Sotos Syndrome: A *Genetic* disorder with *Epigenetic* consequences

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The McKusick-Nathans
Epigenetics and Chromatin Clinic (ECC)

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MEDICINE
DEPARTMENT *of* GENETIC MEDICINE

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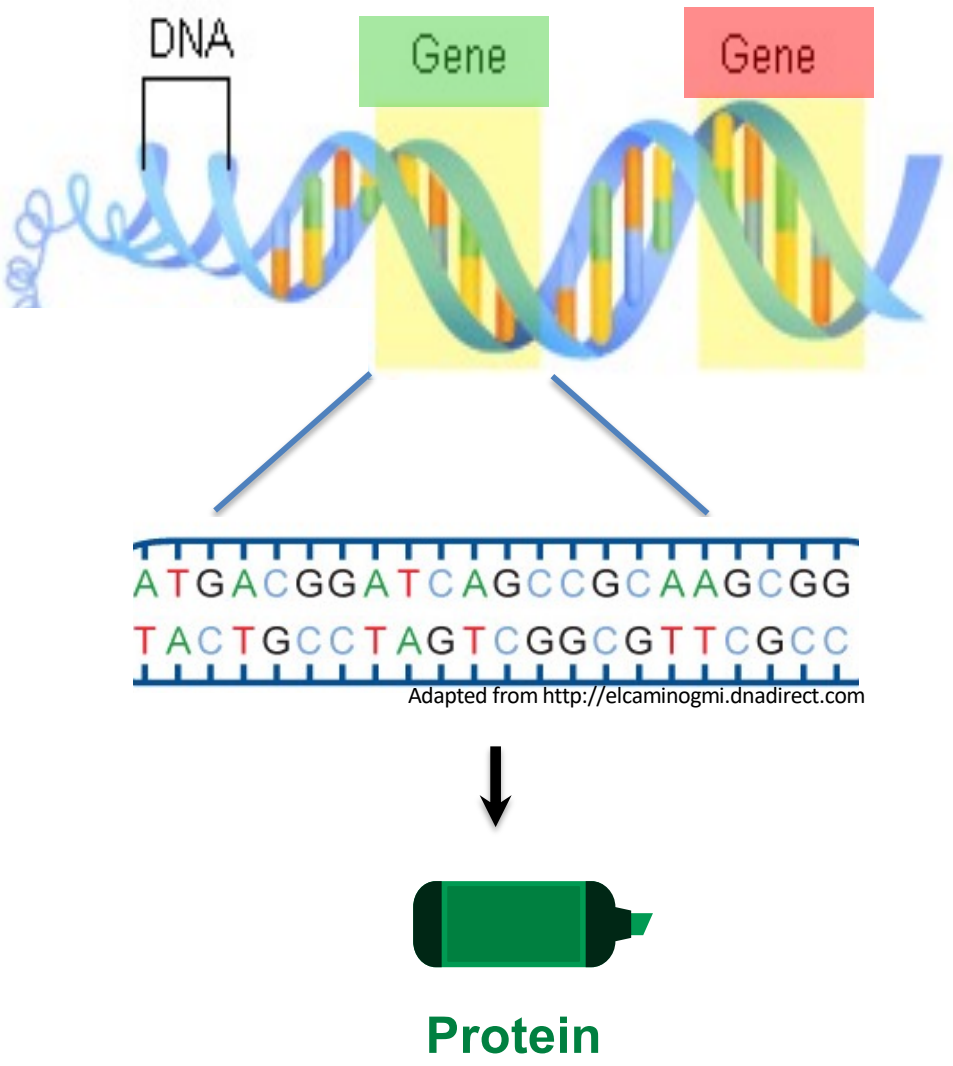
No Disclosures

Objectives

- To introduce concepts of Genetics and Epigenetics
- To understand Sotos syndrome as a genetic disease
- To understand epigenetic consequences of deficiency of *NSD1*
- To provide an update on current knowledge of molecular changes in Sotos syndrome
- To inform you about ongoing research for Sotos syndrome
- To mention our novel & multidisciplinary Epigenetics and Chromatin clinic at Johns Hopkins

DNA, Genes, and the Genetic Code

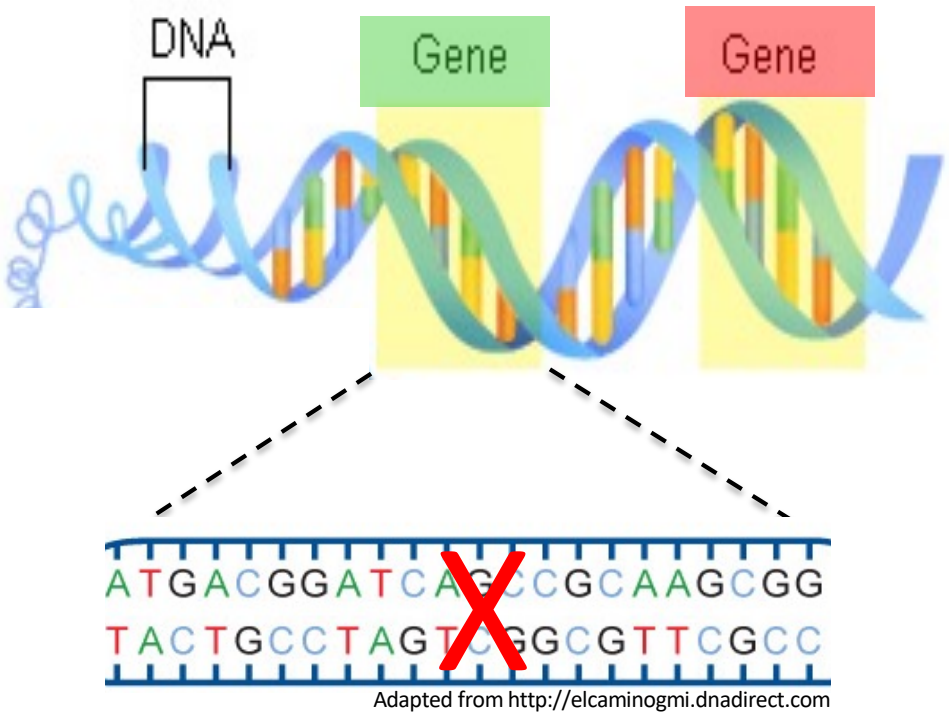
- Our bodies are made up of billions of cells
- Each cell contains genetic material in the form of DNA
- DNA contains ~22,000 genes
- Genes determine traits
- Each gene is a set of instructions (code) to make a protein with a specific function
- Two copies of each gene
- DNA sequence (code) is made up 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 changes in the DNA code cause disease



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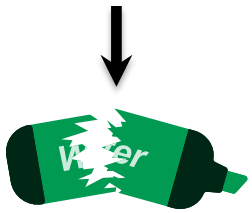
DNA Mutation (Variant)



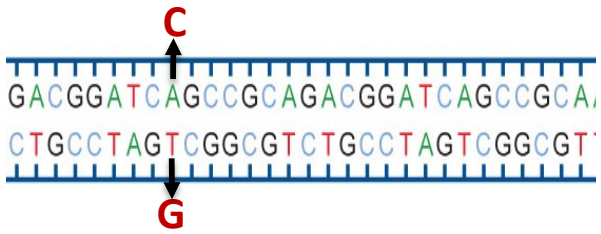
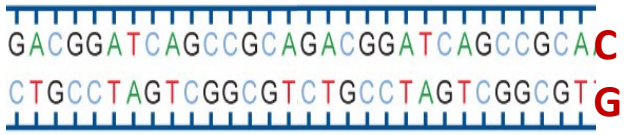
No protein
-OR-
Altered function of protein

Mutations (Variants)

- Spelling errors in the DNA code
- Can be:
  - Missing base(s)
  - Extra base(s)
  - Incorrect base(s)
- Result in:
  - production of a protein with altered function
  - no protein (from that copy)

Adapted from http://rachelscsusm511.blogspot.com/2012/11/unit-4-lesson-4-chromosomes-dna.html

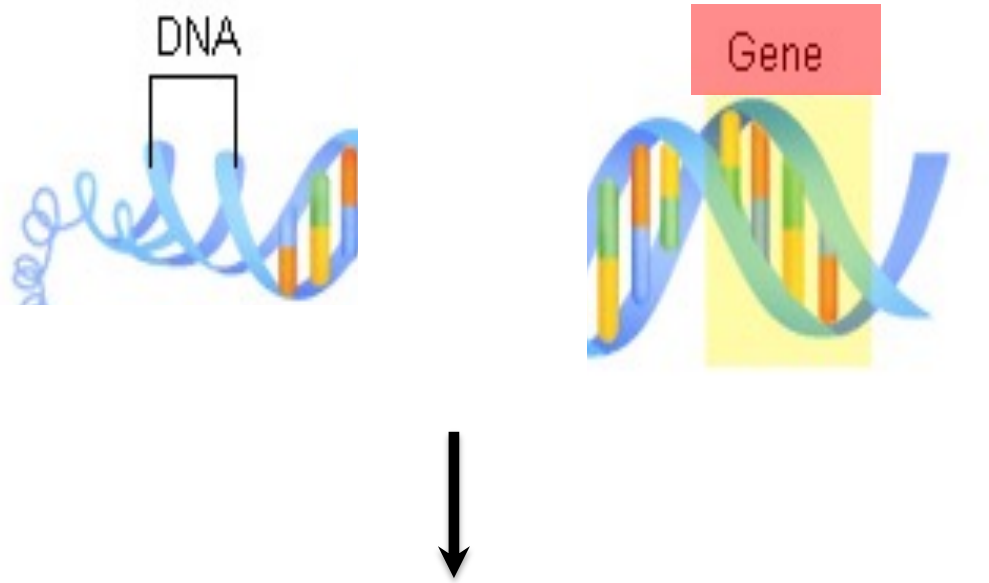
Types of mutations (variants) and their effects

	Gene Mutation (variant)		Effect on protein
Normal		→	 None
Missense (misspelling)		→	 Reduced function
Insertion of base(s)		→	No protein
Deletion of base(s)		→	No protein

These are what we are referring to when we say Sotos syndrome due to a “mutation.”

A different type of genetic change (a larger deletion) in the DNA code can cause Sotos syndrome

DNA Deletion
(5q35 deletion)



No protein

Deletions

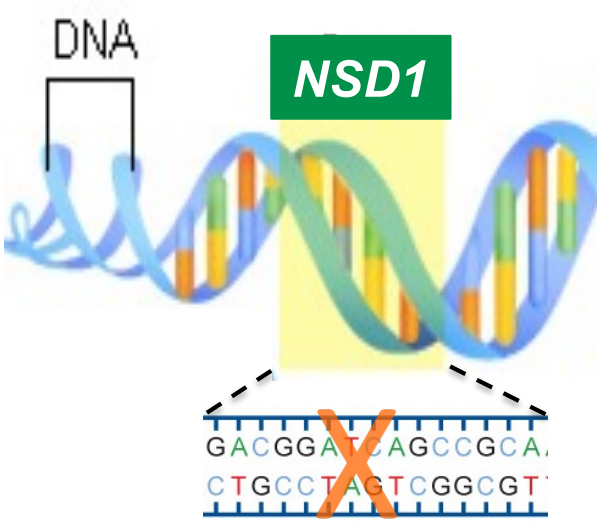
- Missing pieces of DNA
- Can include:
  - A single gene
  - Multiple genes
- Result in
  - no protein from that copy of the gene

This is what we are referring to when we say Sotos syndrome due to a “deletion.”

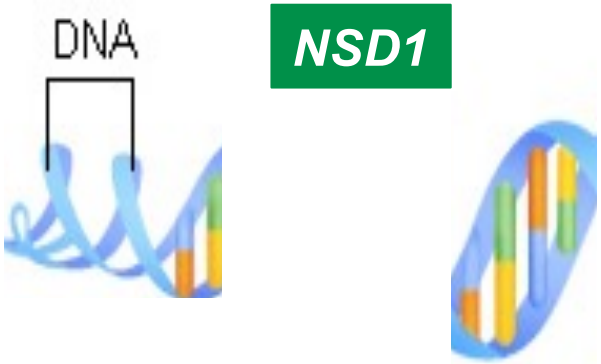
Adapted from http://rachelscsusm511.blogspot.com/2012/11/unit-4-lesson-4-chromosomes-dna.html

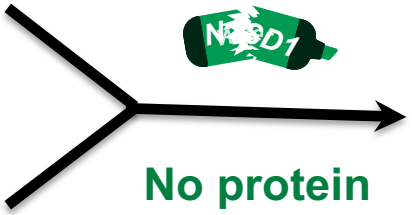
Mutations or Deletions of the *NSD1* gene cause Sotos syndrome

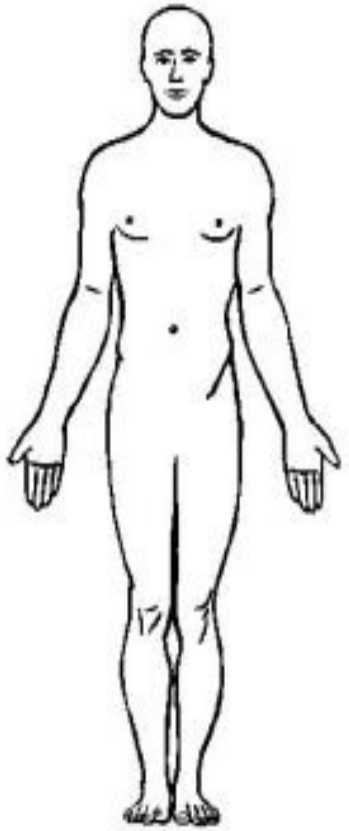
Mutation



Deletion

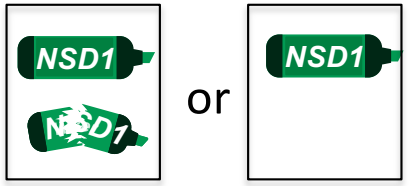






Sotos syndrome

Deficiency of NSD1



Adapted from http://elcaminogmi.dnadirect.com

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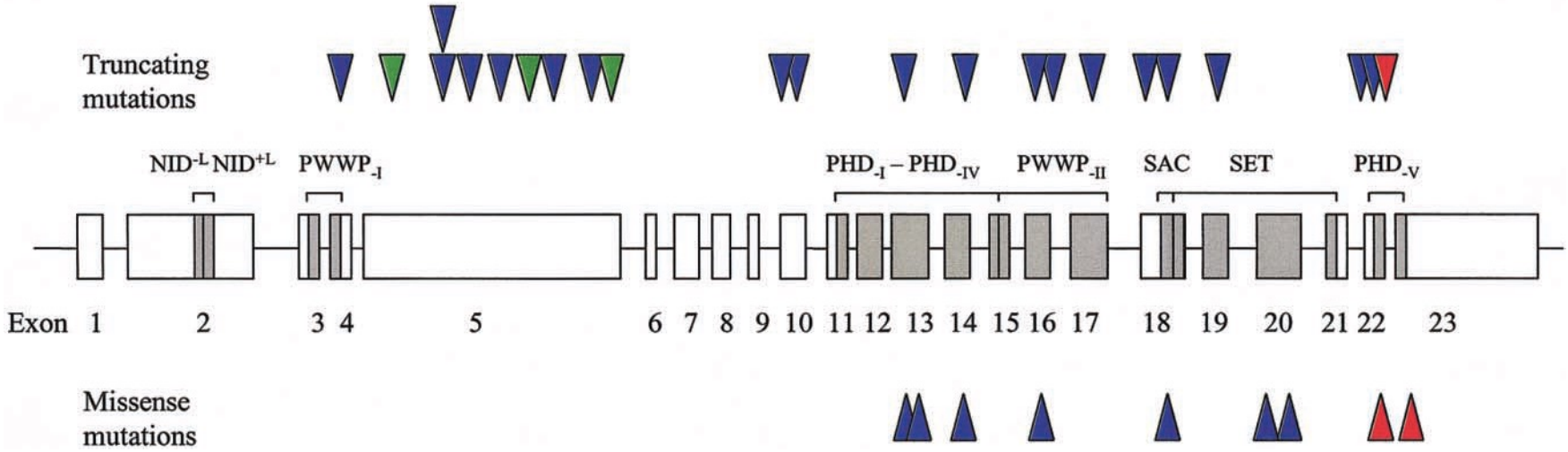
Sotos syndrome is caused by heterozygous *de novo* mutations in *NSD1*



- Inherited in an autosomal dominant manner
- *De novo,* unique mutations predominate
- Loss of function (truncating) mutations occur throughout (top)
- Missense mutations occur in the functional domains (bottom)
- Mutational mechanism haploinsufficiency
- ~90% of individuals with features of Sotos syndrome have identifiable mutations in *NSD1*
  - 80% intragenic mutations
  - 10% whole gene deletions +/- additional genes
  - 10% unknown versus misdiagnosis

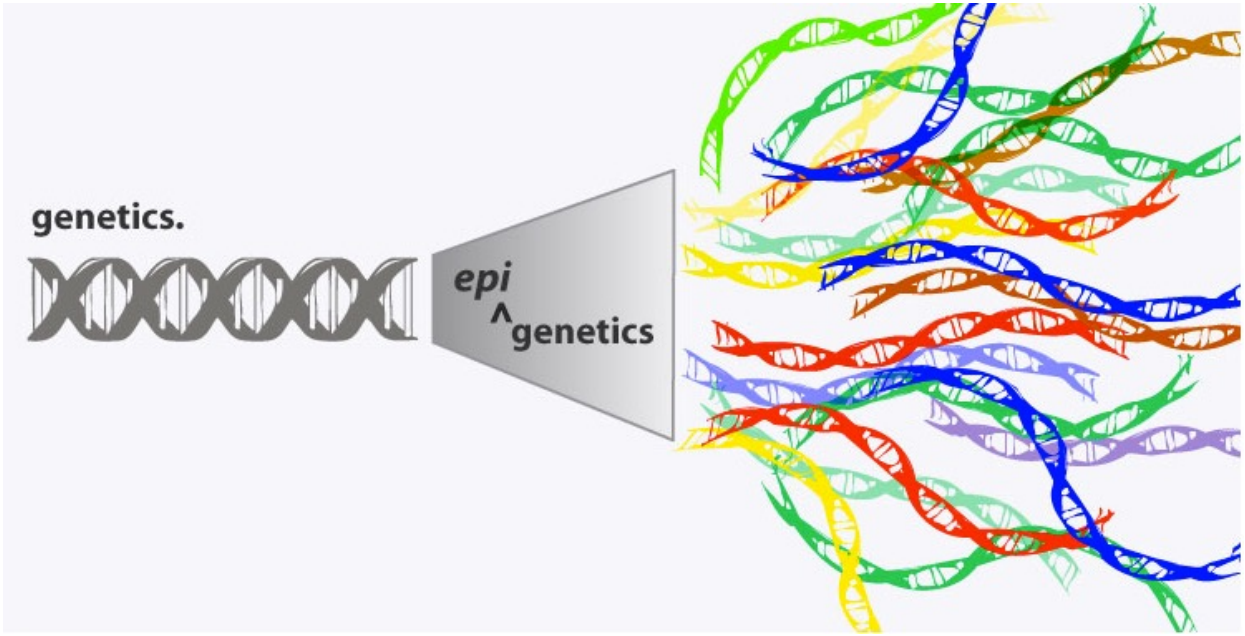
Douglas et al, AJHG 2003

Summary 1

- DNA is the genetic material and contains genes
- Genes encode proteins that have particular functions in the body
- Genetic mutations are spelling errors in the DNA code that cause disease
- Deletions of genes cause disease because the gene is missing
- Mutations or deletions of *NSD1* → Deficiency of NSD1 → Sotos syndrome

Sotos syndrome is a *Genetic* disorder with *Epigenetic* consequences

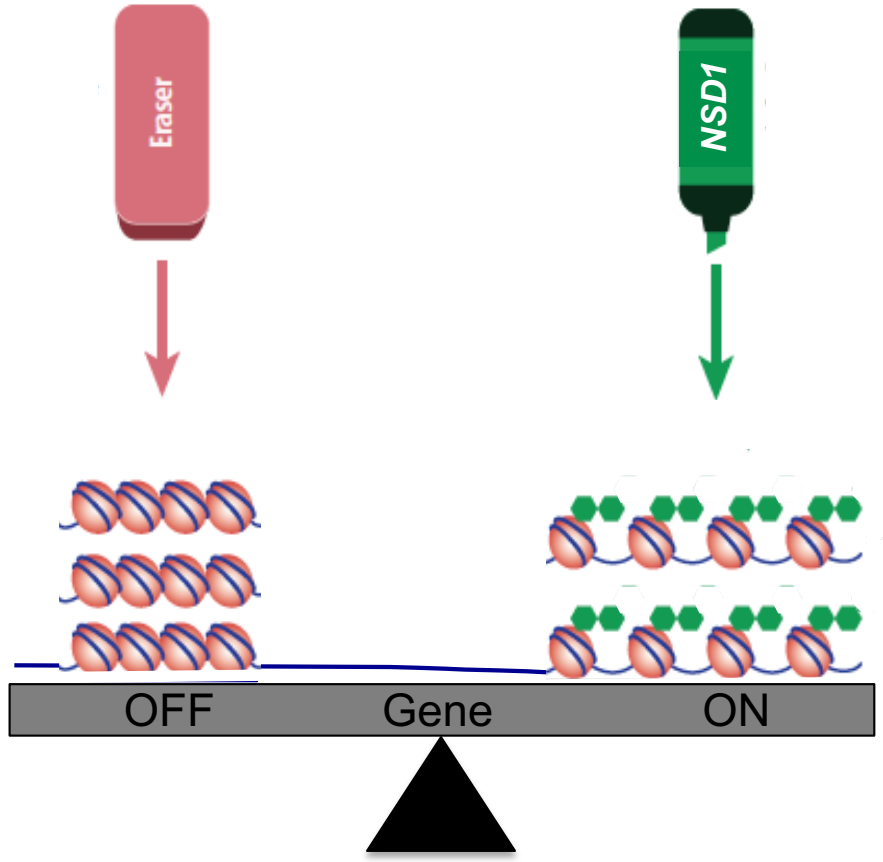
Epigenetic Machinery: The Genome's “Highlighter”



knowingneurons.files.wordpress.com

Epigenetics allows cells with the same genetic information to turn genes on and off differently

Deficiency of NSD1 may cause Sotos syndrome by disrupting epigenetic marks and expression of other genes



Adapted from Fahrner and Bjornsson, *Ann Rev Gen & Hum Gen* 2014

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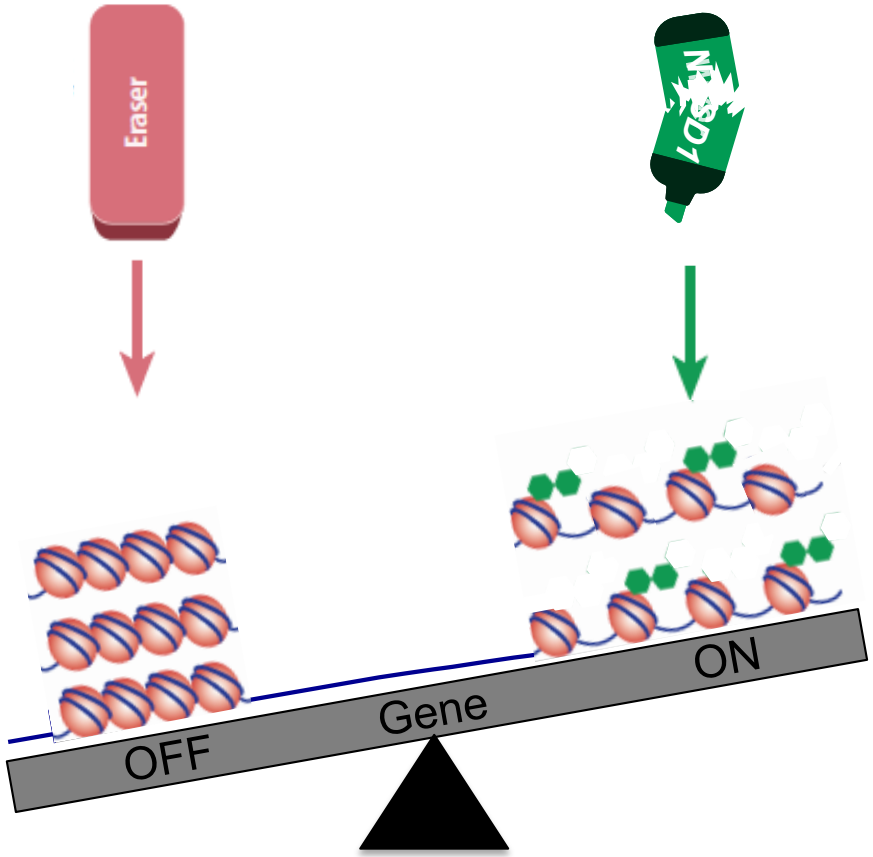

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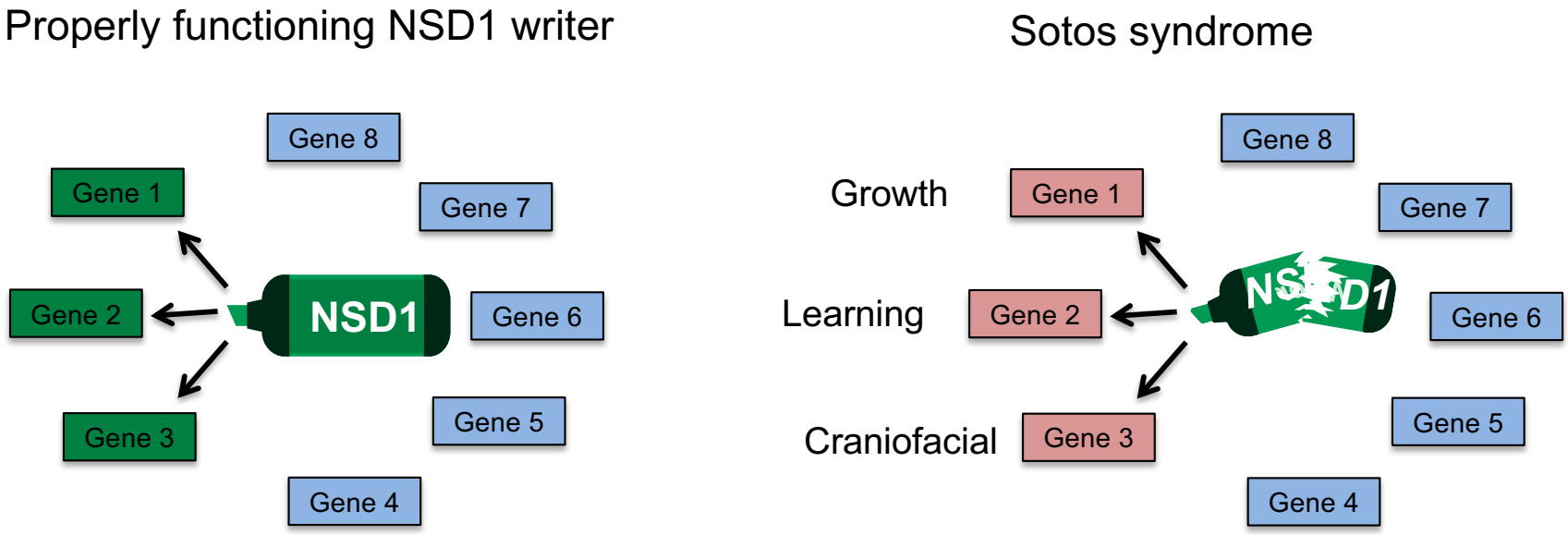
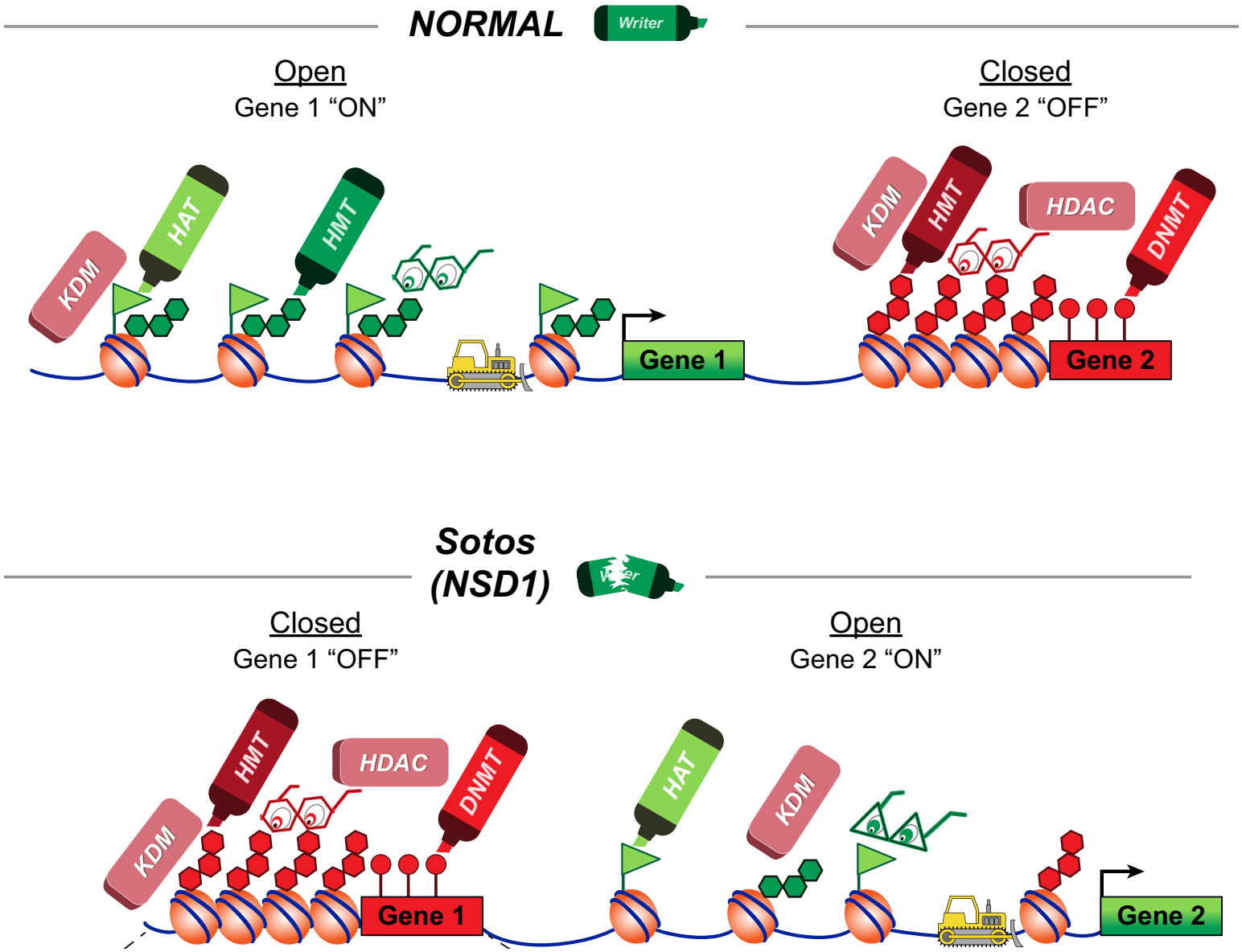


Direct and indirect effects on target genes in Sotos syndrome



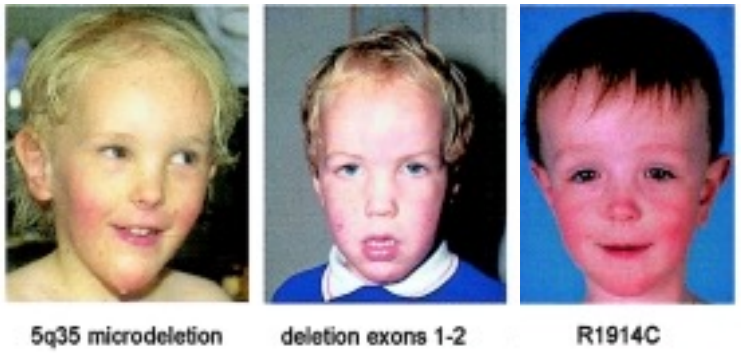
Fahrner and Bjornsson, *Hum Molec Genet* 2019

Summary 2

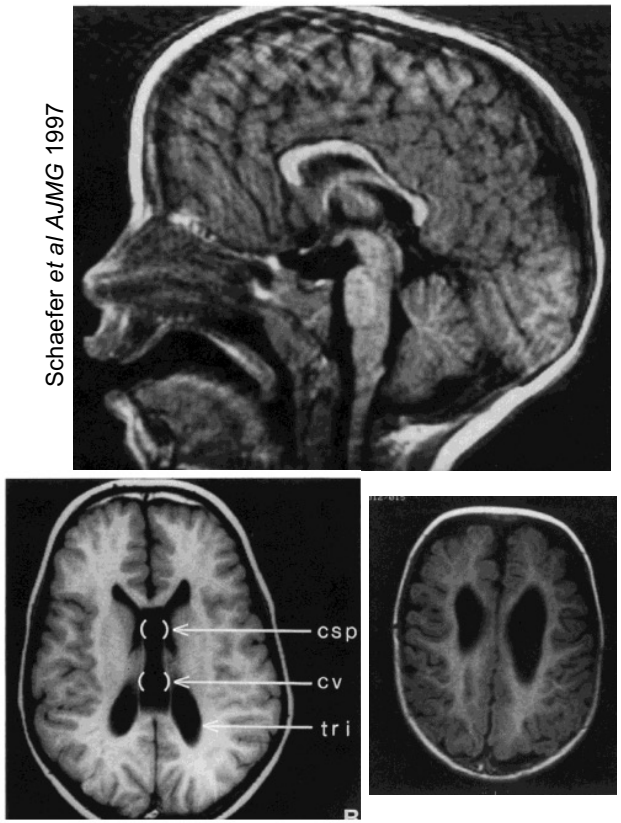
- Epigenetic marks “highlight” certain genes to be turned ON or OFF so that cells can function properly
- NSD1 is a writer of an epigenetic mark (histone methylation on H3K36)
- Deficiency of NSD1→ alters histone methylation → genes not turned on and off correctly
- NSD1 target genes determine the clinical features of Sotos syndrome

Common features in individuals with Sotos Syndrome

Modified, Tatton-Brown *et al. AJHG* 2005



Schaefer *et al AJMG* 1997



Overgrowth

Intellectual disability/developmental delay

Characteristic facial features

Characteristic behaviors

Other findings

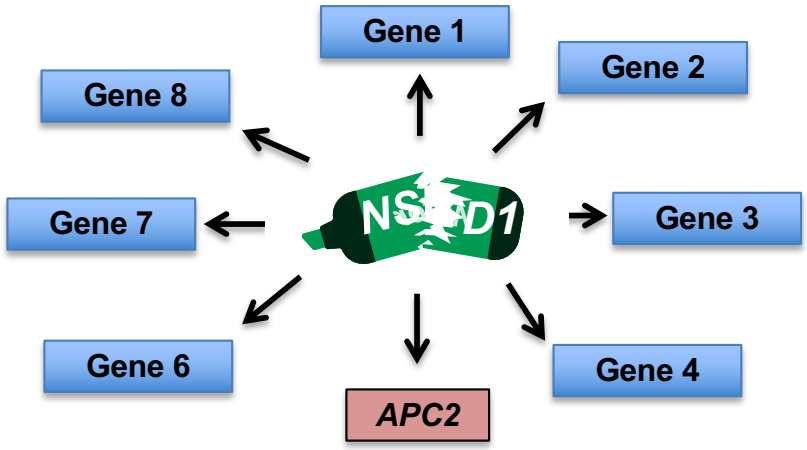
- Advanced bone age
- Hypotonia
- Joint laxity
- Scoliosis
- Seizures
- Eye findings
- Cardiac anomalies
- Renal anomalies

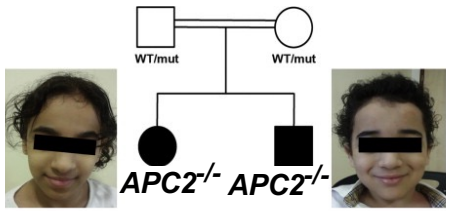
Characteristic brain MRI findings

- Thinning of corpus callosum
- Enlarged lateral ventricles
- Prominent subarachnoid spaces

Recent, ongoing, and upcoming research on Sotos syndrome and related disorders

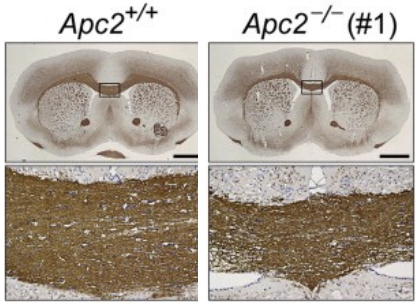
Deficiency of NSD1 may cause Sotos Syndrome by Disrupting Epigenetic Marks and Target Gene Expression

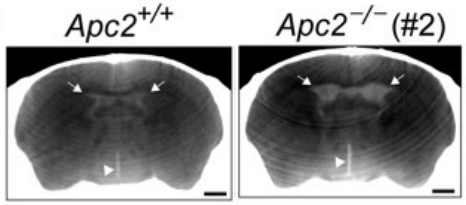


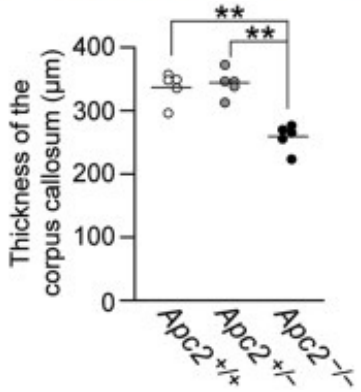


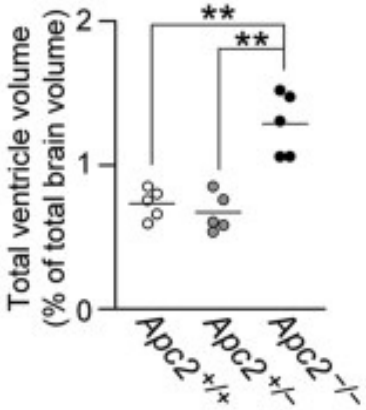
-Macrocephaly +/- tall
-Intellectual disability
-Characteristic behaviors
-Brain findings
-Some SS facial features

APC2$^{-/-}$ mice
-Relative macrocephaly
-Abnormal head shape
-Impaired learning/ memory/behavior



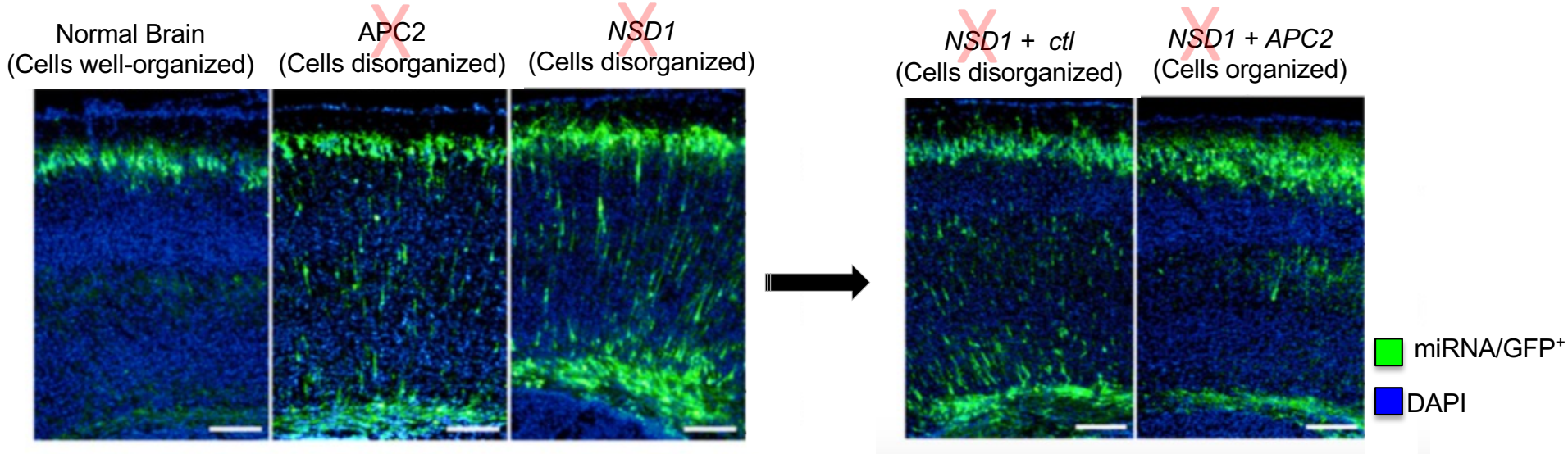






Almuriekhi *et al. Cell Reports* 2015

APC2 is a target of NSD1 and is responsible for some features of Sotos syndrome



Conclusions

APC2 is target of *NSD1*

APC2 responsible for

- -Impaired learning
- -Abnormal behaviors
- -Macrocephaly
- -Brain malformations

APC2 not responsible for other features of SS

Elegant work but this is not a mouse model of Sotos syndrome because it does not target NSD1 (but rather APC2).

Almuriekhi *et al. Cell Reports* 2015

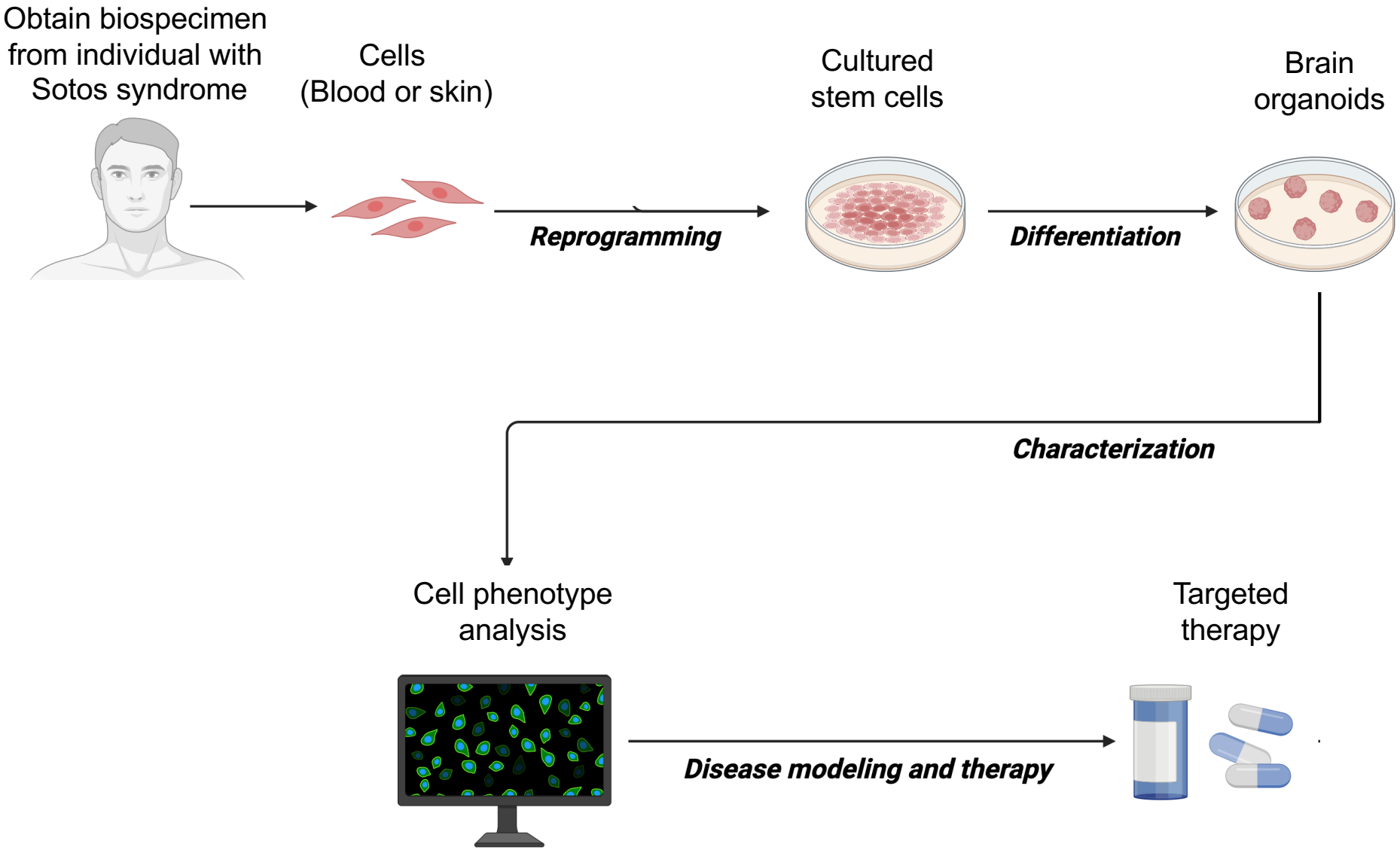
A newer mouse model of Sotos syndrome

- *NSD1* expressed mostly in neurons (brain cells) in key brain regions
  - Cerebral cortex/hippocampus/subventricular zone
- Behavioral tests
  - Sotos syndrome mice showed altered social interactions with other mice
  - No difference in learning/memory
- Growth
  - No difference in body weight or brain size
  - Did not assess other growth parameters (body length, head size, bone size)

(Oishi *et al., Genes, Brain, & Behavior* 2020)

Further studies of this mouse are needed. I am currently applying for funding to do this and to make a new mouse model of Sotos syndrome.

Human cell models of Sotos syndrome will be used to study disease mechanisms and test therapies



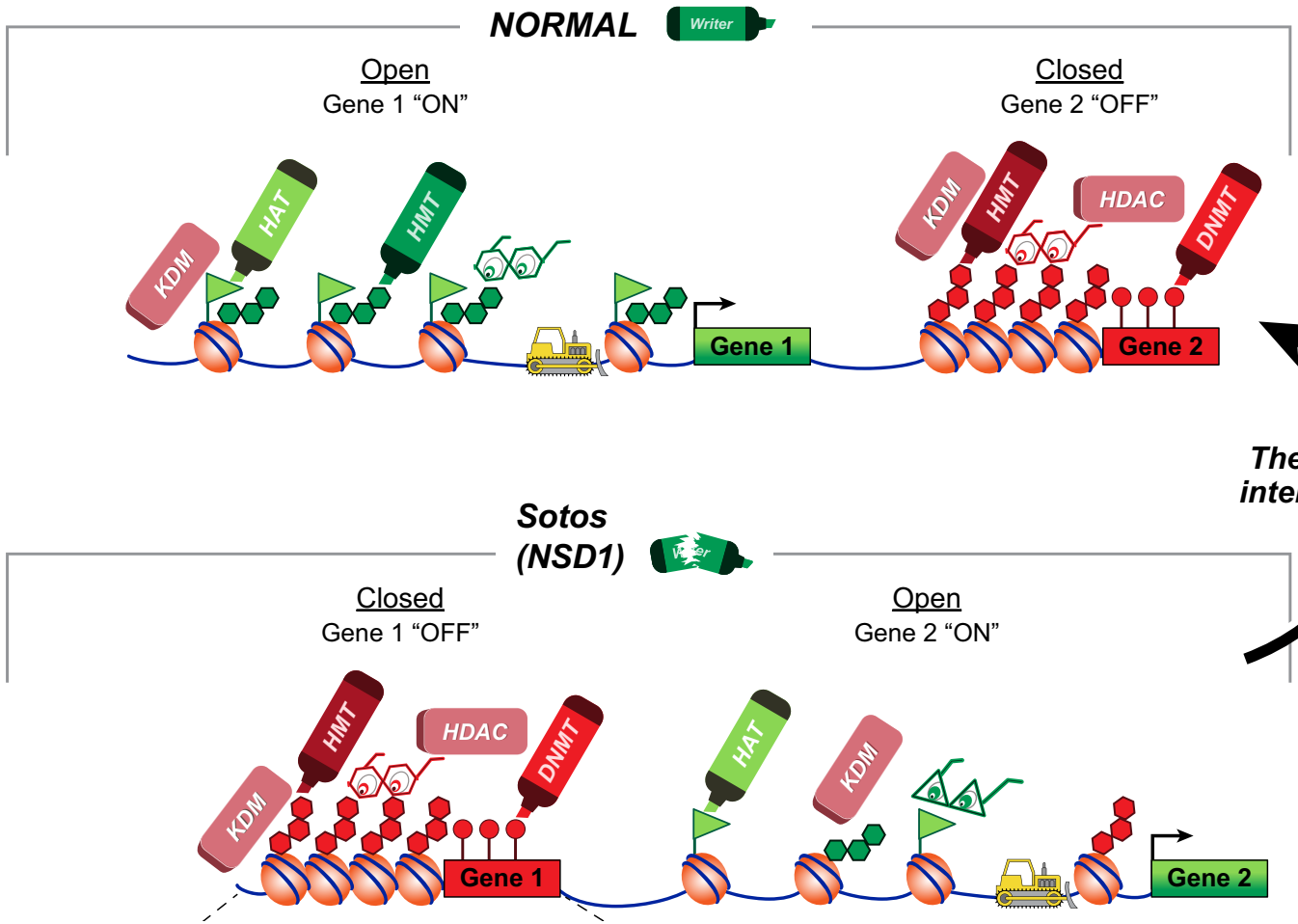
Adapted, Biorender.com

Why is this important?

- Understanding disorders at the molecular level is the first step in thinking about designing therapies

- Medications have to be tested in animal models (*and/or human cell models*) before being given to patients

Potential future treatments for Sotos Syndrome



Therapeutic interventions

Potential therapies

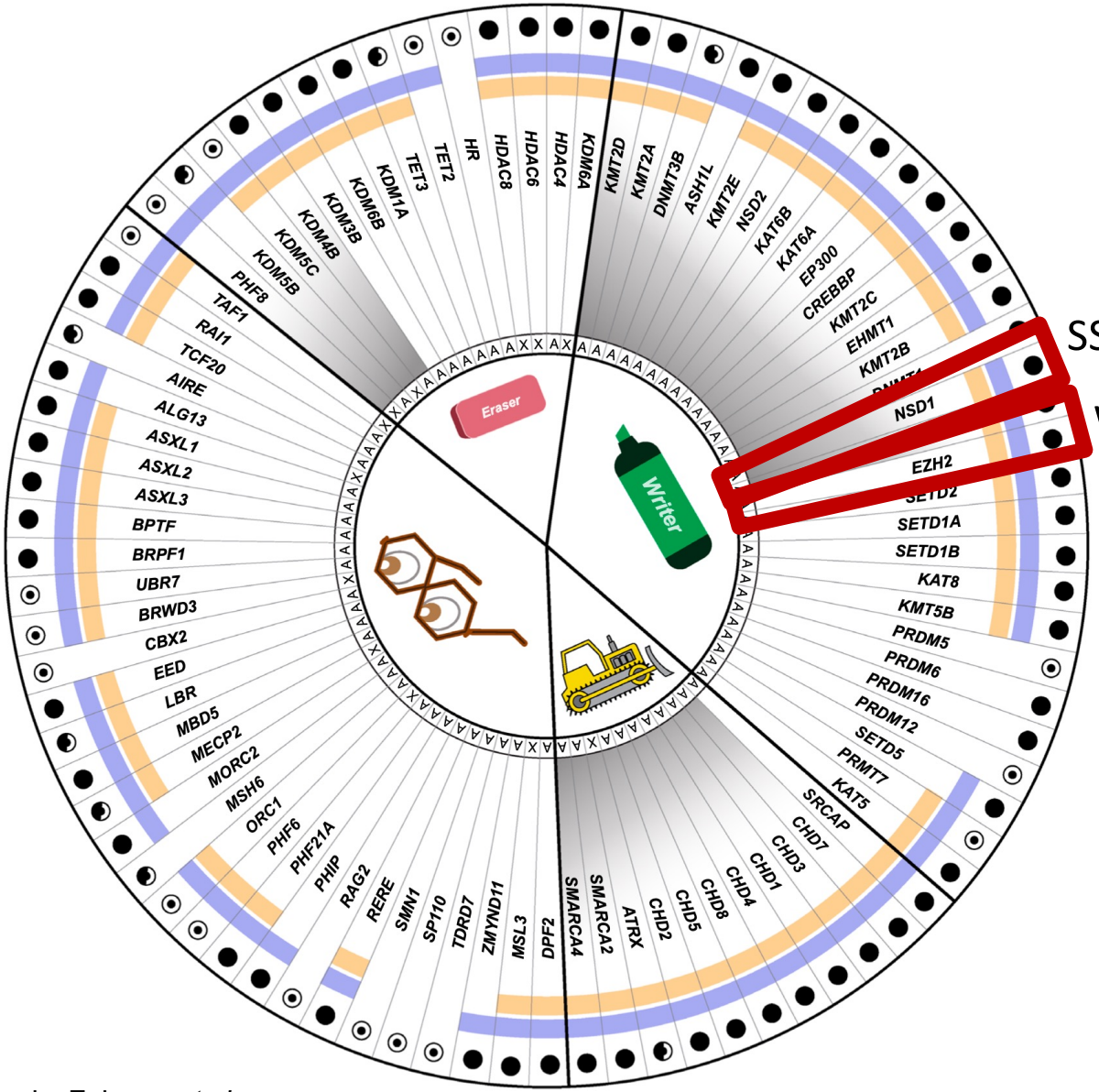
1. CRISPR gene editing
2. CRISPR dCas9-*NSD1*
3. Target gene-specific therapy
4. Correct balance of chromatin

Adapted from Fahrner and Bjornsson, *Hum Molec Genet* 2019

Correct the balance of chromatin as a therapeutic approach

- Epigenetic (or chromatin) marks are more malleable than genetic (DNA sequence) changes
- Specific drugs targeting chromatin are already available and can be repurposed
- This type of approach has worked to improve learning/memory in another related disorder (KS1)

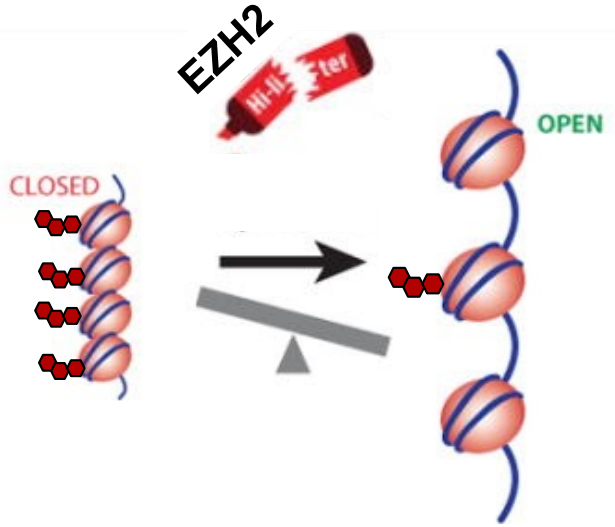
Weaver syndrome is closely related to Sotos syndrome and both disorders are in a larger group of Mendelian disorders of the epigenetic machinery



SS

WS

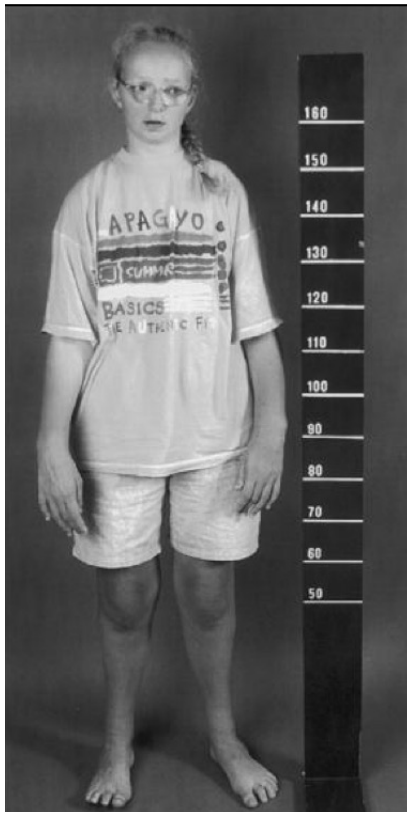
Deficient writer of
H3K27me3 silencing mark



Harris, Fahrner *et al.*
Hum Genet 2023

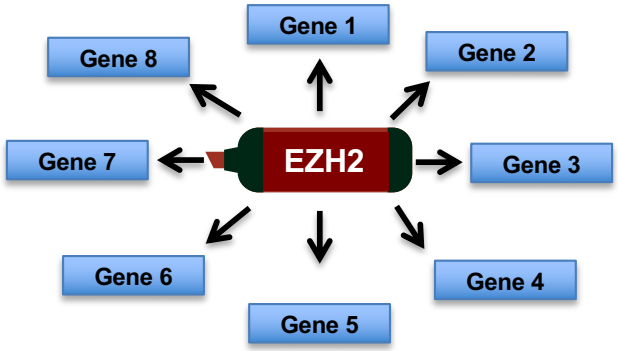
Adapted from Fahrner and Bjornsson
Ann Rev Gen & Hum Gen 2014

Weaver syndrome has features similar to Sotos syndrome

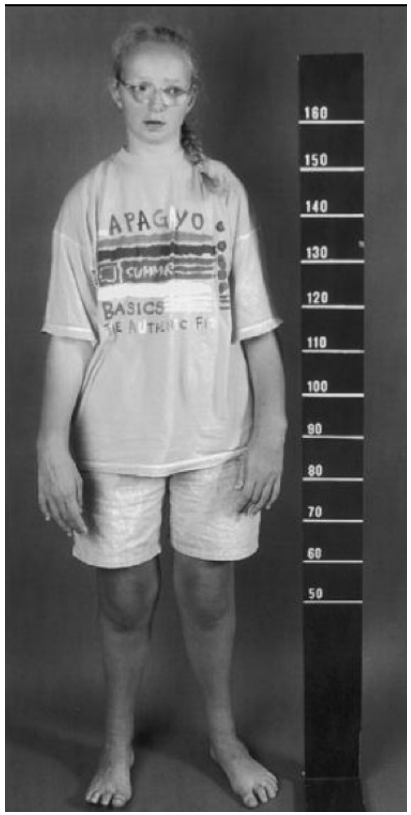


12.5 years

- Overgrowth
- Intellectual disability
- Characteristic facial features (distinct from Sotos)
- Other findings



Research links Sotos and Weaver syndromes further at the molecular level: similar types of target genes



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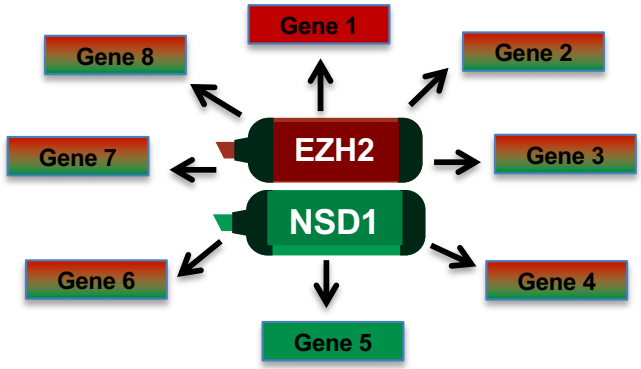
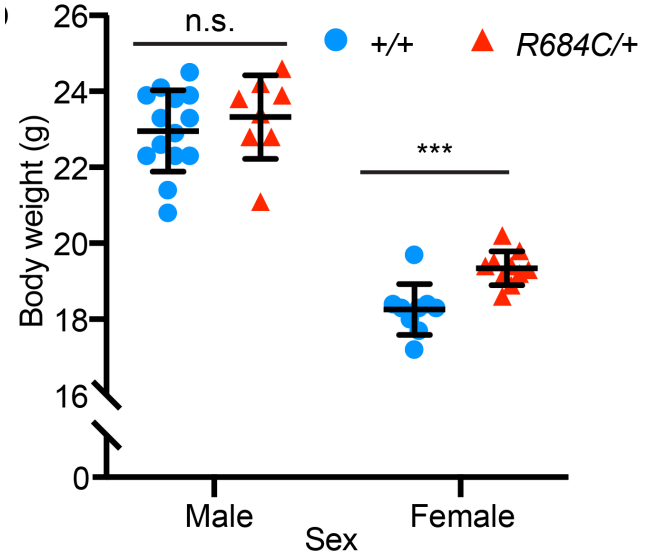


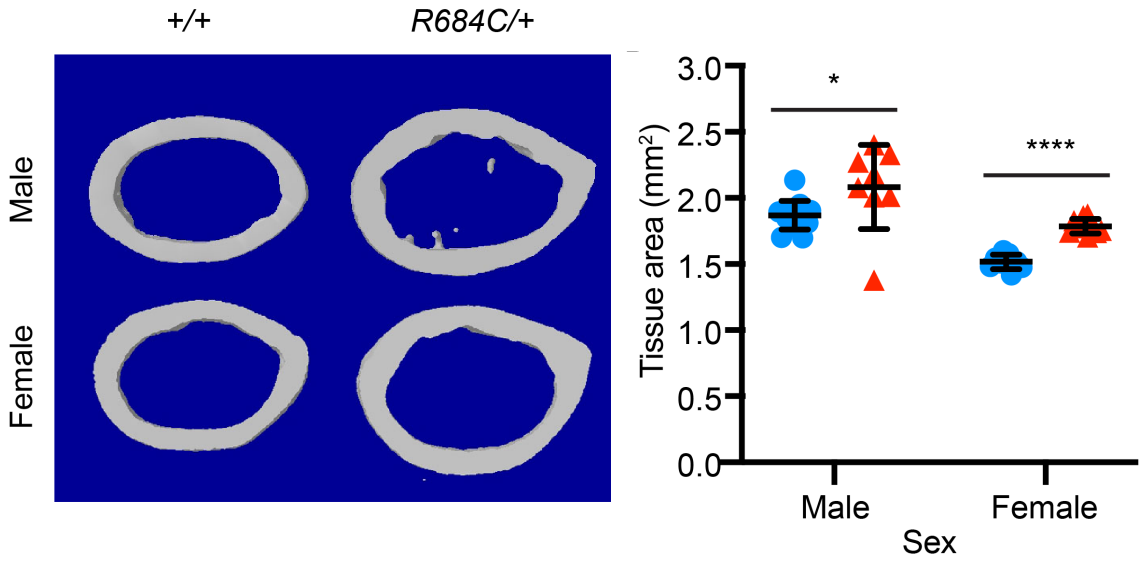
Brennan *et al., Hum Mol Genet 2022*

Weaver syndrome mice have skeletal overgrowth

Female WS mice larger than controls

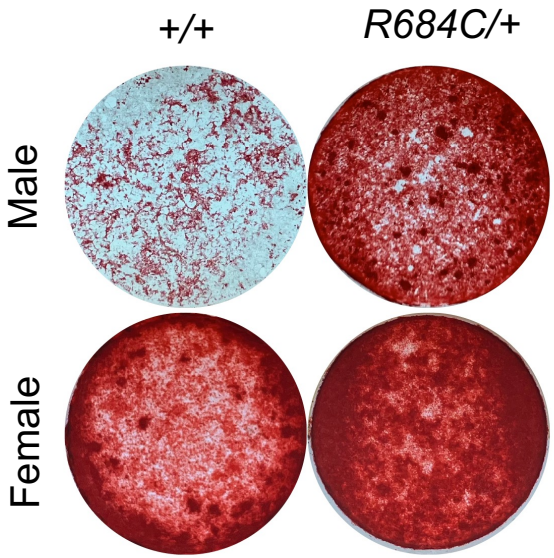


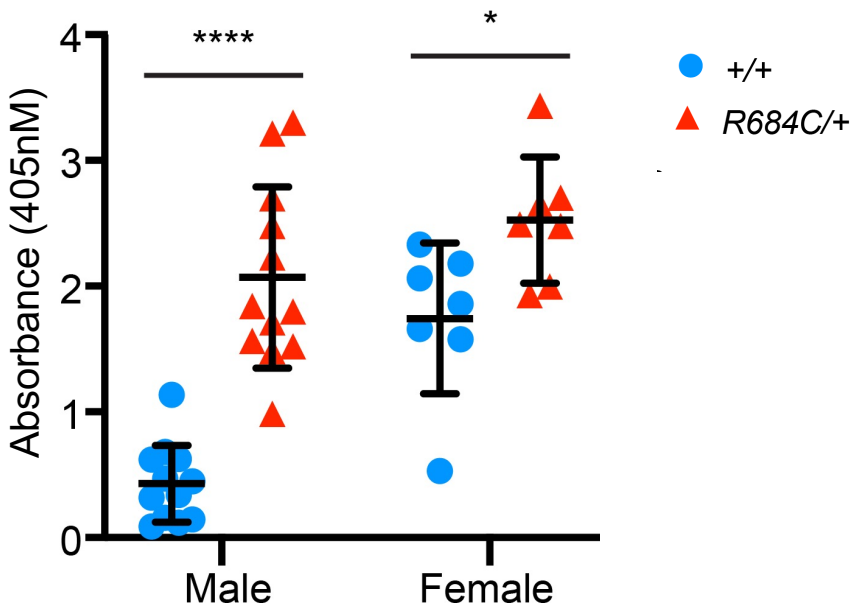
WS mouse bones larger than controls



Gao, Lin *et al. JCI Insight* 2024

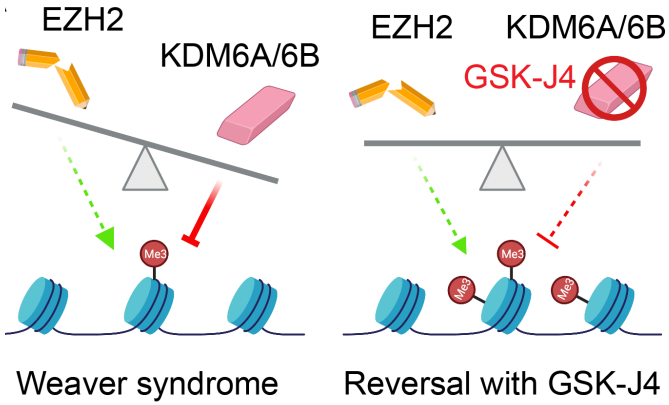
Skeletal overgrowth is due to overactive osteoblasts (cells that make bone)

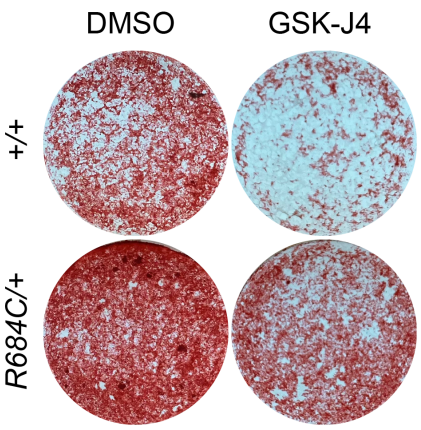


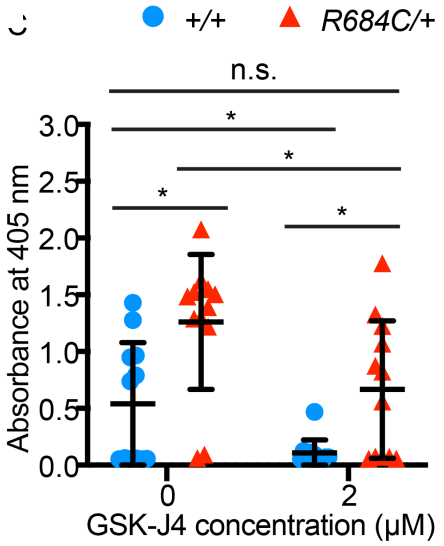


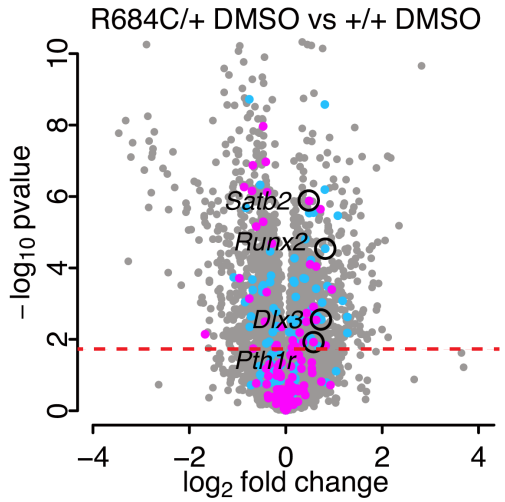
Gao, Lin *et al. JCI Insight* 2024

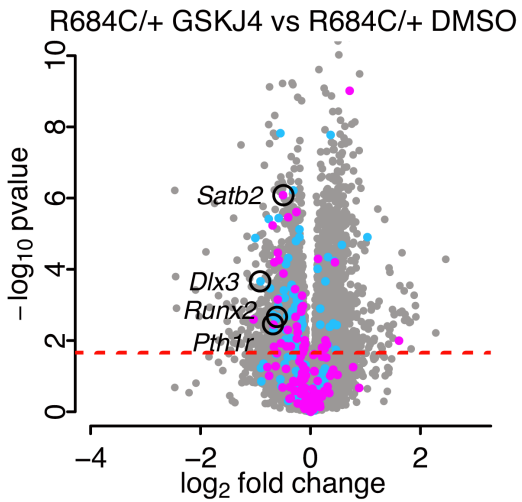
Inhibiting the opposing eraser corrects excess bone formation and gene expression

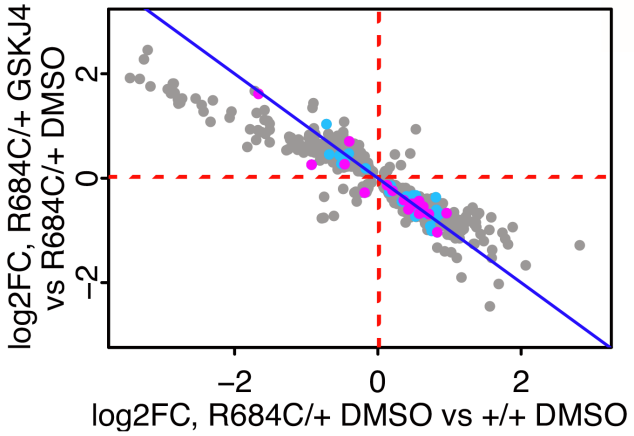












1,045 / 1,075 (97%) of shared genes reverse directionality!

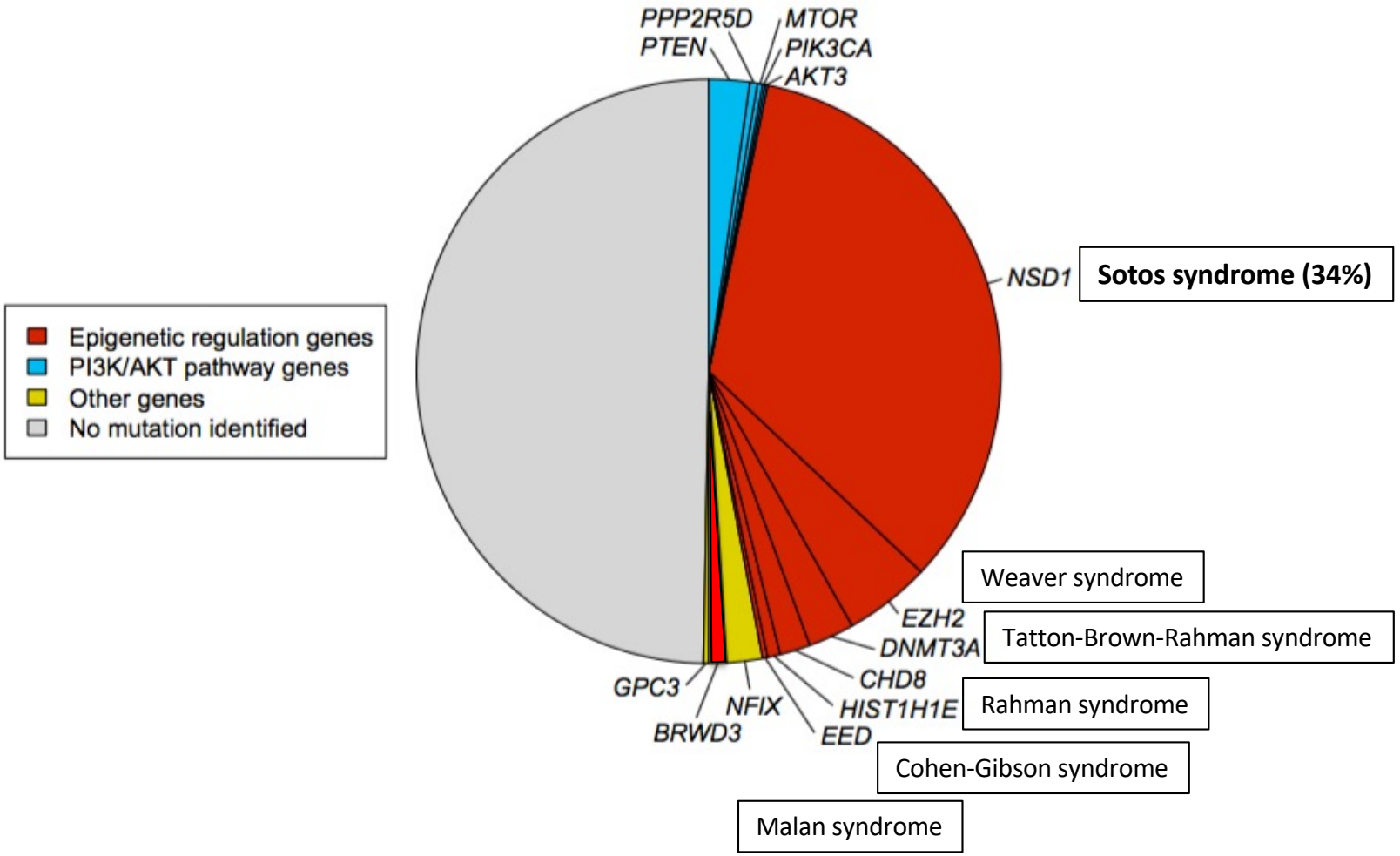
Gao, Lin *et al. JCI Insight* 2024

Future research

- Test the ability of the epigenetic therapy GSKJ4 to treat overgrowth and neurobehavioral features in living Weaver (and Sotos) mice
- Generate human cellular models of Sotos (and Weaver) syndrome
  - Make stem cells (iPSCs) from blood samples taken from individuals with Sotos syndrome
  - Use stem cells to make neurons (brain cells) and bone cells to study disease mechanisms
  - Use human brain organoids (“mini brains” in a dish) to study disease mechanisms and potential treatments

What about individuals with features similar to Sotos syndrome but without *classic* Sotos or without *NSD1* mutations?

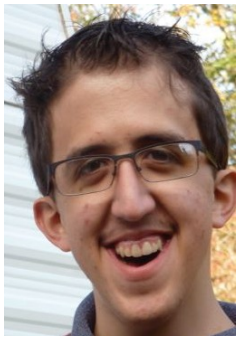
Many disorders overlap with Sotos syndrome and 45% are due to Mutations in Epigenetic Machinery Genes



Modified from Tatton-Brown *et al. AJHG* 2017

Through our prior study, we have identified a cause for some individuals with Sotos-like findings

Malan syndrome (*NFIX*)



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RESEARCH ARTICLE

WILEY HGVS HUMAN GENOME VARIATION SOCIETY

Further delineation of Malan syndrome

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CHD8

Weaver syndrome (*EZH2*)

Other study updates

-Many still undergoing analysis

We identified a new disorder: *TET3* deficiency (or Beck-Fahrner Syndrome)

REPORT

Delineation of a Human Mendelian Disorder of the DNA Demethylation Machinery: *TET3* Deficiency

David B. Beck,[1] Ana Petracovici,[2,3,4] Chongsheng He,[3,4,5] Hannah W. Moore,[6] Raymond J. Louie,[6] Muhammad Ansar,[7] Sofia Douzgou,[8,9] Sivagamy Sithambaram,[9] Trudie Cottrell,[9] Regie Lyn P. Santos-Cortez,[10] Eloise J. Prijoles,[6] Renee Bend,[6] Boris Keren,[11] Cyril Mignot,[11,12] Marie-Christine Nougues,[13] Katrin Õunap,[14,15] Tiia Reimand,[14,15,16] Sander Pajusalu,[14,15,17] Muhammad Zahid,[7] Muhammad Arif Nadeem Saqib,[18] Julien Buratti,[11] Eleanor G. Seaby,[19,20] Kirsty McWalter,[21] Aida Telegrafi,[21] Dustin Baldridge,[22] Marwan Shinawi,[22] Suzanne M. Leal,[23] G. Bradley Schaefer,[24] Roger E. Stevenson,[6] Siddharth Banka,[8,9] Roberto Bonasio,[3,4] and Jill A. Fahrner[2]

ARTICLE **OPEN**

Check for updates

Deficiency of *TET3* leads to a genome-wide DNA hypermethylation episignature in human whole blood

Michael A. Levy[1,25], David B. Beck[2,25], Kay Metcalfe[3,4], Sofia Douzgou[3,4], Sivagamy Sithambaram[4], Trudie Cottrell[4], Muhammad Ansar[5], Jennifer Kerkhof[1], Cyril Mignot[6], Marie-Christine Nougues[7], Boris Keren[8], Hannah W. Moore[9], Renske Oegema[10], Jacques C. Giltay[10], Marleen Simon[10], Richard H. van Jaarsveld[10], Jessica Bos[11], Mieke van Haelst[11], M. Mahdi Motazacker[12], Elles M. J. Boon[13], Gijs W. E. Santen[14], Claudia A. L. Ruivenkamp[14], Marielle Alders[15], Teresa Romeo Luperchio[16], Leandros Boukas[16,17], Keri Ramsey[18], Vinodh Narayanan[18], G. Bradley Schaefer[19], Roberto Bonasio[20,21], Kimberly F. Doheny[16,22], Roger E. Stevenson[9], Siddharth Banka[3,4], Bekim Sadikovic[1,23,25]✉ and Jill A. Fahrner[16,24]✉

We initially identified 11 individuals from 8 families with Beck-Fahrner syndrome, and we now know of ~60 affected individuals.

McKUSICK-NATHANS INSTITUTE

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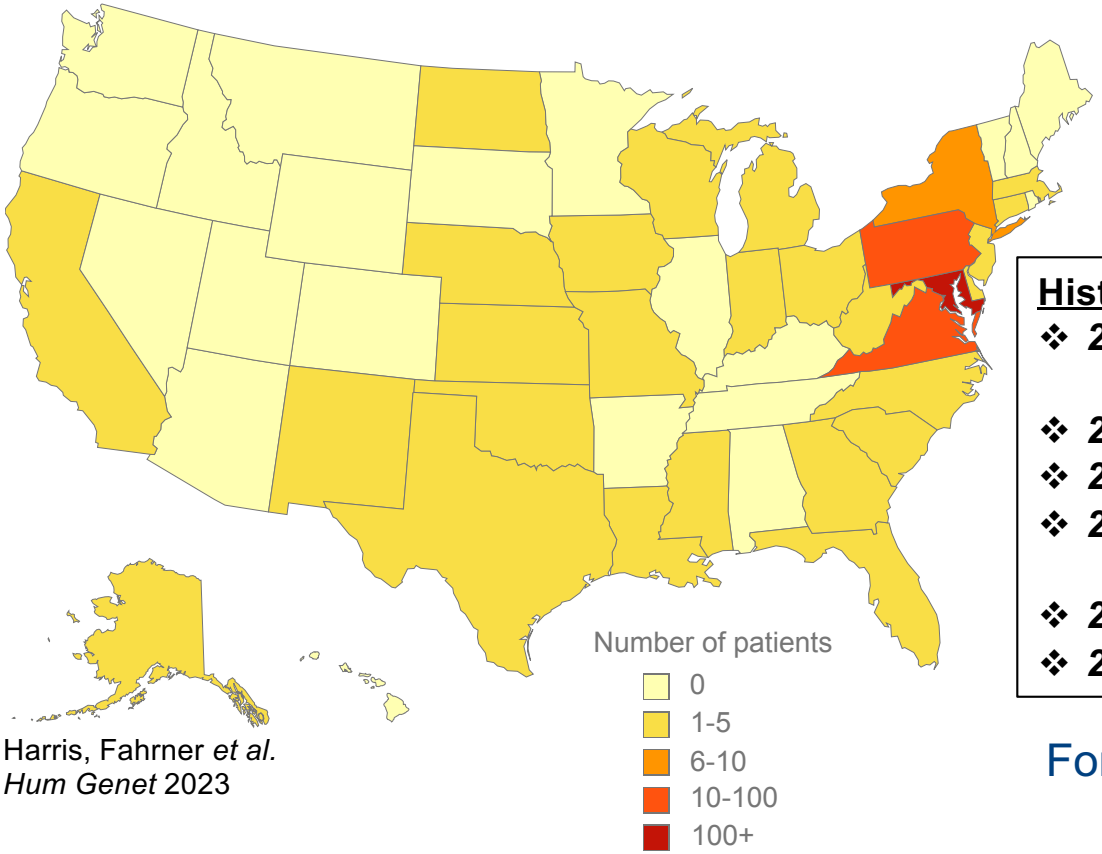

Harris, Fahrner *et al.*
Hum Genet 2023

History

- ***2012:*** Founded by Dr. Hans Bjornsson (geneticist) & Ms. Carolyn Applegate (genetic counselor)
- ***2013:*** Dr. Jill Fahrner (geneticist) joined
- ***2014:*** Ms. Jacquelyn Britton (GC) joined
- ***2018:*** Dr. Jacqueline Harris joined as neurologist/ NDD specialist, making it multidisciplinary
- ***2020:*** Dr. Jill Fahrner became director
- ***2021:*** Dr. Rowena Ng joined (neuropsychologist)

For more information (research or clinic visit), please email: jfahrne1@jhmi.edu

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Director

Jacqueline Harris, MD, MS
Neurodevelopmental Neurologist

Jacquelyn Britton, MGC, CGC
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Neuropsychologist

Hans Bjornsson, MD, PhD
Associate Director

Carolyn Applegate, MGC, CGC
Sr Genetic Counselor

Felicia Bartee
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