

The logo for 'prisms' features the word in a bold, lowercase, sans-serif font. The letter 'i' is replaced by a vertical DNA double helix structure. Above the top of the DNA helix is a small, stylized icon of a prism or a lens, consisting of a semi-circle with radiating lines. A thin horizontal line is positioned below the text.

prisms

EDUCATION | AWARENESS | RESEARCH

*prisms.org*



**prisms**  
**2022**

**AUGUST 4-6, 2022**

# *Envisioning the Possibilities*

11TH INTERNATIONAL CONFERENCE | DALLAS, TX



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**prisms  
2022**

*Envisioning  
the Possibilities*

## Cutting-Edge DNA Sequencing Technologies and Smith-Magenis Syndrome

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Baylor College of Medicine  
Genetics and Genomics Graduate Program

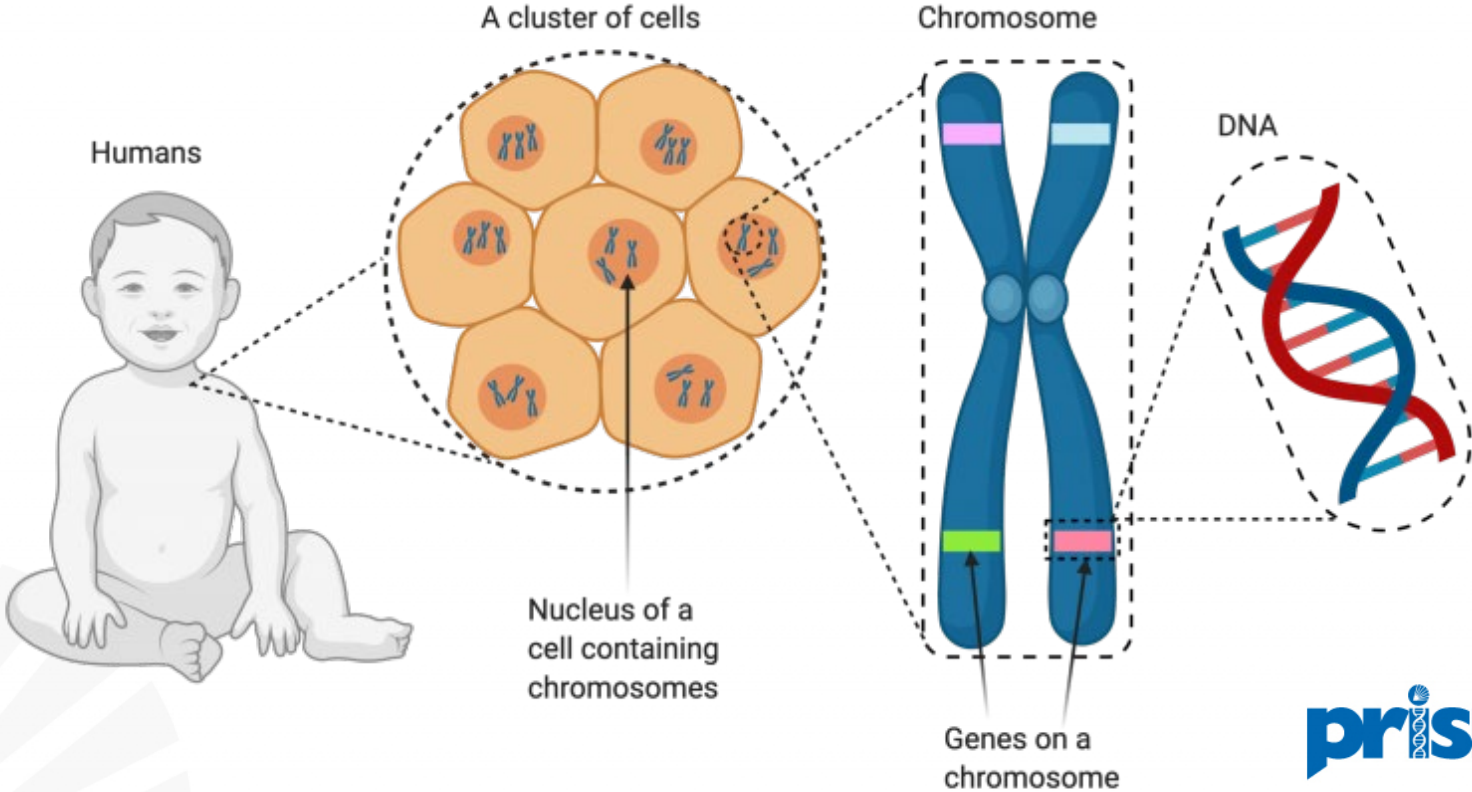
August 6<sup>th</sup>, 2022

Baylor  
College of  
Medicine

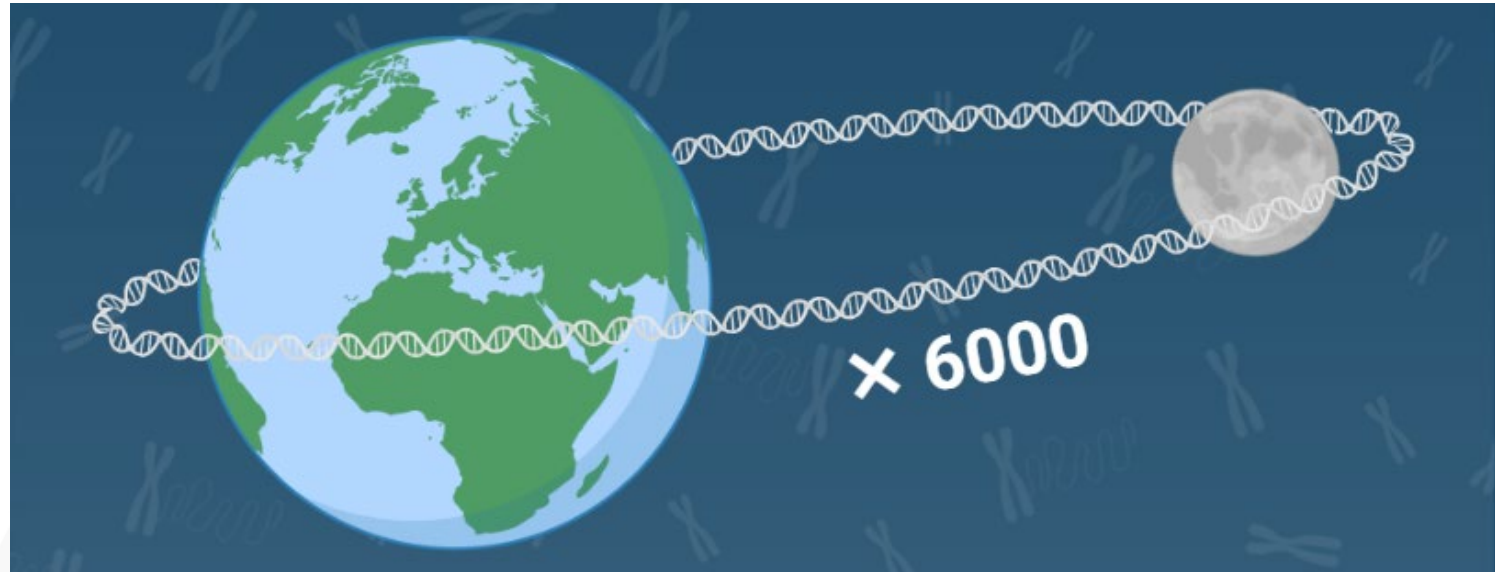
**prisms**



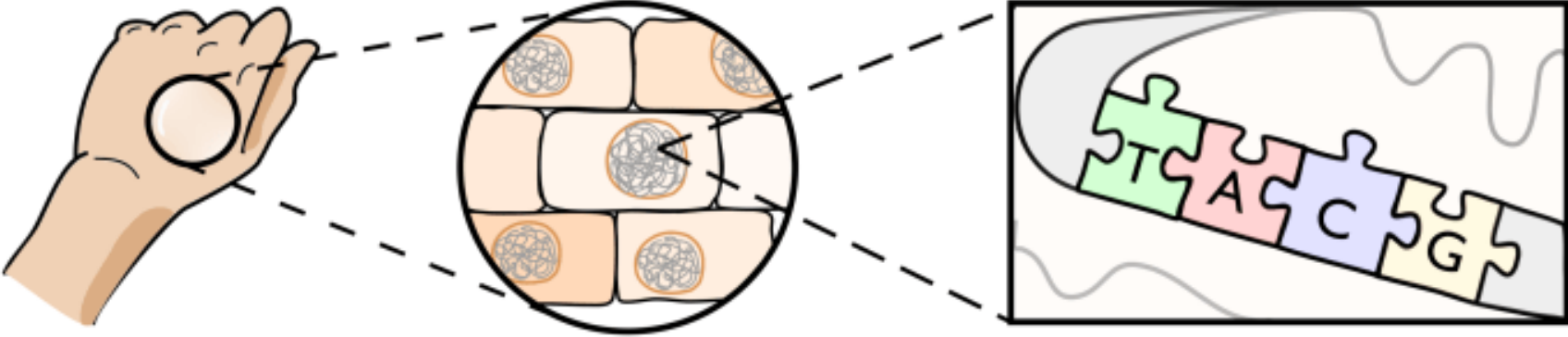
# What makes us up?



**Fun Fact: DNA in a single cell is 2 meters long. DNA in all the cells of your body is enough to reach the moon 6000 times!**



DNA is made up of four different molecules: A, T, C, G



# A,T,C,G- Our Body's Alphabets

Alphabet



Word

abcdefghijklmnopqrstuvwxyz



"silent"

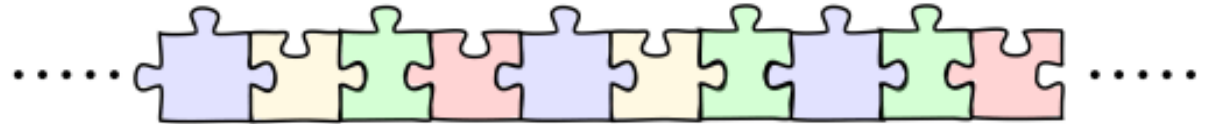
"listen"

*\*These words use the same selection of letters, but have different meanings*

DNA molecules



Gene



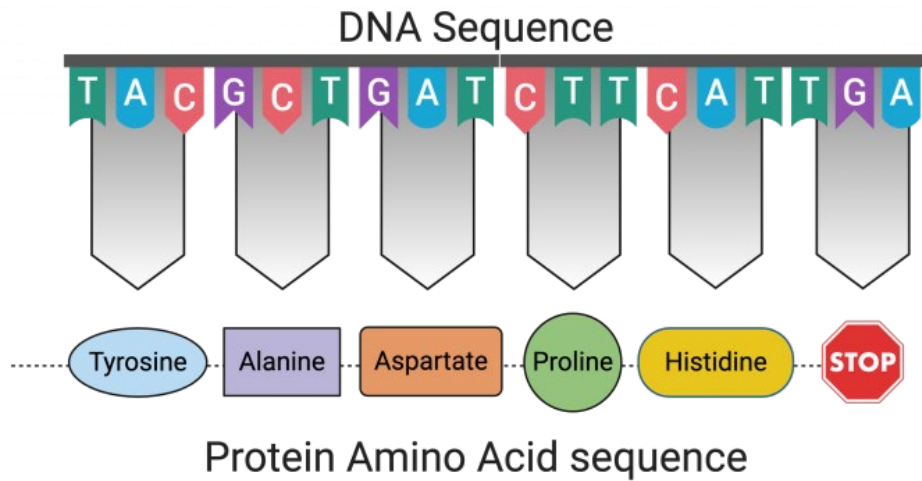
Genes are the instructions for life



Genes



# How do genes make proteins?



# Genetic variation



**GENOME**  
(A book)



**CHROMOSOME**  
(A chapter of a book)



**GENETIC VARIANT**  
(A spelling typo in a sentence)



**NORMAL:**

“I LIKE TO SWIM IN THE OCEAN BUT I DO NOT LIKE TO SWIM IN THE POOL.”

**DELETION:**

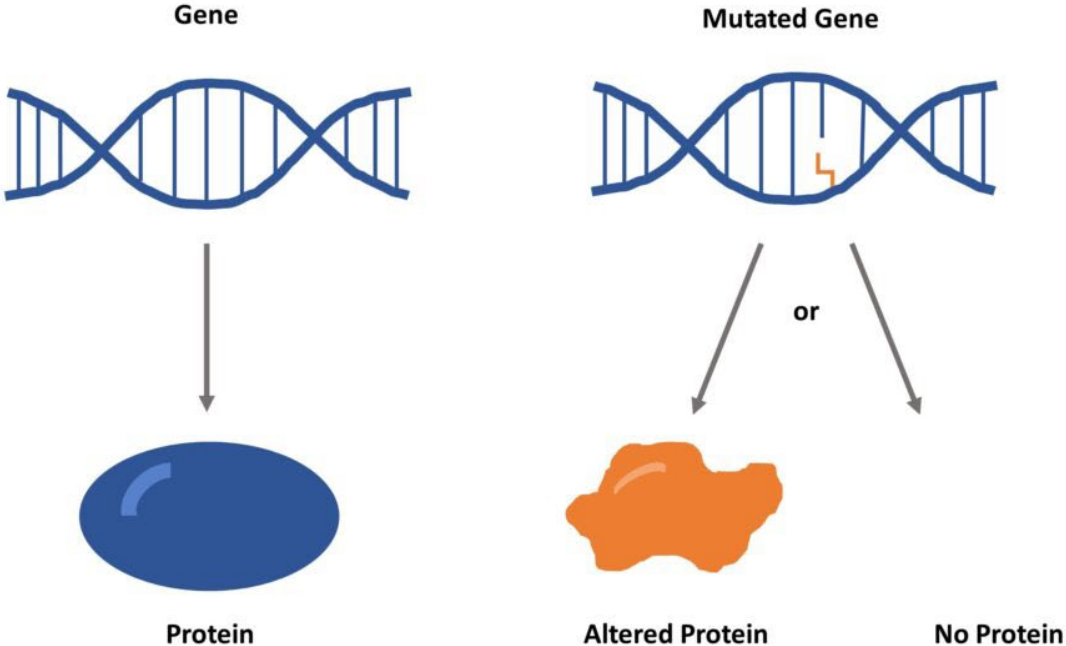
“I LIKE TO SWIM IN THE POOL.”

**DUPLICATION:**

“I LIKE TO SWIM IN THE OCEAN BUT I DO NOT LIKE TO SWIM IN THE OCEAN BUT I DO NOT LIKE TO SWIM IN THE POOL.”

*Adapted from L. Potocki & J. R. Lupski*

# Genetic variation



# Smith-Magenis Syndrome (SMS)

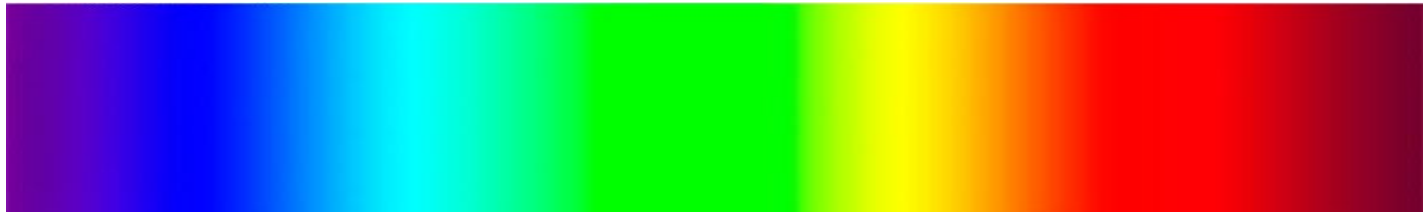


Ann Smith



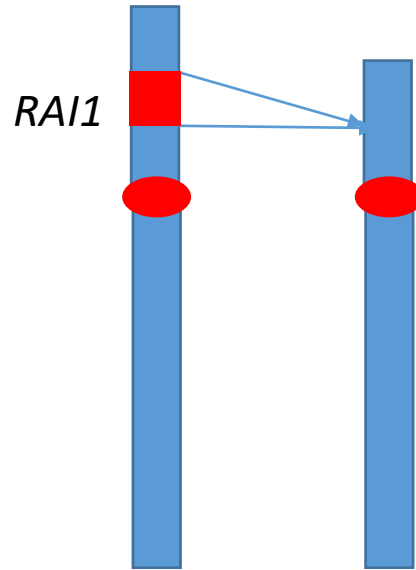
Ellen Magenis

## SMS has a wide clinical spectrum



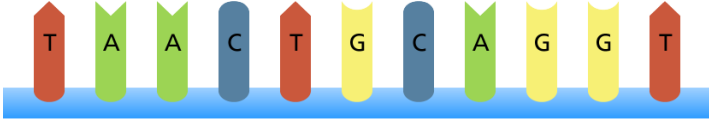
# The Genetics of SMS

## Chr.17 Microdeletion

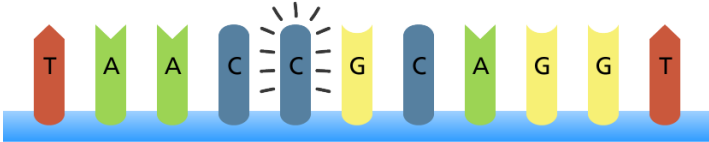


# RAI1 Pathogenic Variants

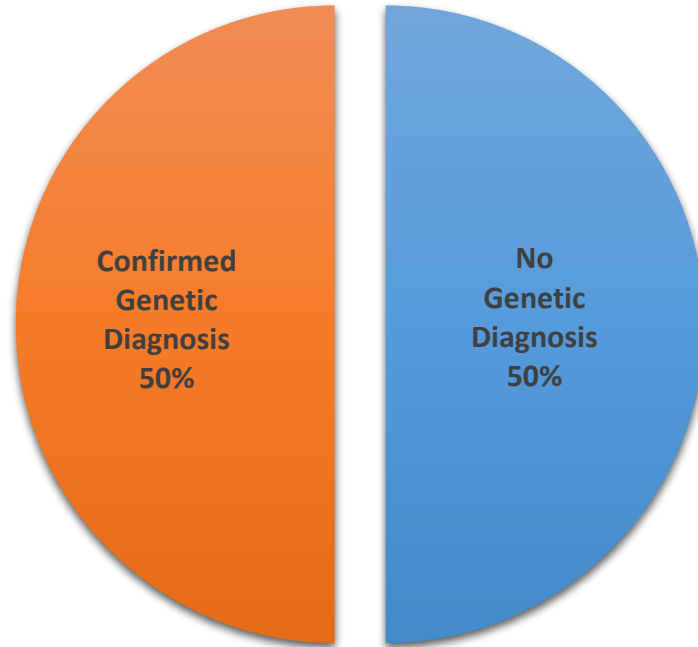
Original sequence



Base substitution



# The genetic cause for 50% of individuals with suspected SMS is unknown!



Rinaldi *et. al.* *Genes* **2022**, *13*, 335.

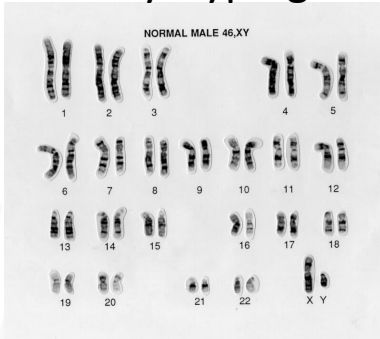
## Our Goal

Further investigation of additional SMS associated variants and genes and their underlying mechanisms.

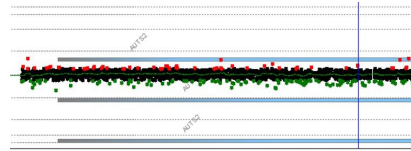




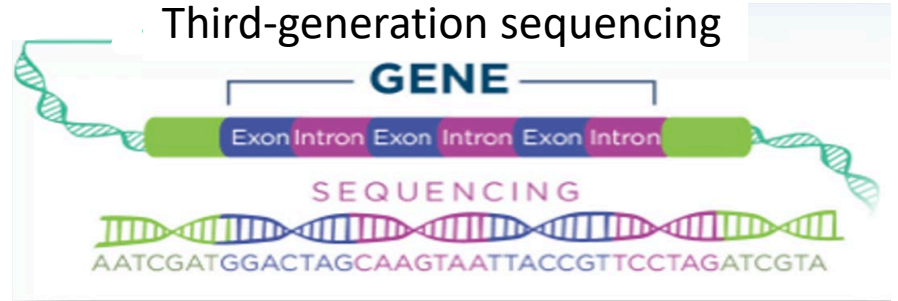
## Karyotyping



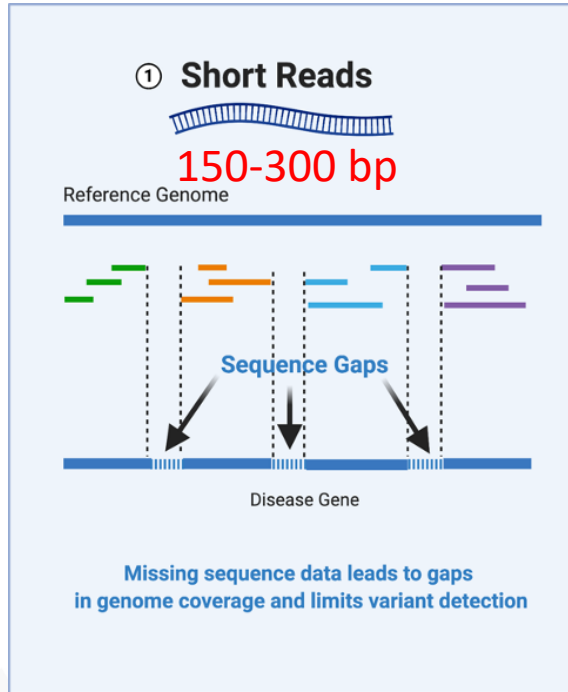
## Array CGH



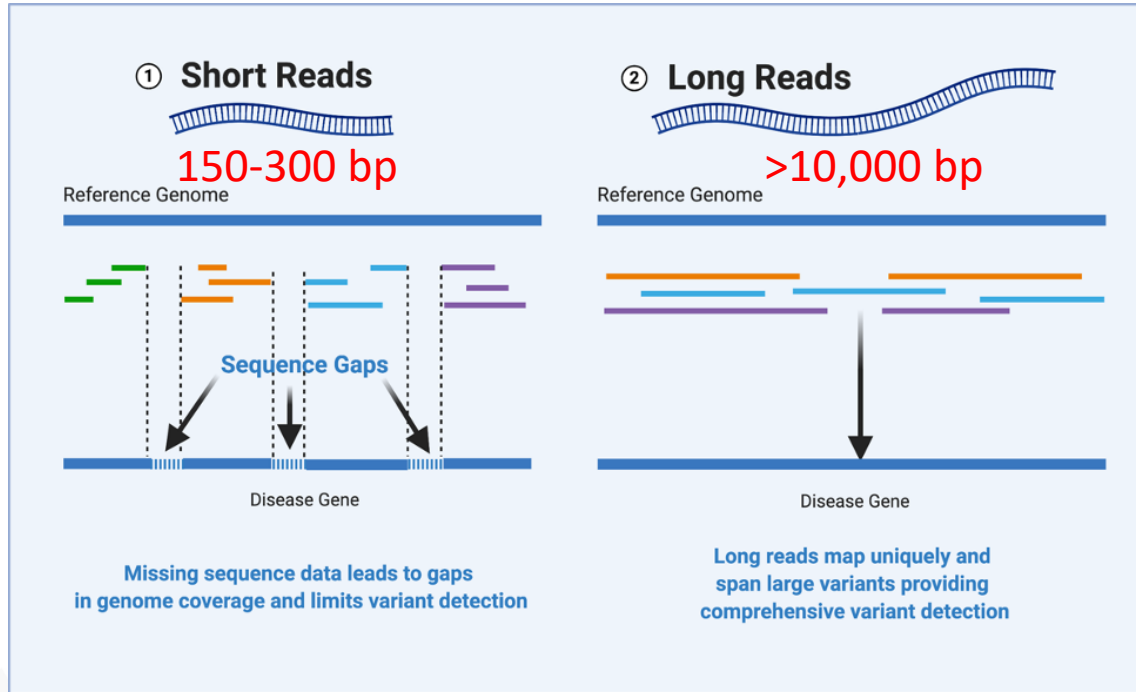
## Third-generation sequencing



# 2<sup>nd</sup> generation VS. 3<sup>rd</sup> generation DNA sequencing



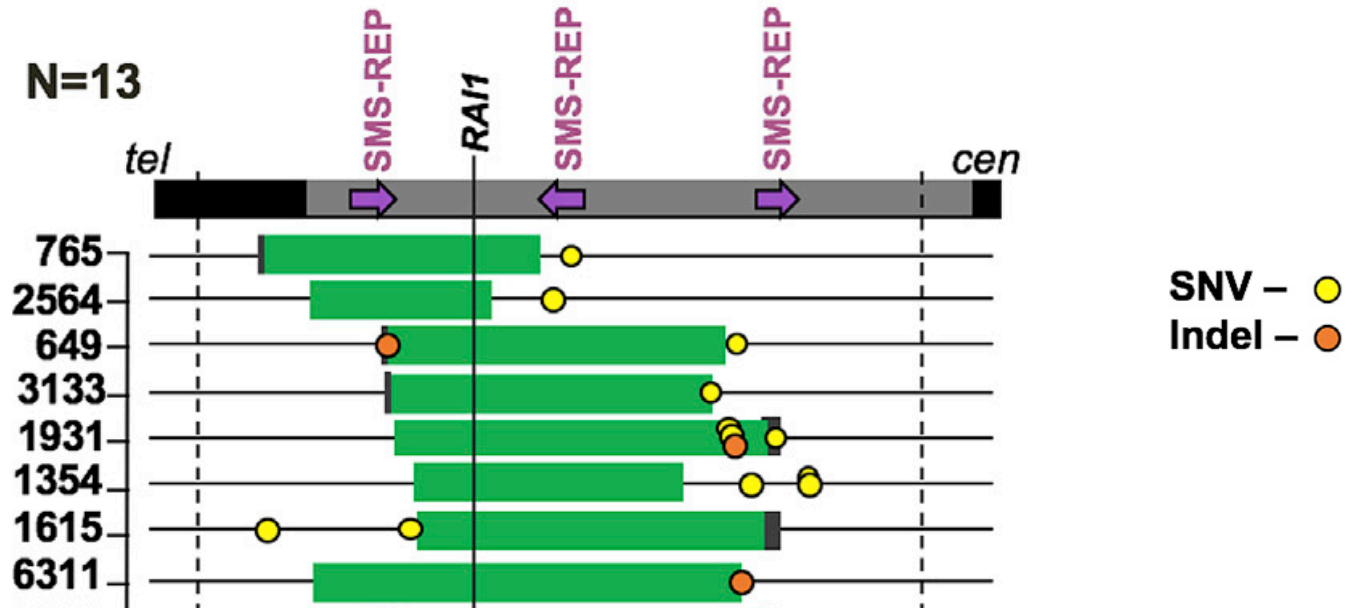
# 2<sup>nd</sup> generation VS. 3<sup>rd</sup> generation DNA sequencing



## Third-generation sequencing can reveal additional genetic variants in SMS individuals



# De novo variants accompany Chr17. microdeletion

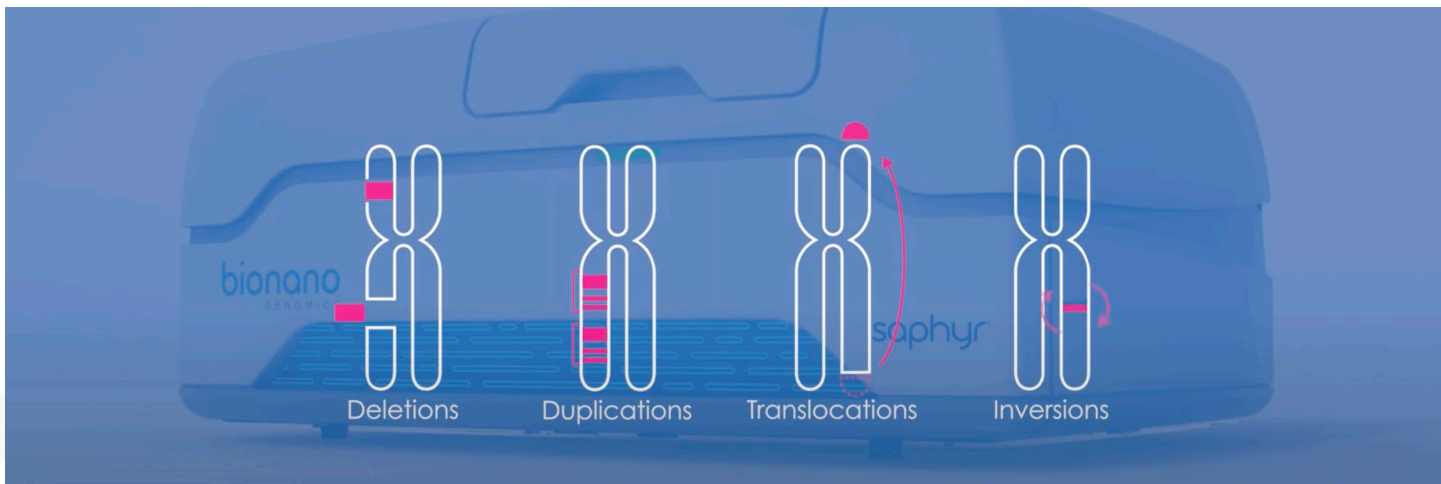


## 2/3 of the genome is highly repetitive

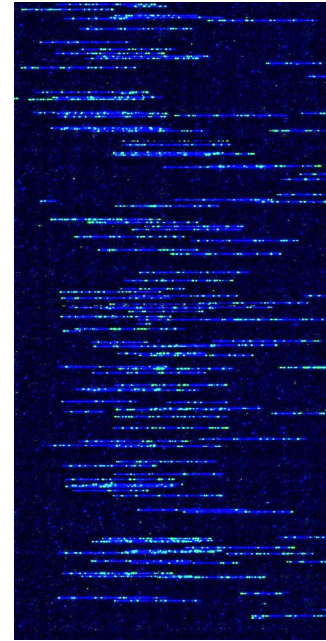
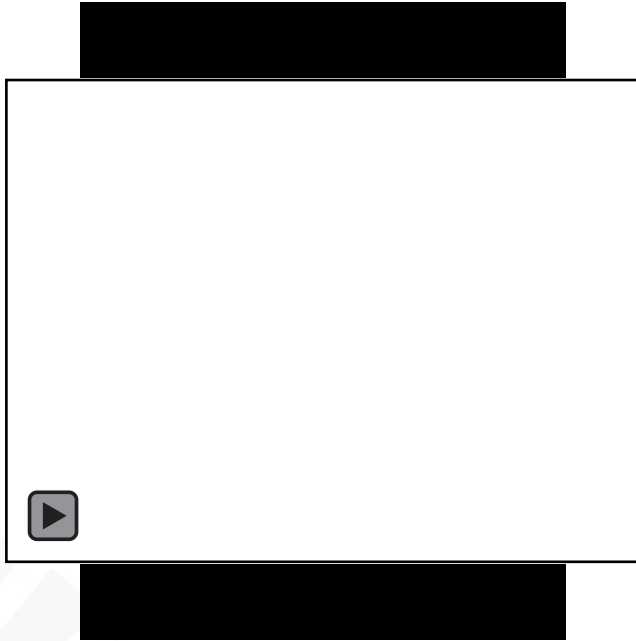


# Optical Genome Mapping

- Identify structural variants ranging from 500 bp to whole chromosome lengths, with sensitivity as high as 99%.

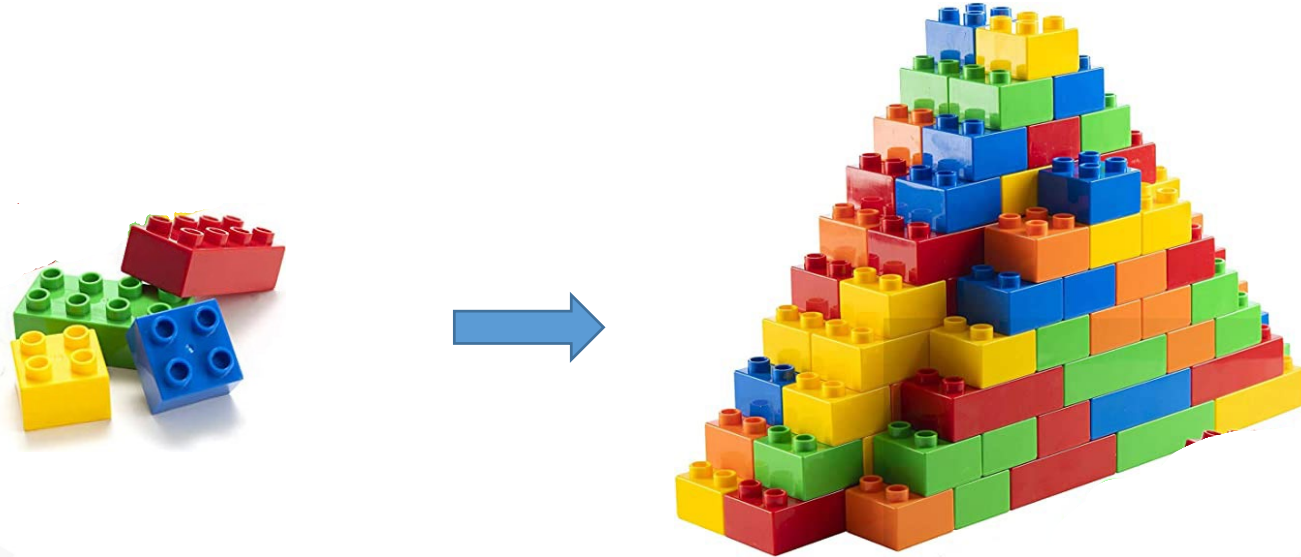


# Optical Genome Mapping



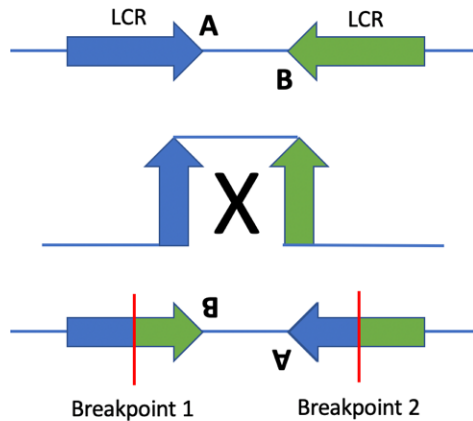


# Third-generation sequencing can refine the final genomic architecture

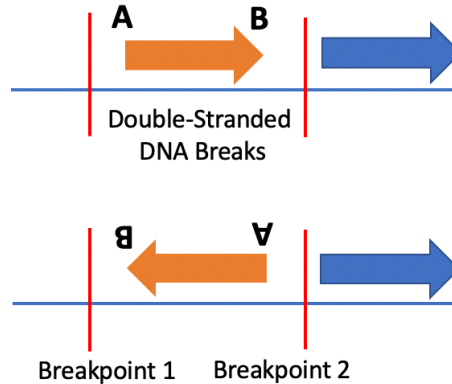


# Third-generation sequencing can delineate the underlying mutational mechanism

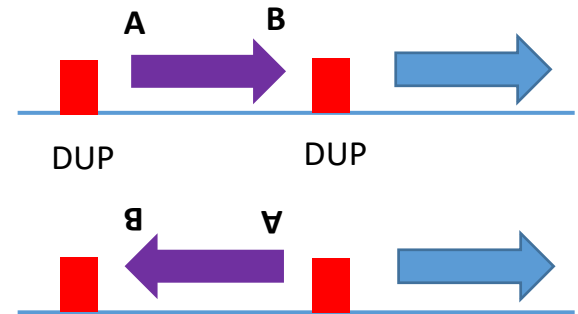
Non-Allelic Homologous Recombination (NAHR)



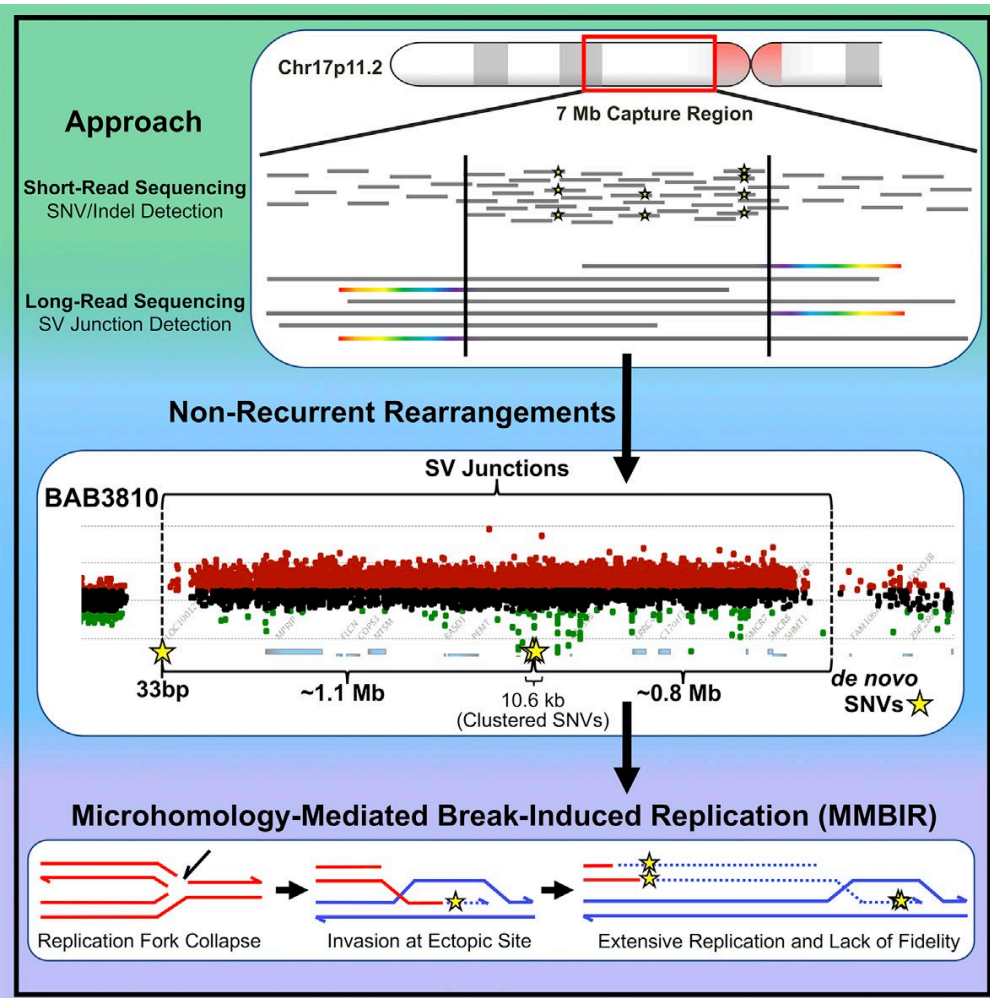
Non-Homologous End Joining (NHEJ)



Microhomology-Mediated Break-Induced Replication (MMBIR)



# Combining Technologies to Resolve genomic Structures and underlying mechanisms



Adapted from Beck *et al.*  
*Cell* (2019) 176 (1310-1324).

## Key Takeaways

- Severity of the SMS phenotypes might be attributed to genetic variability.
- The exact way DNA molecules (A, T, C, G) are ordered is important.
- Advanced DNA sequencing allows scientists and doctors to work out the order of A, T, C, G so to understand the biological meaning for SMS diagnosis and potential treatment.

# Thank you!

James R. Lupski

Christopher M. Grochowski

Claudia Carvalho

Jennifer Posey

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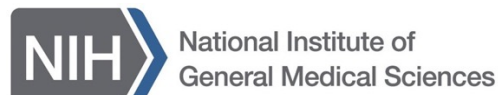
Ruizhi Duan

Shalini Jhangiani

Fritz Sedlazeck

Betty Fernandini

Marjorie Withers



R35 NS105078 to JRL

UM1 HG006542 to JRL

