MyHC$-$I$ expression</td>
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Why was Malan syndrome previously called Sotos-like syndrome or Sotos 2?

- Sotos syndrome and Malan syndrome have very similar features
- Many individuals with Malan syndrome previously had a clinical diagnosis of Sotos syndrome but no mutation in *NSD1*
- We now know Malan syndrome is a distinct disorder
- Many other distinct disorders resemble Sotos syndrome and Malan syndrome
- Malan syndrome is no longer called Sotos 2 (or Sotos-like syndrome)
We know the molecular cause of half of the overgrowth and intellectual disability disorders that overlap closely with Sotos and Malan syndromes.

Modified from Tatton-Brown et al. AJHG 2017
Acknowledgements

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Sotos Syndrome Support Association

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