Malan Syndrome: A distinct disorder of overgrowth and neurodevelopment

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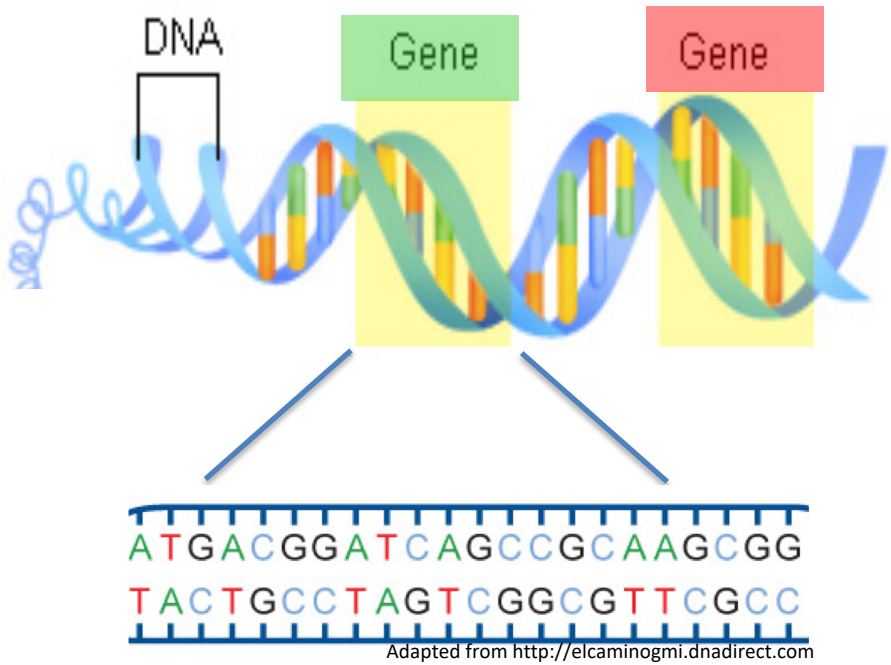
No Disclosures

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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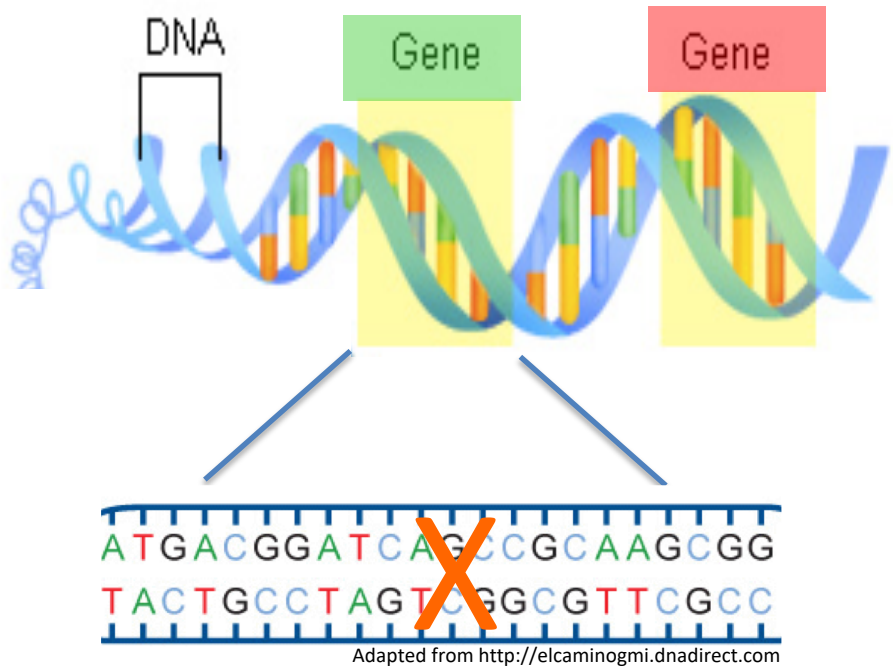

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Mutation

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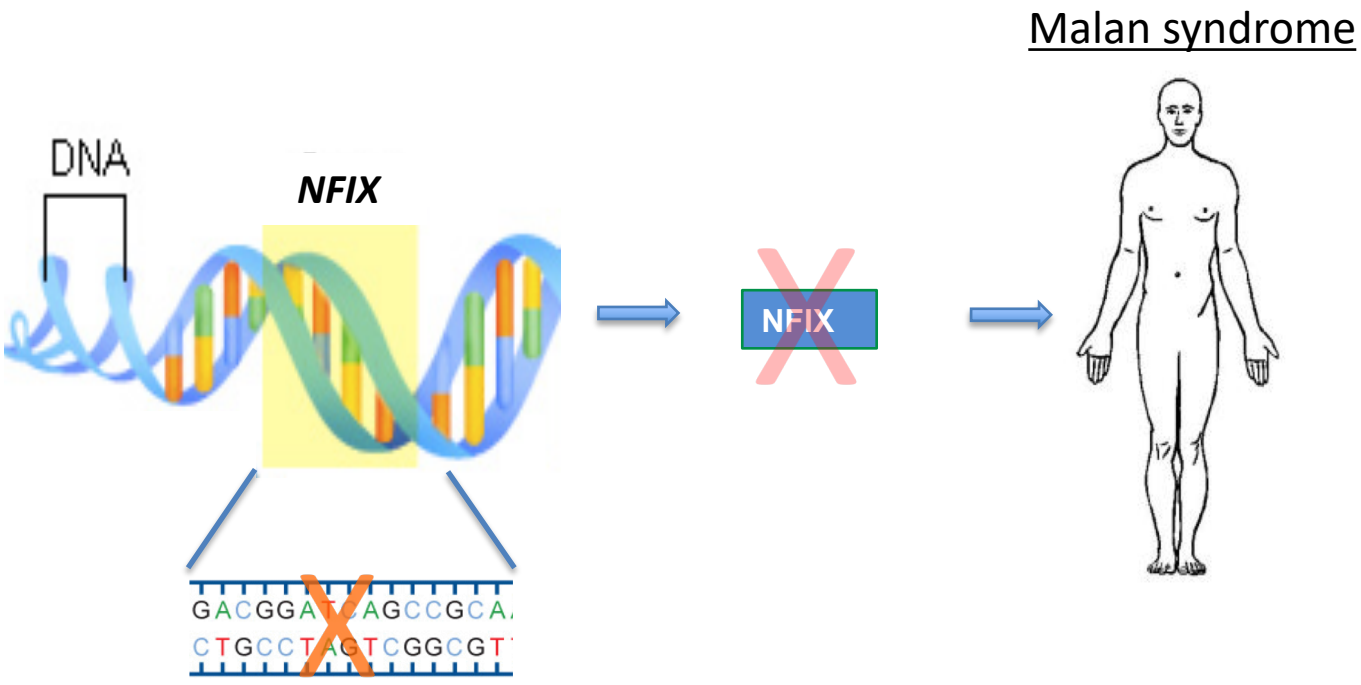
Mutations in the *Nuclear Factor one X (NFIX)* gene cause Malan syndrome



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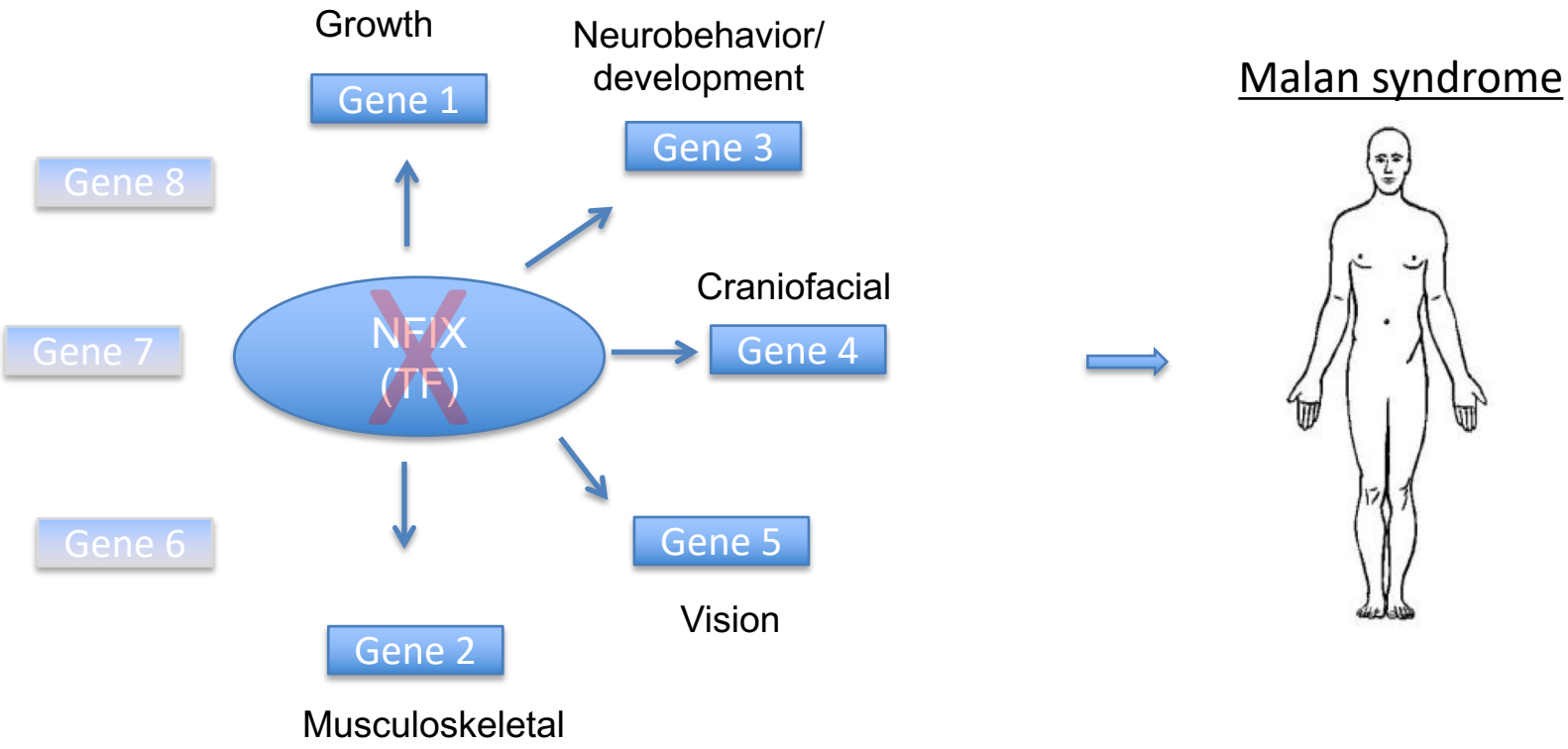
Summary 1

- 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)

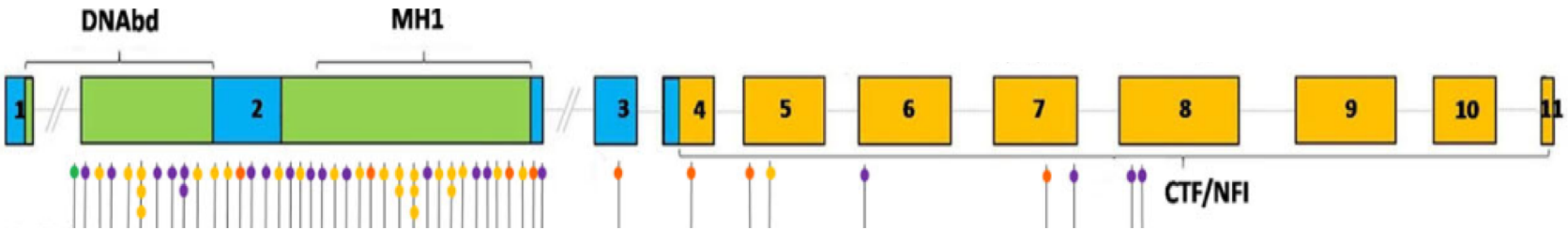
How do mutations in *NFIX* cause Malan syndrome?

NFIX encodes a transcription factor that turns many genes (with many functions) on and off



When *NFIX* 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

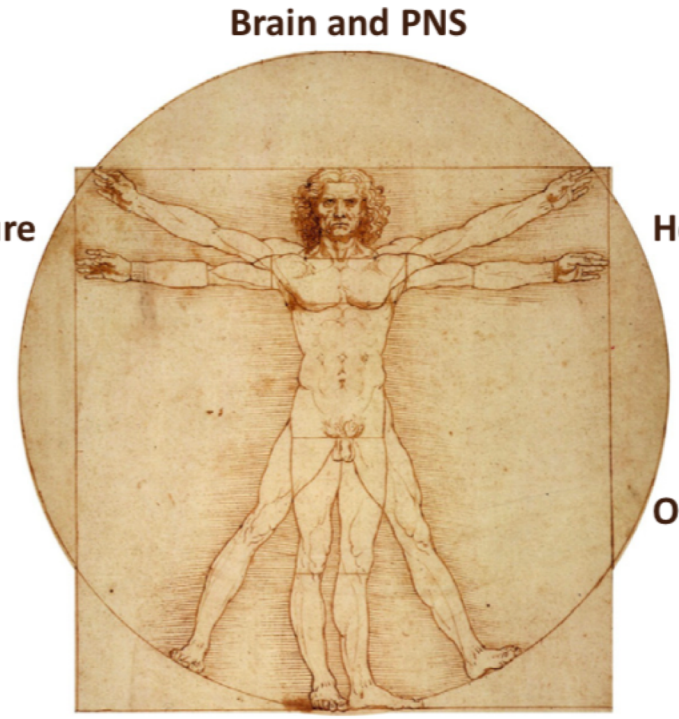
Work-up for individuals with Malan syndrome

- 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

NFIX is involved in multiple organs systems



Craniofacial development
Eyes
Blood vessels

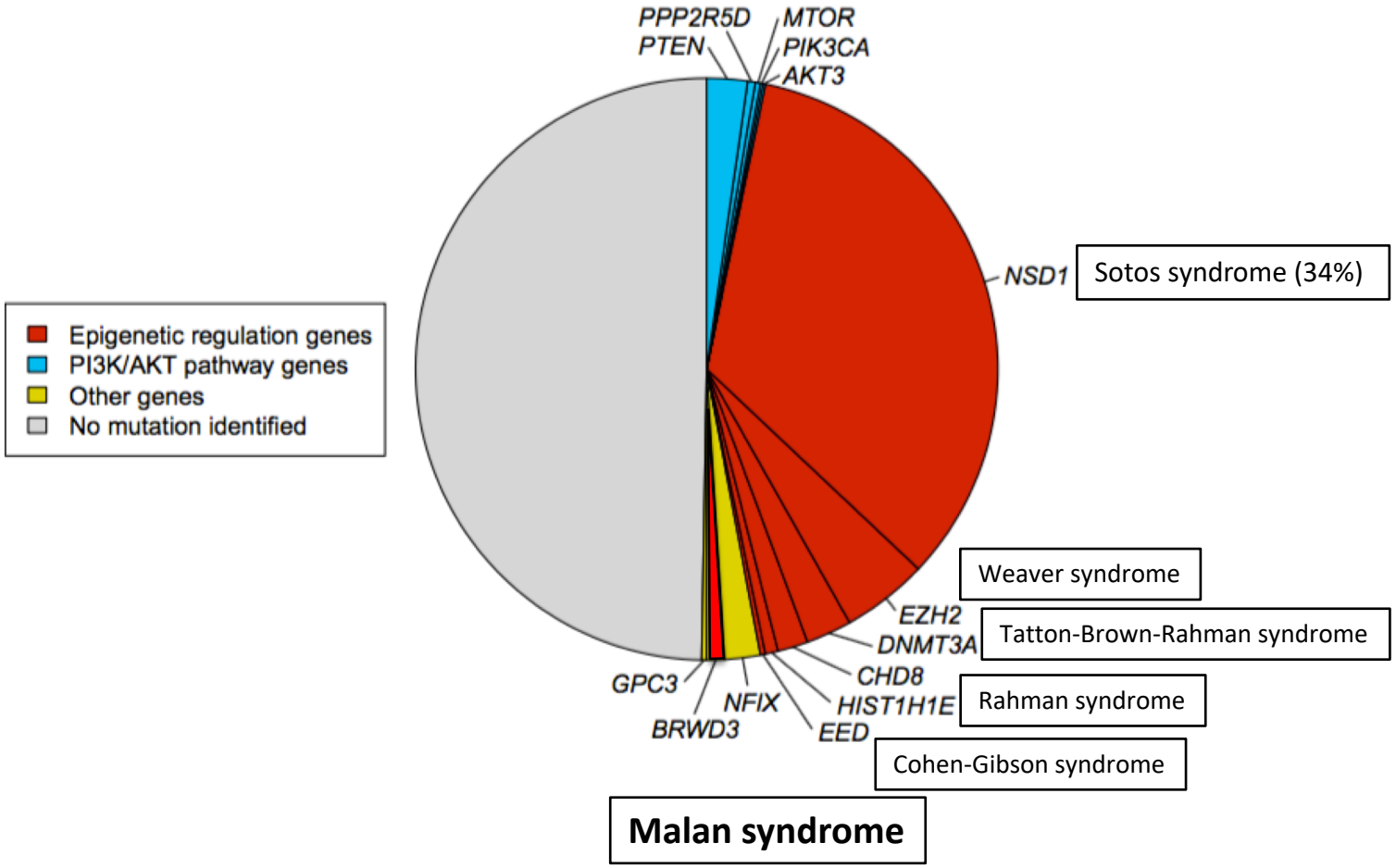
Organ system or disease	Evidence for role of NFIX
CNS (brain size)	*Nfix*$^{-/-}$ mice have significantly larger brains
CNS (hippocampus)	Delayed hippocampal progenitor cell differentiation in *Nfix*$^{-/-}$ mice
	Reduced symmetric neural stem cell divisions in *Nfix*$^{-/-}$ mice
	Bias towards oligodendrogenesis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

Piper *et al. Trends Cell Biol* 2019

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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https://igm.jhmi.edu/ecc-clinic
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