

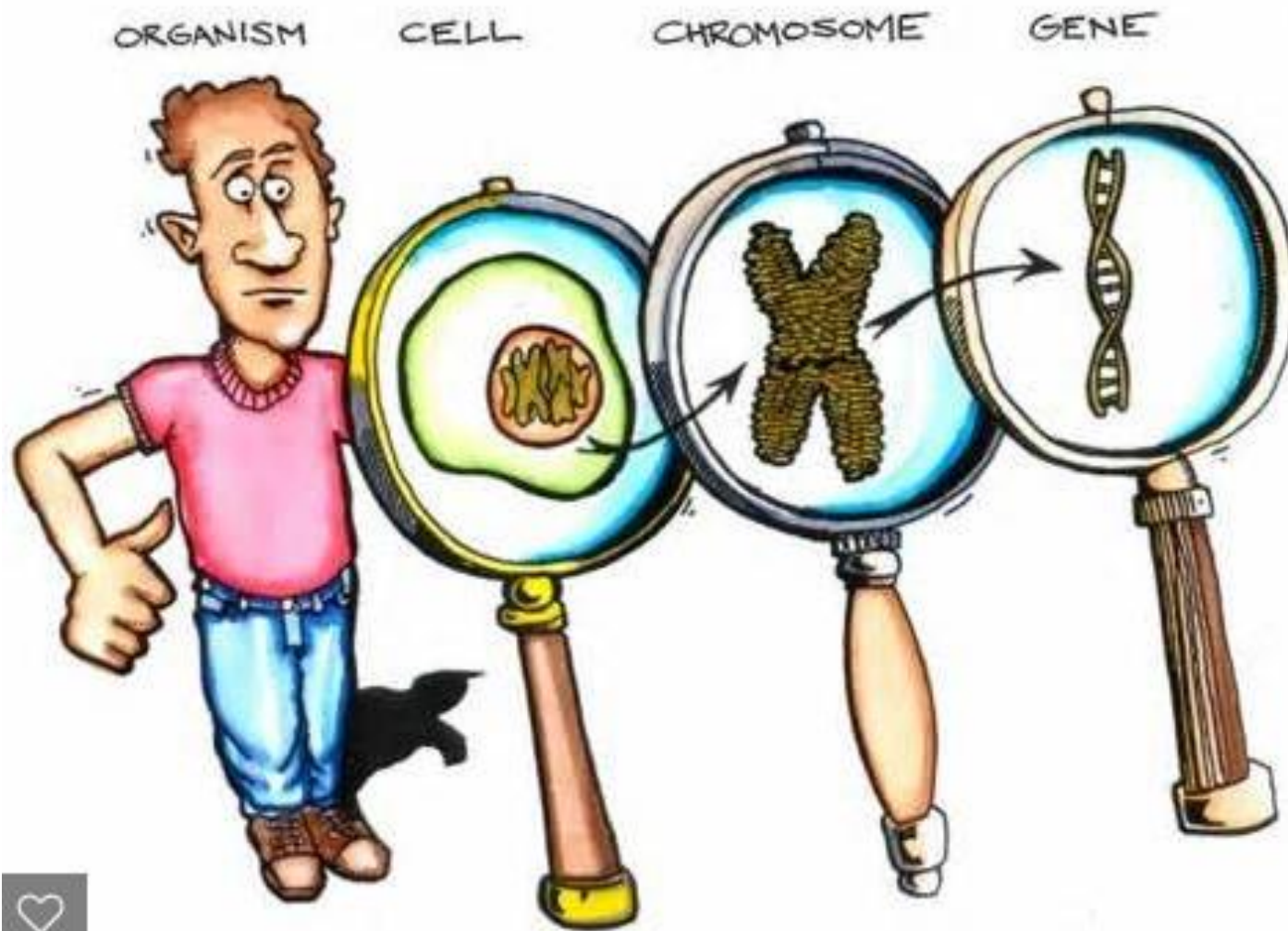
Genetics in Tuberous Sclerosis Complex

Jen Glass, LGC, CGC

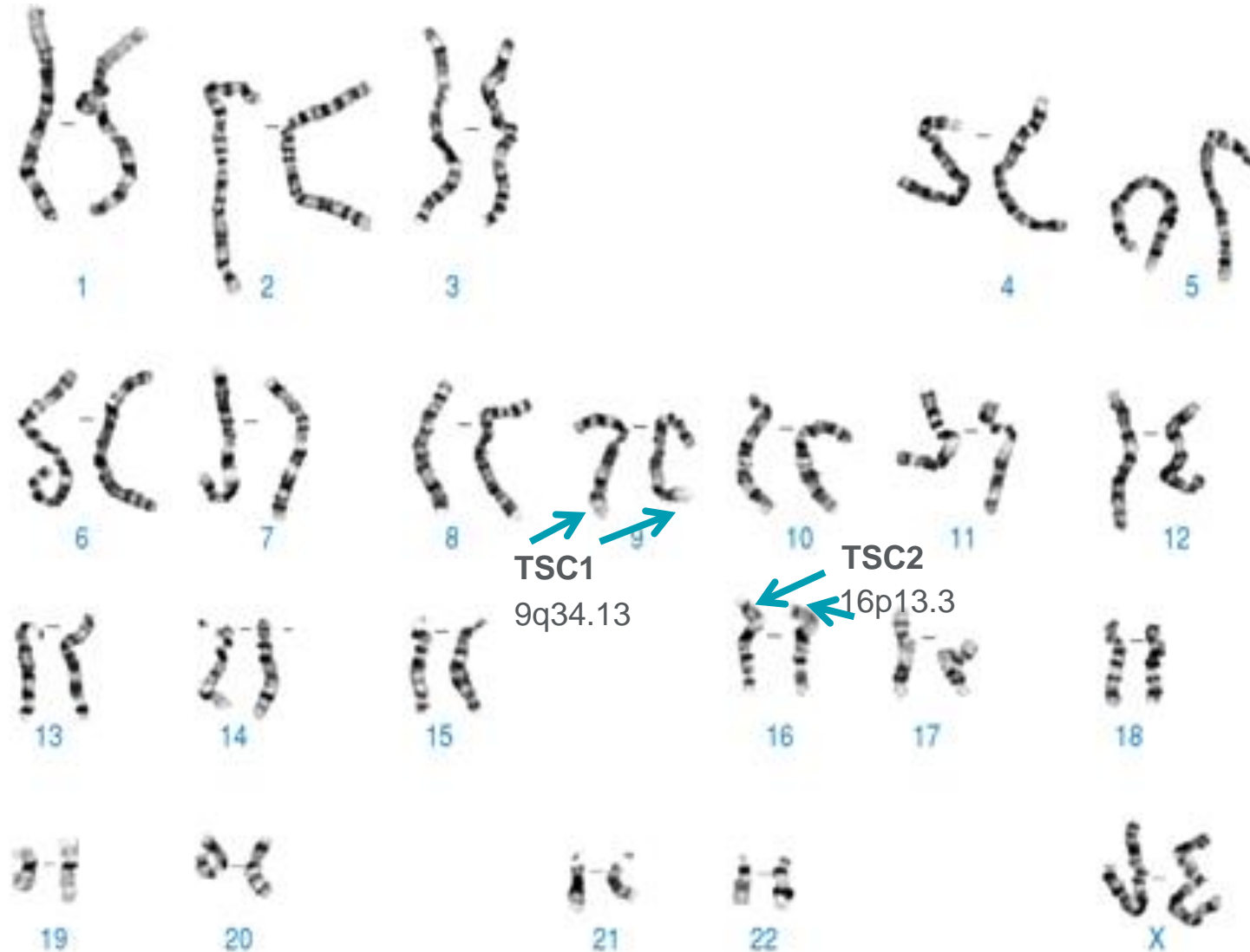
Genetic Counselor

Cincinnati Children's Hospital Medical Center

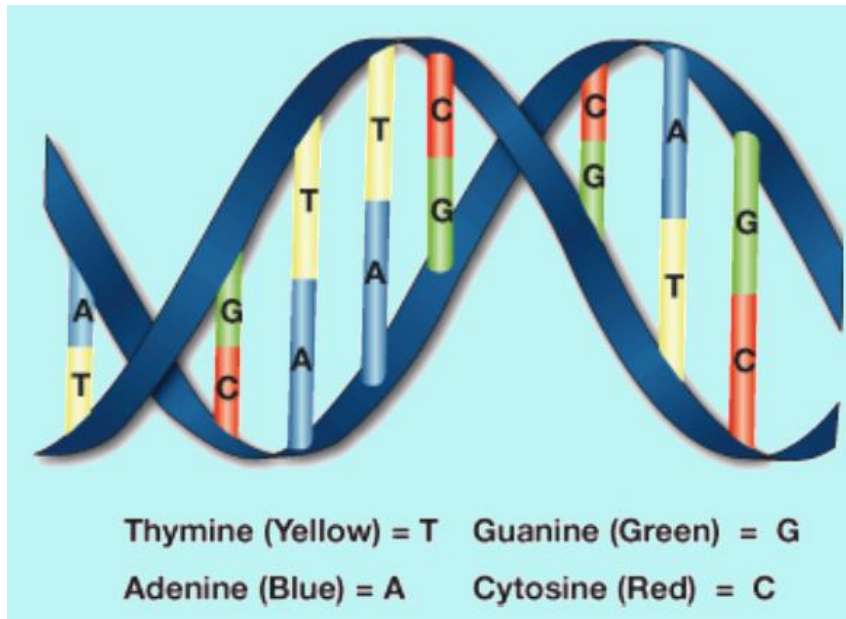
Genetics 101



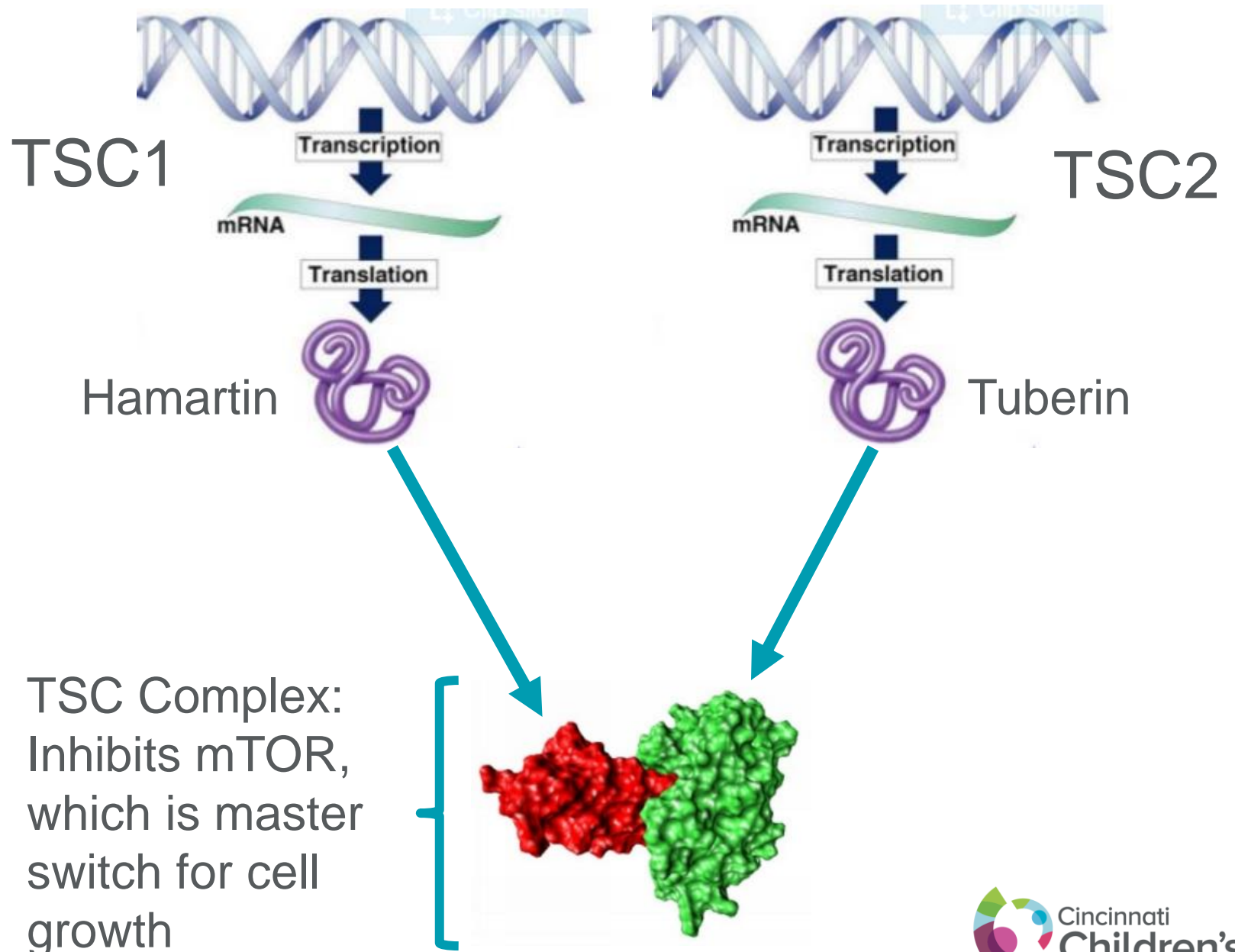
TSC genes

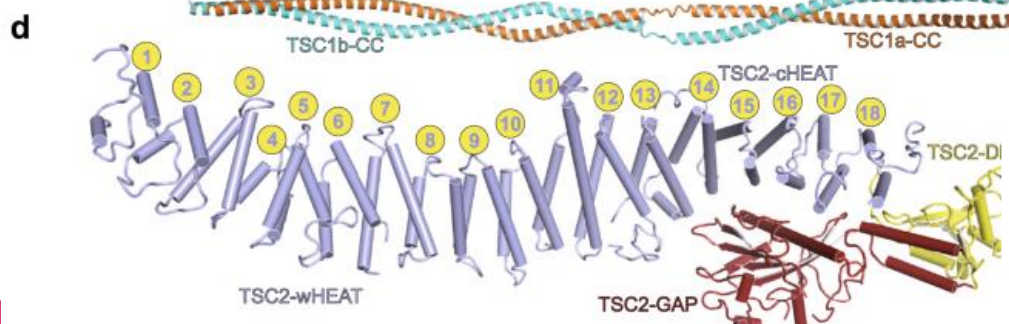
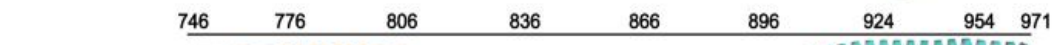
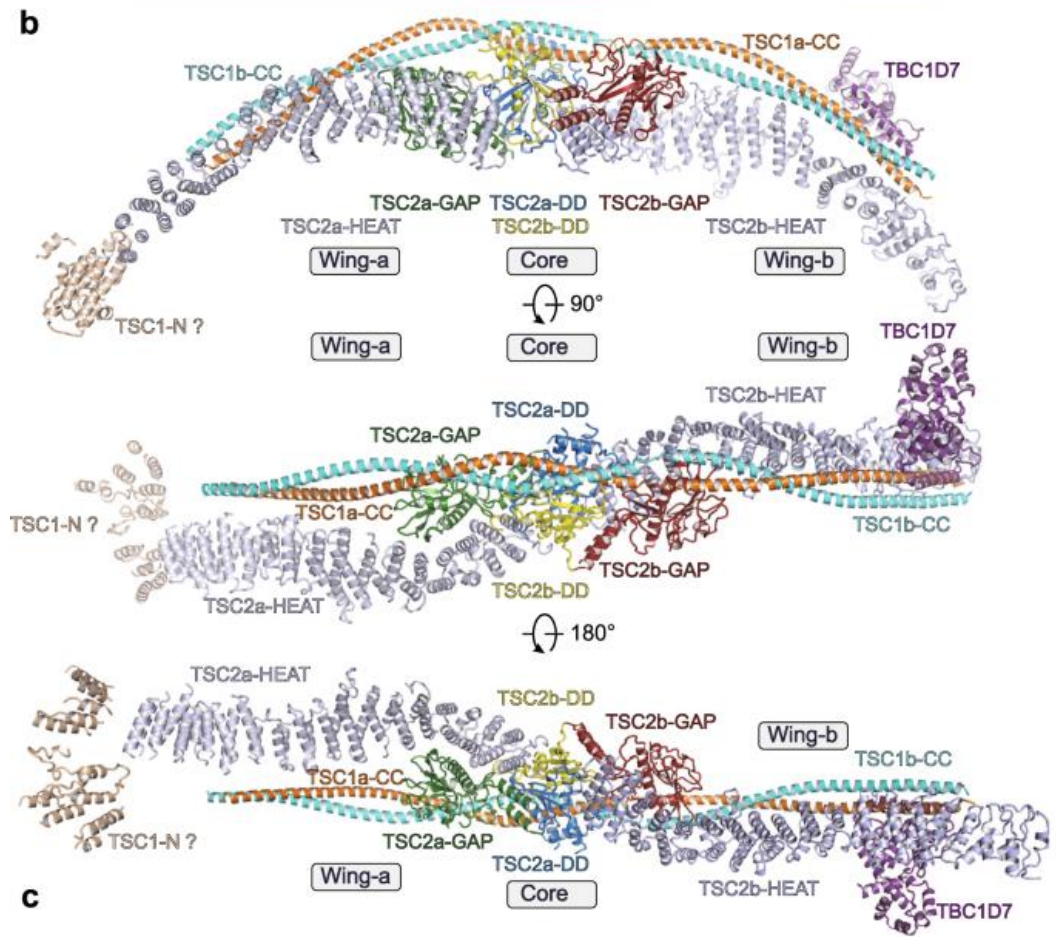
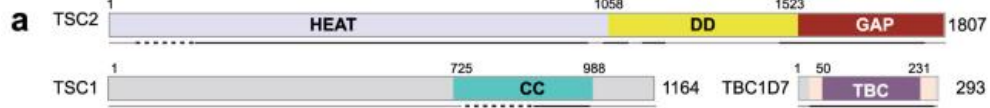


DNA sequence variants

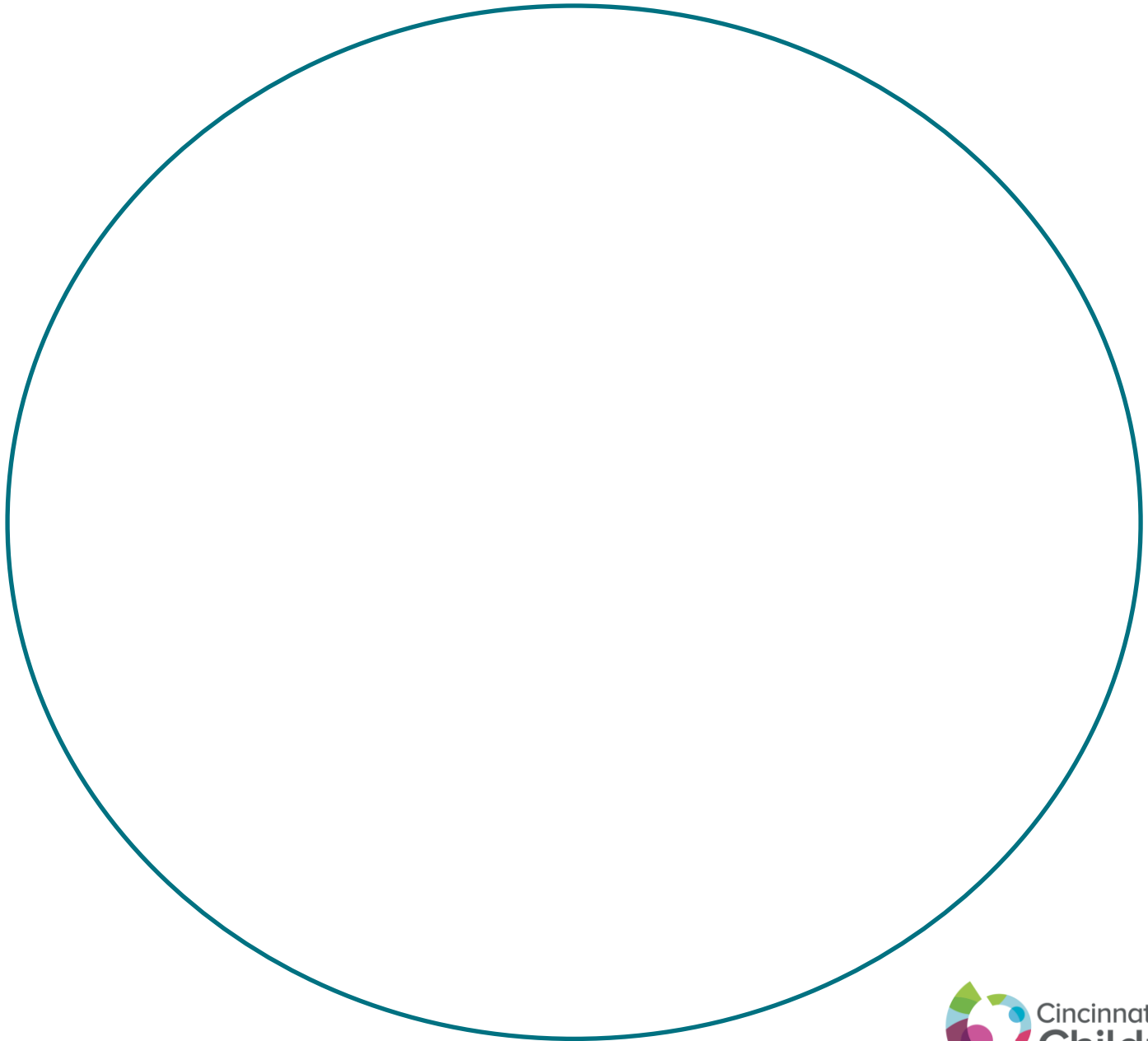


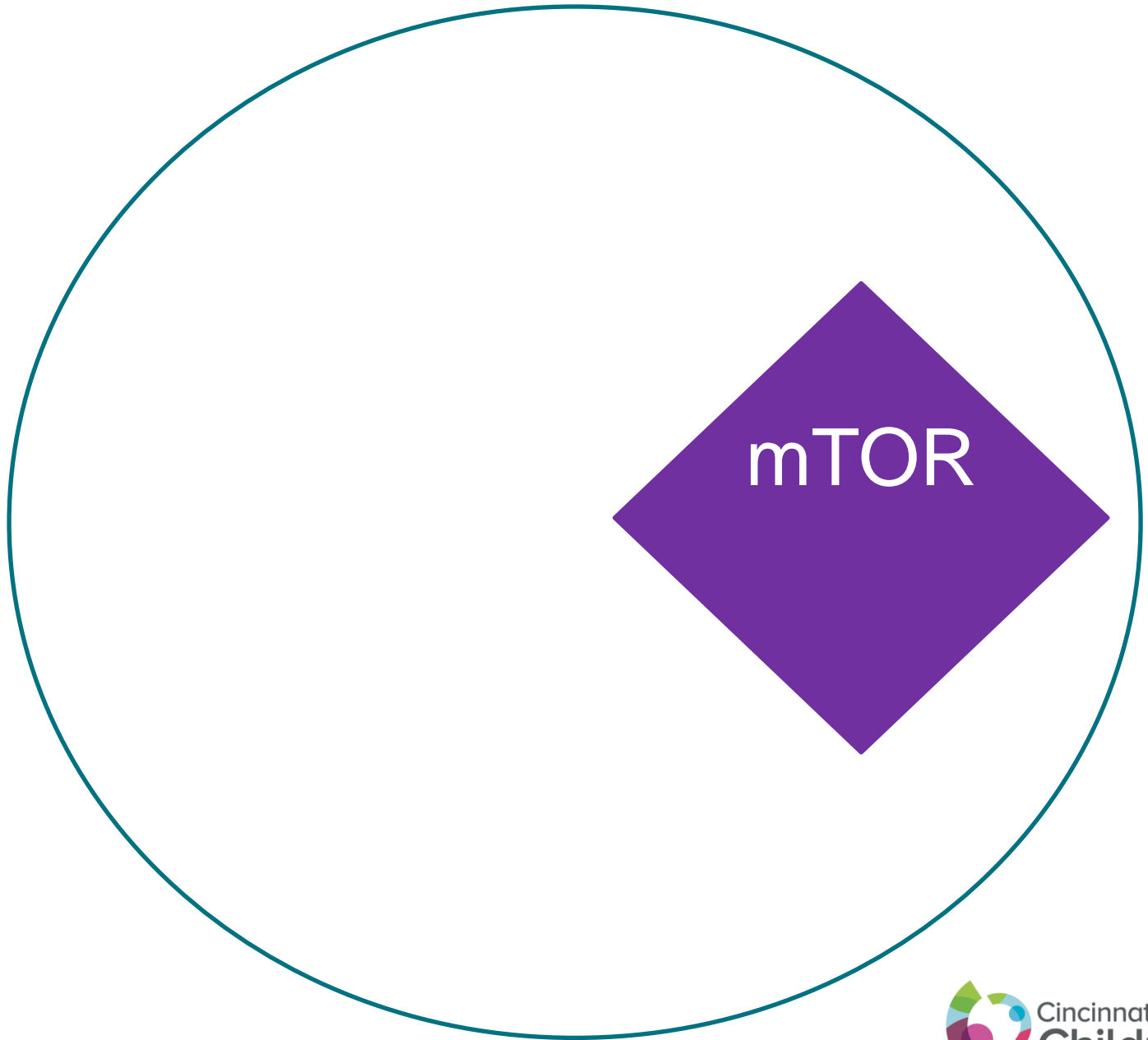
- “Normal” or “Reference” sequence
- Anything difference is considered a “variant”
- Some variants are known to be benign
- Some variants are known to be pathogenic (mutations)
- Some variants are unknown



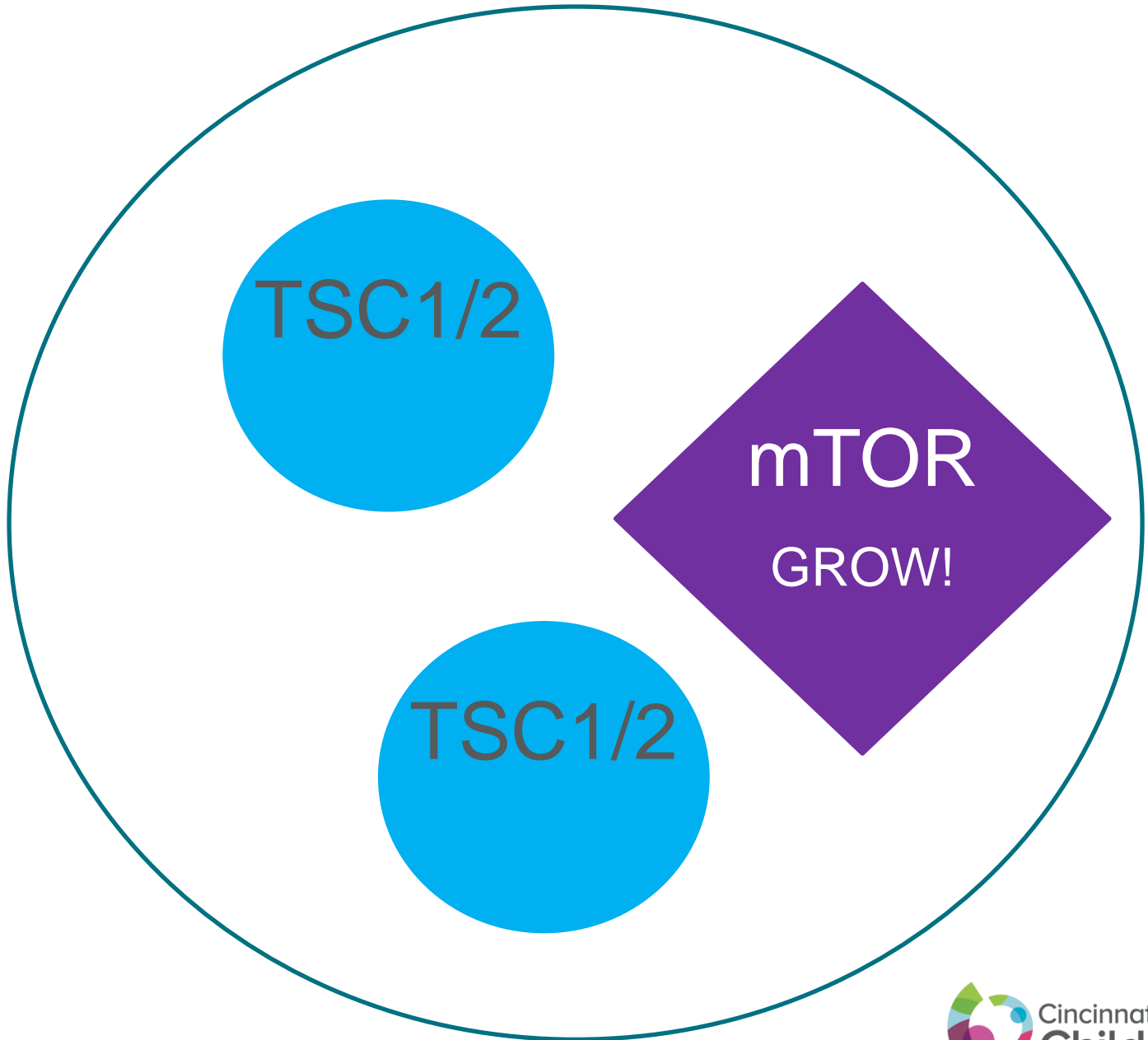


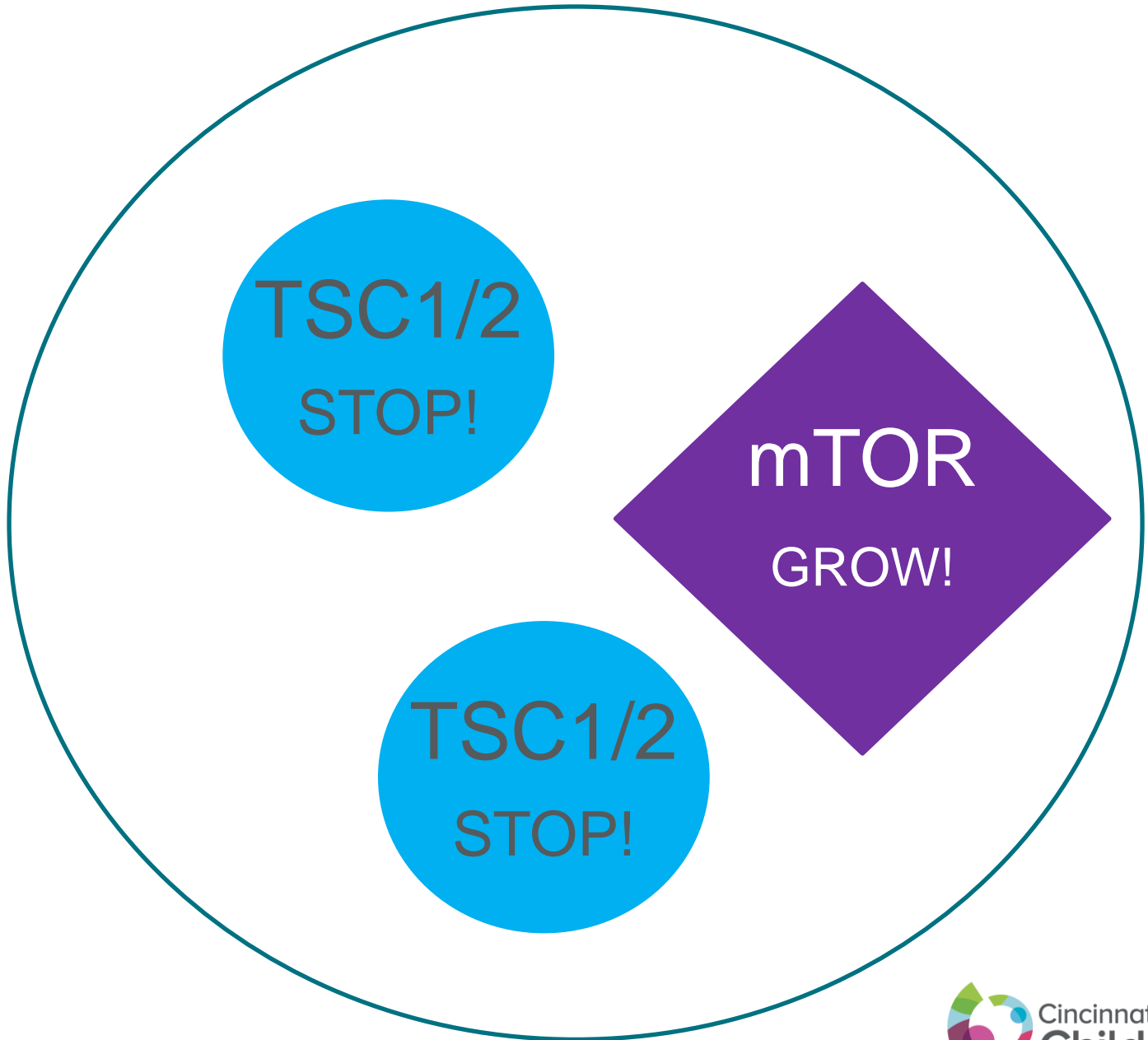
Yang et al.
 Nature
 Communications.
 January 2021

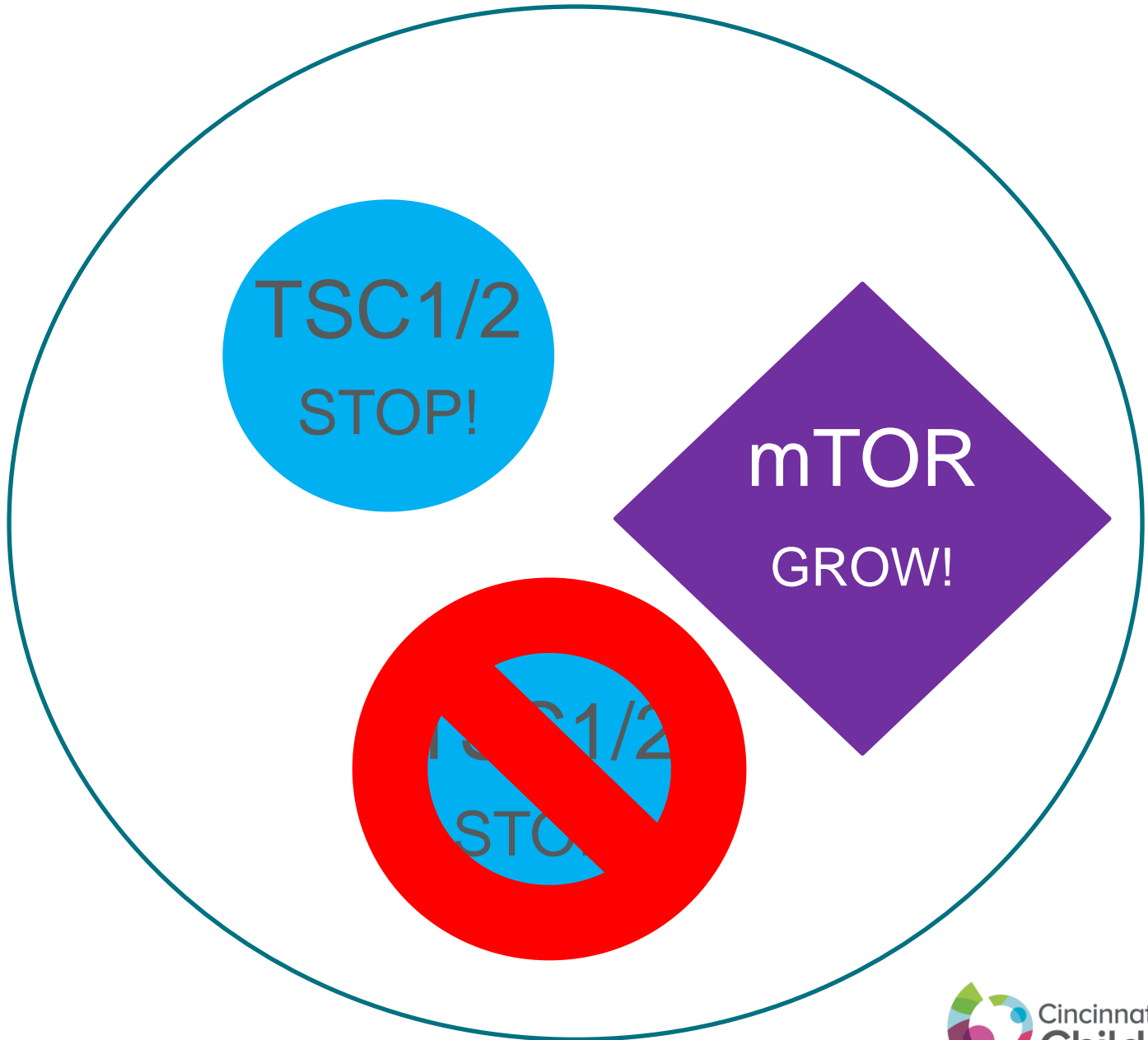


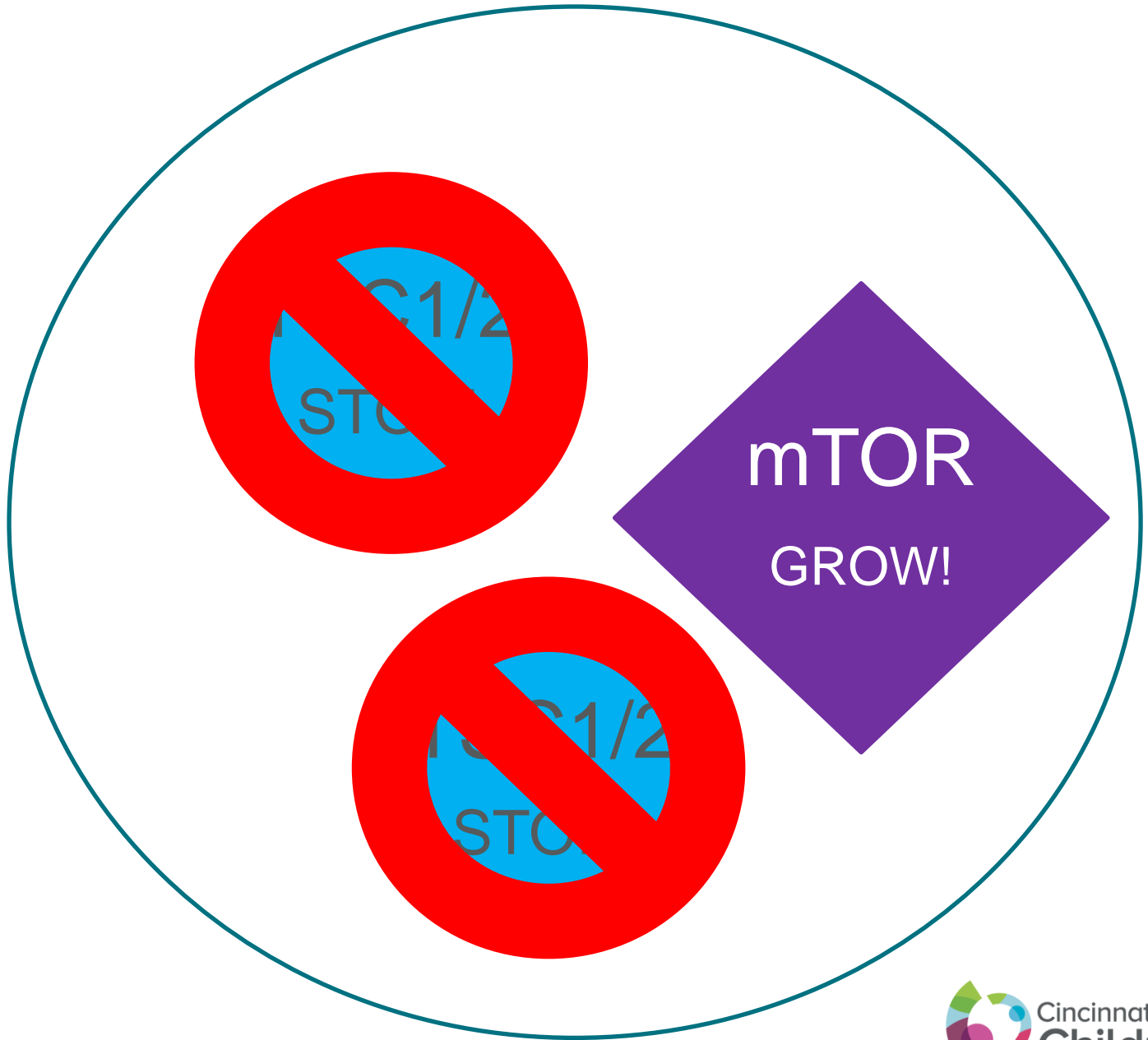


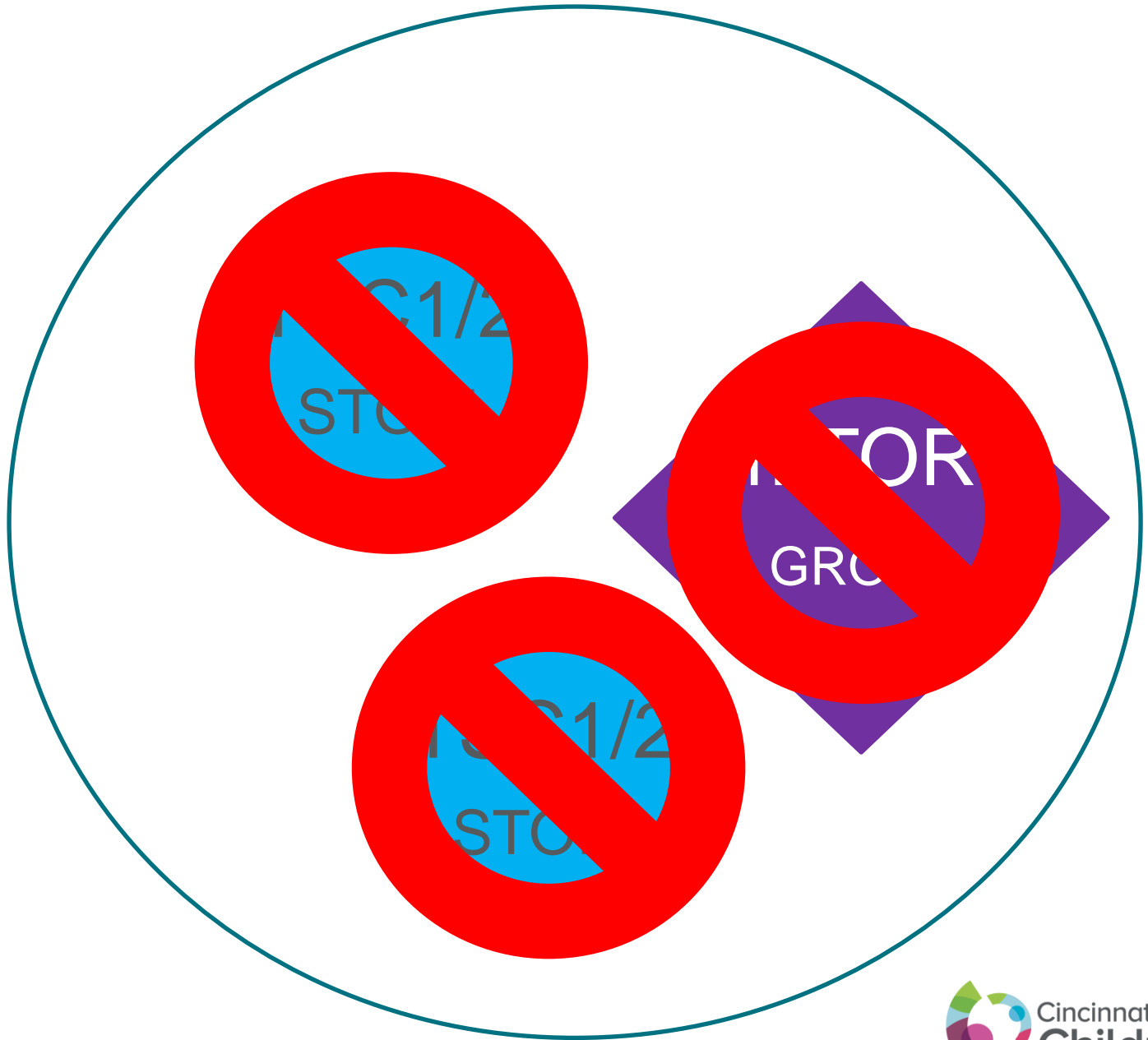




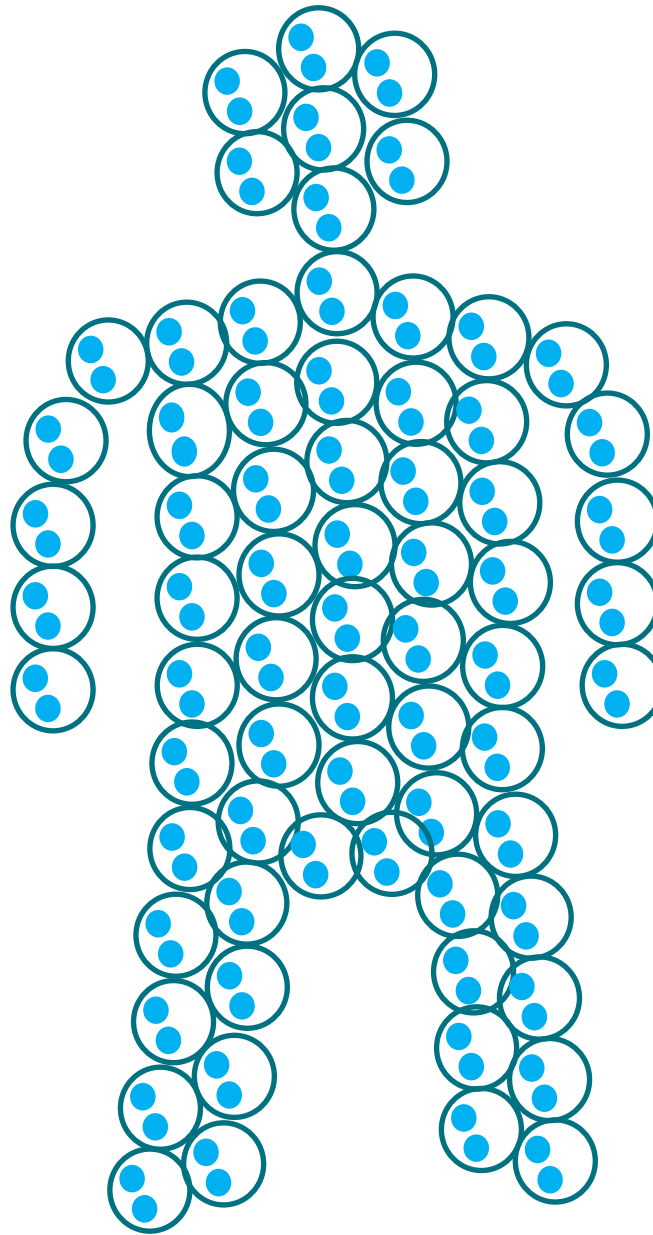






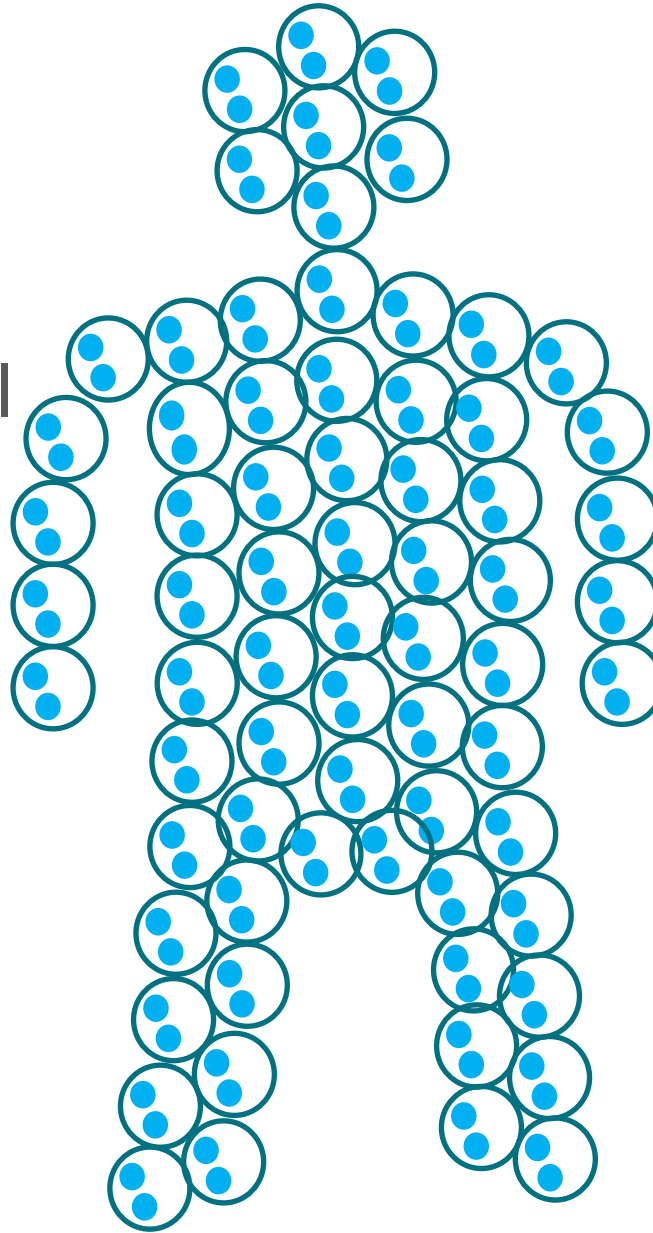


Person without TSC



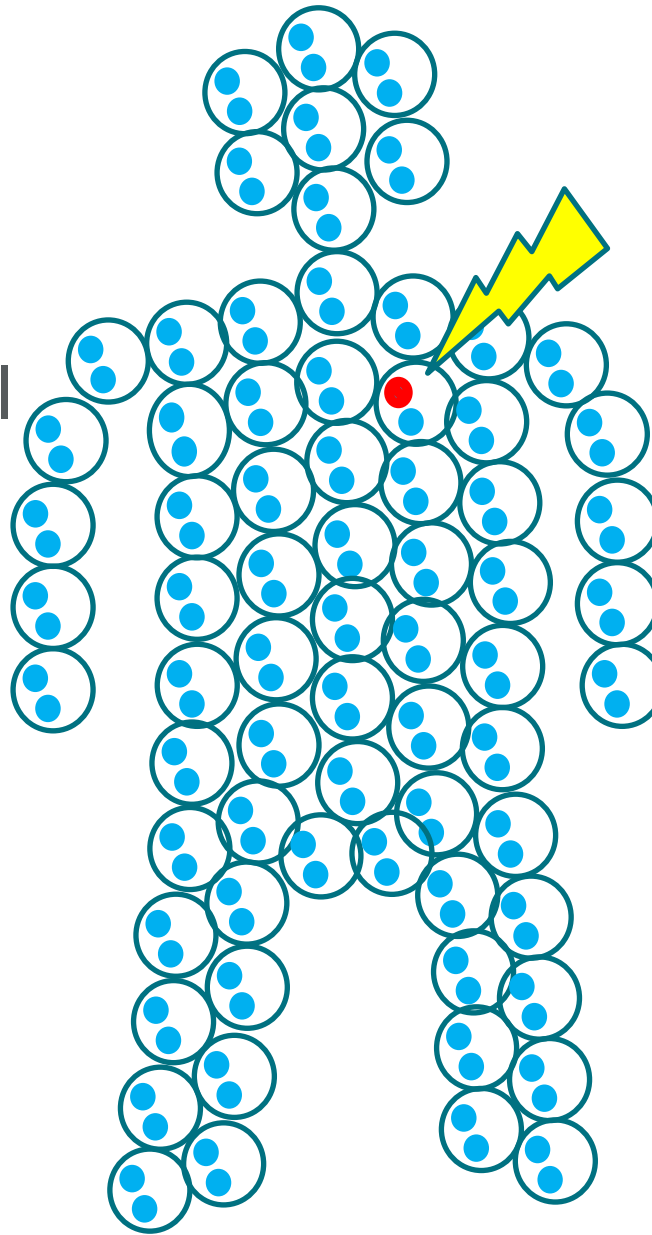
Person without TSC

Random /
Environmental
Mutations



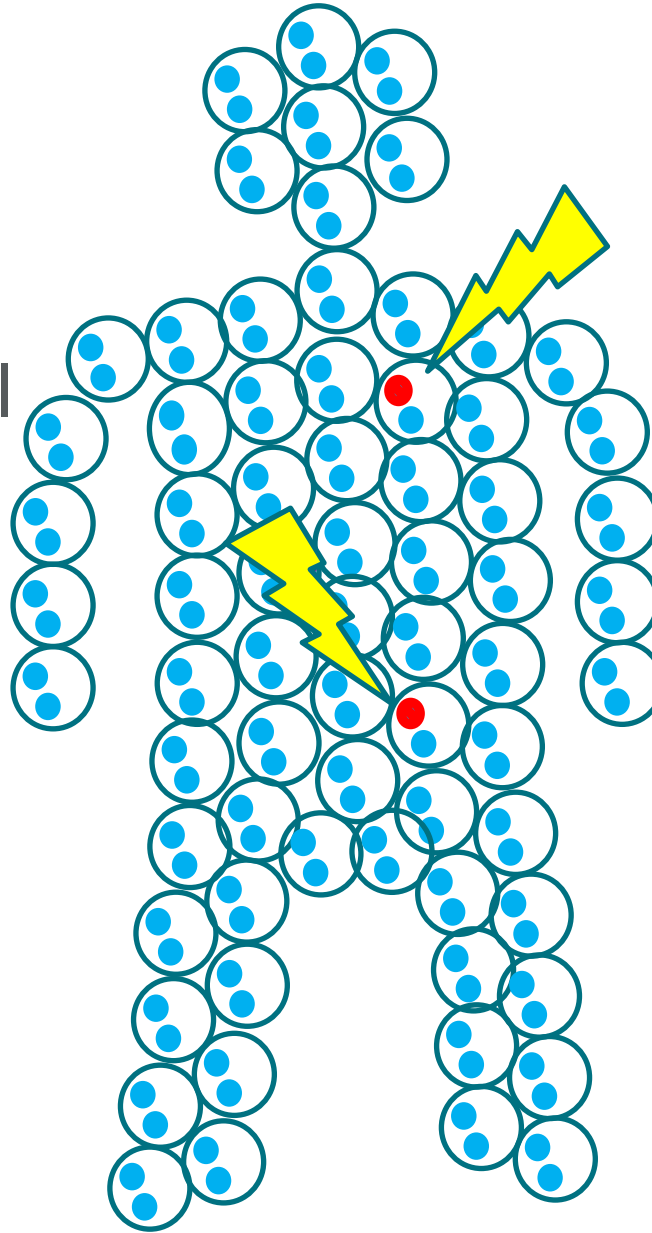
Person without TSC

Random /
Environmental
Mutations



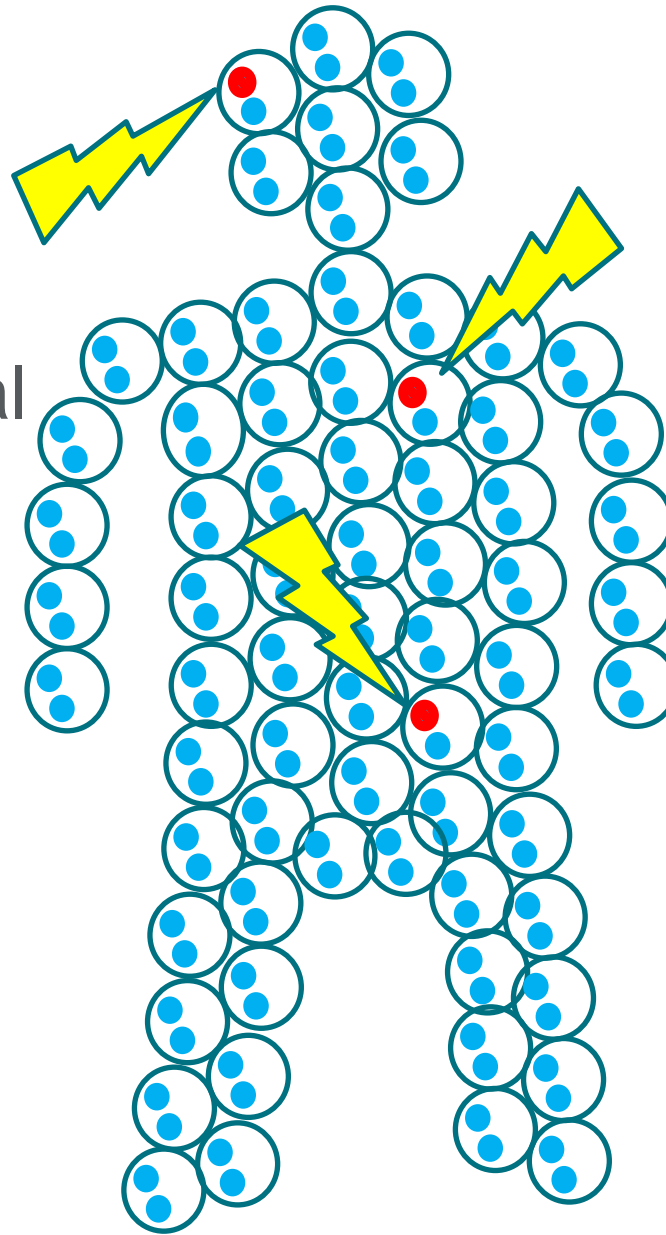
Person without TSC

Random /
Environmental
Mutations



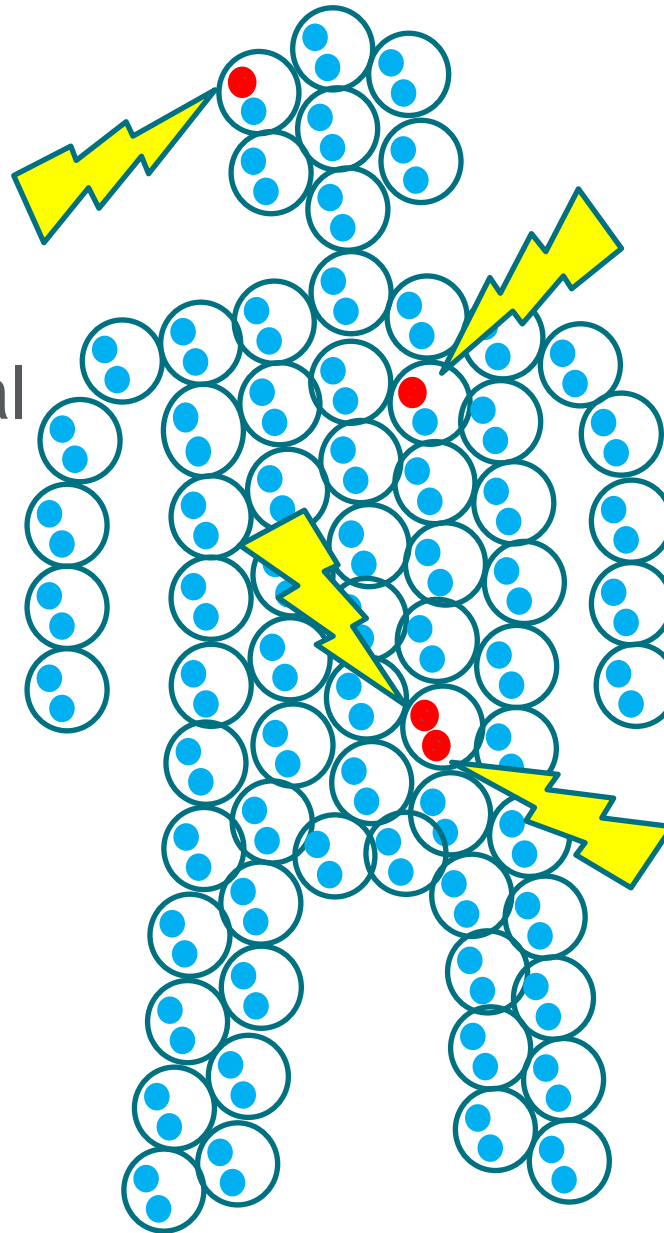
Person without TSC

Random /
Environmental
Mutations



Person without TSC

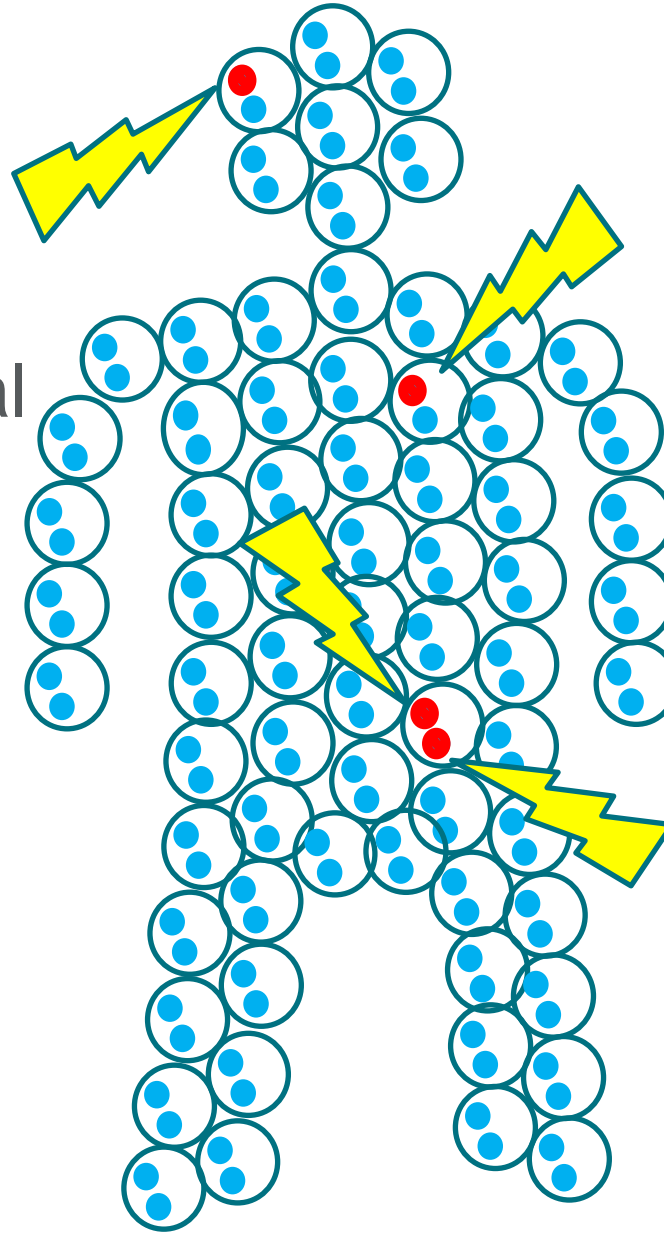
Random /
Environmental
Mutations



Second
random hit
in the
same cell

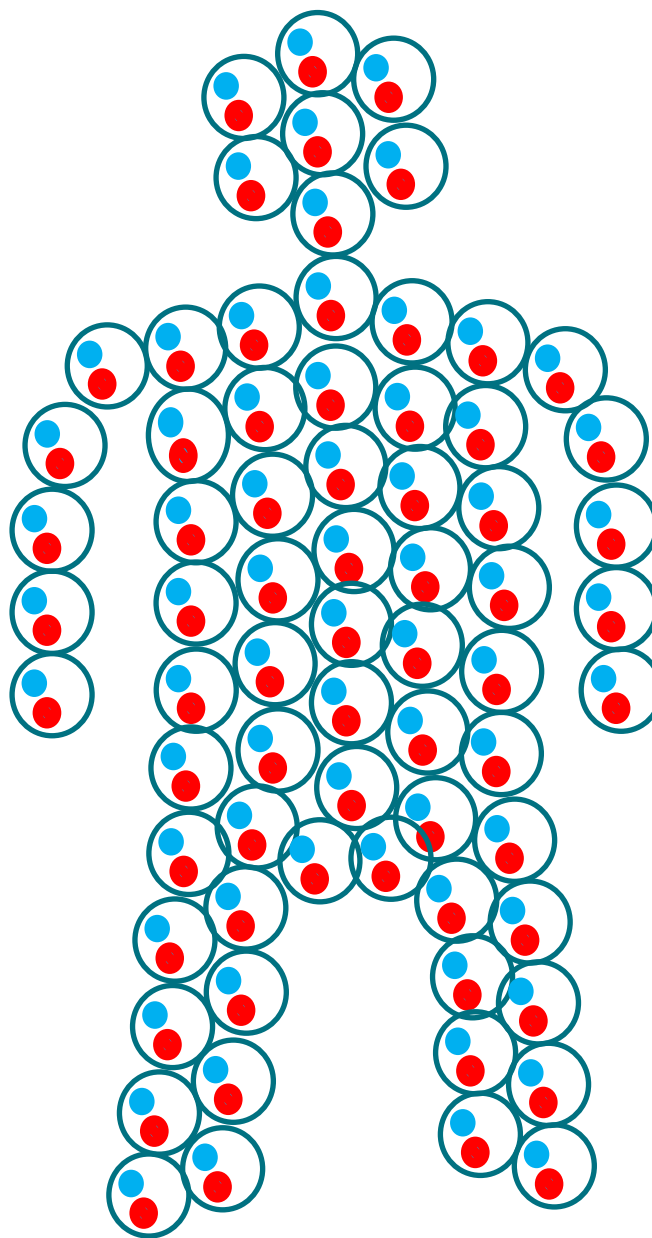
Person without TSC

Random /
Environmental
Mutations

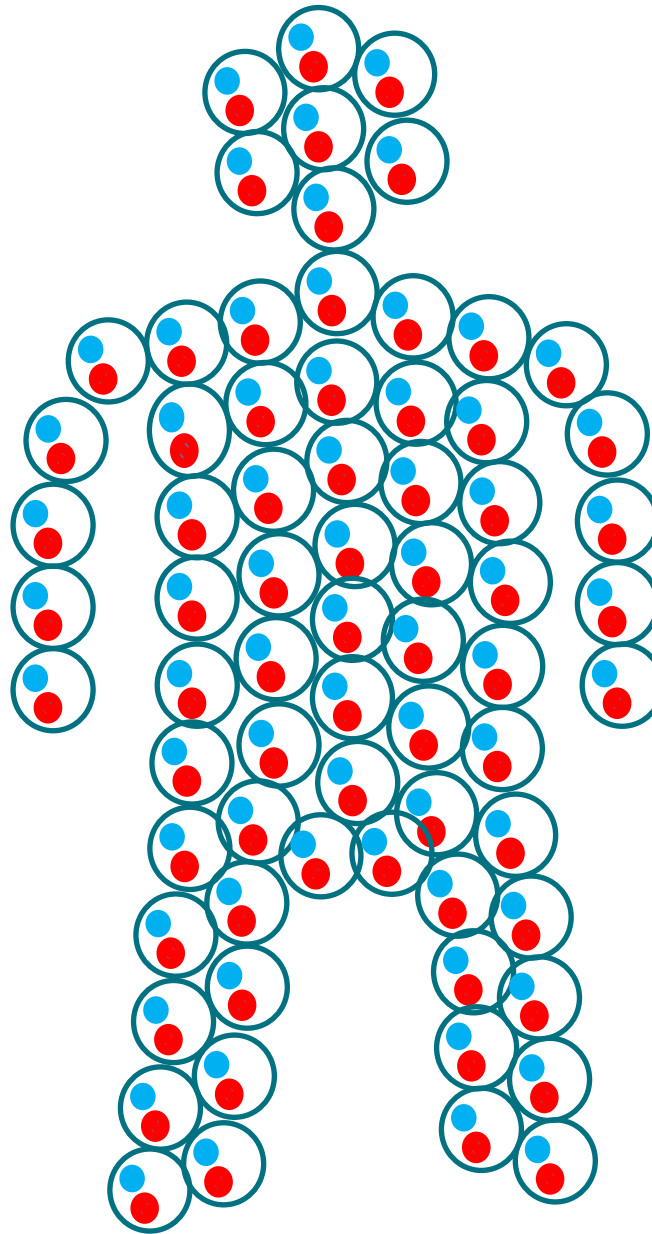


Second
random hit
in the
same cell

Person with TSC

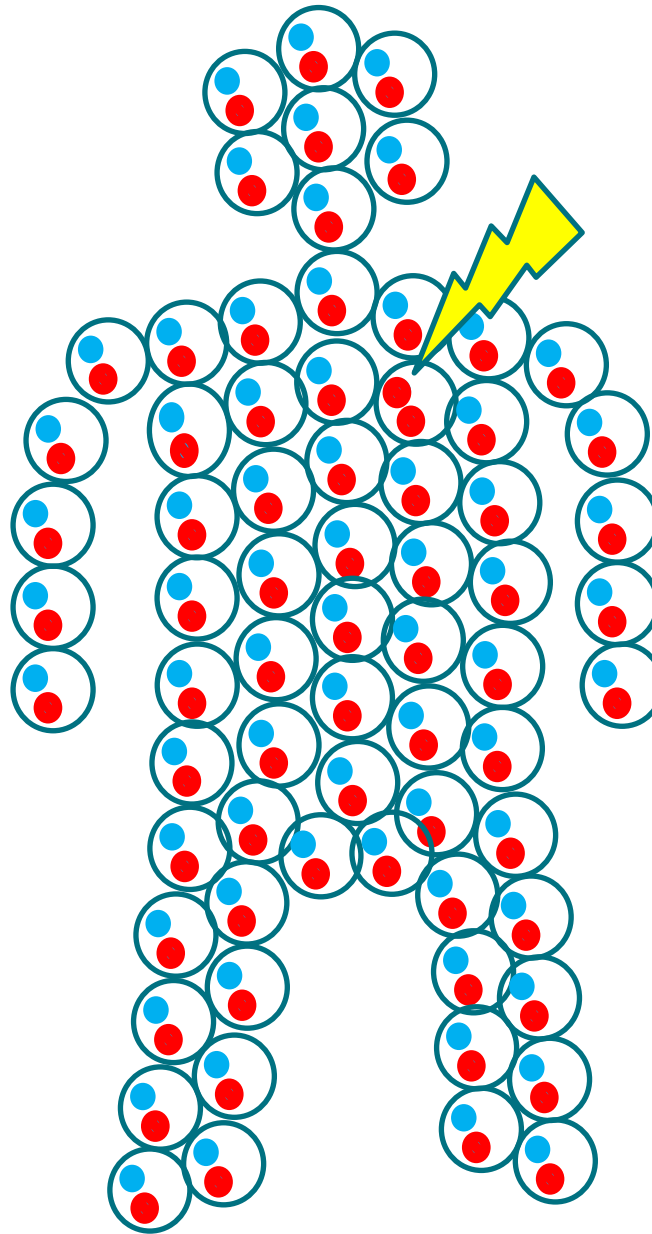


Person with TSC



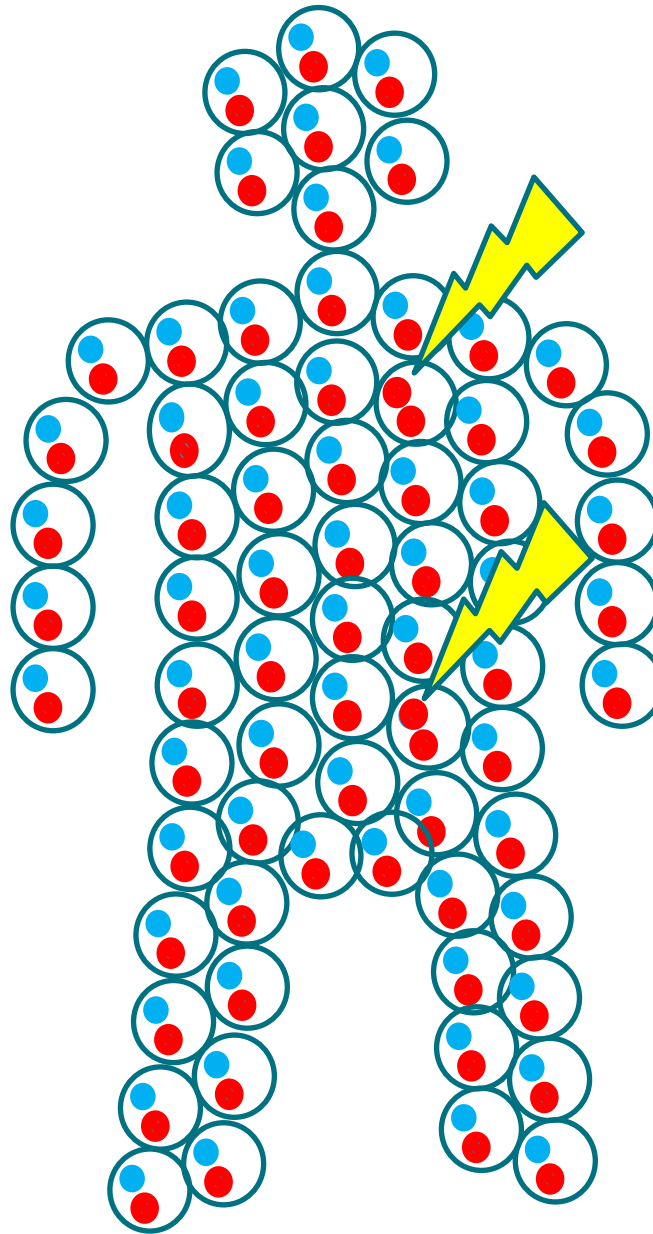
Random /
Environmental
Mutations are all
second hits

Person with TSC



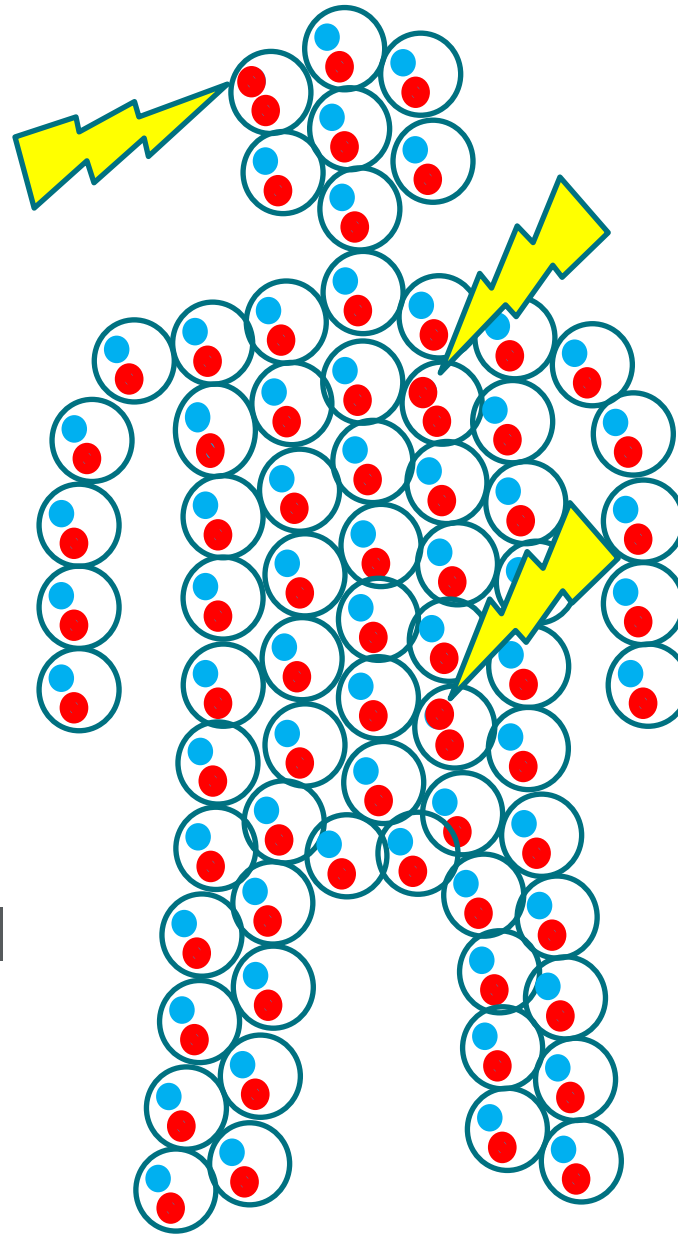
Random /
Environmental
Mutations are all
second hits

Person with TSC



Random /
Environmental
Mutations are all
second hits

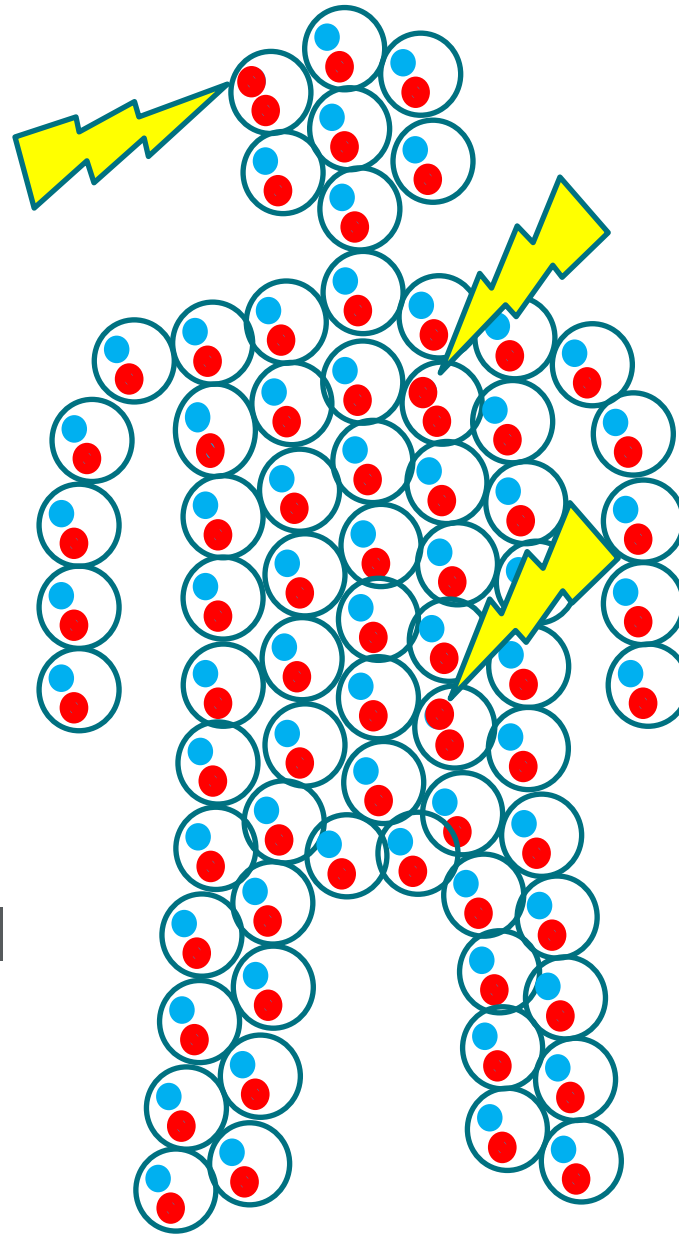
Person with TSC



Random /
Environmental
Mutations are all
second hits

Why mTOR
Inhibitors can
be affective
against a
number of
symptoms in
TSC

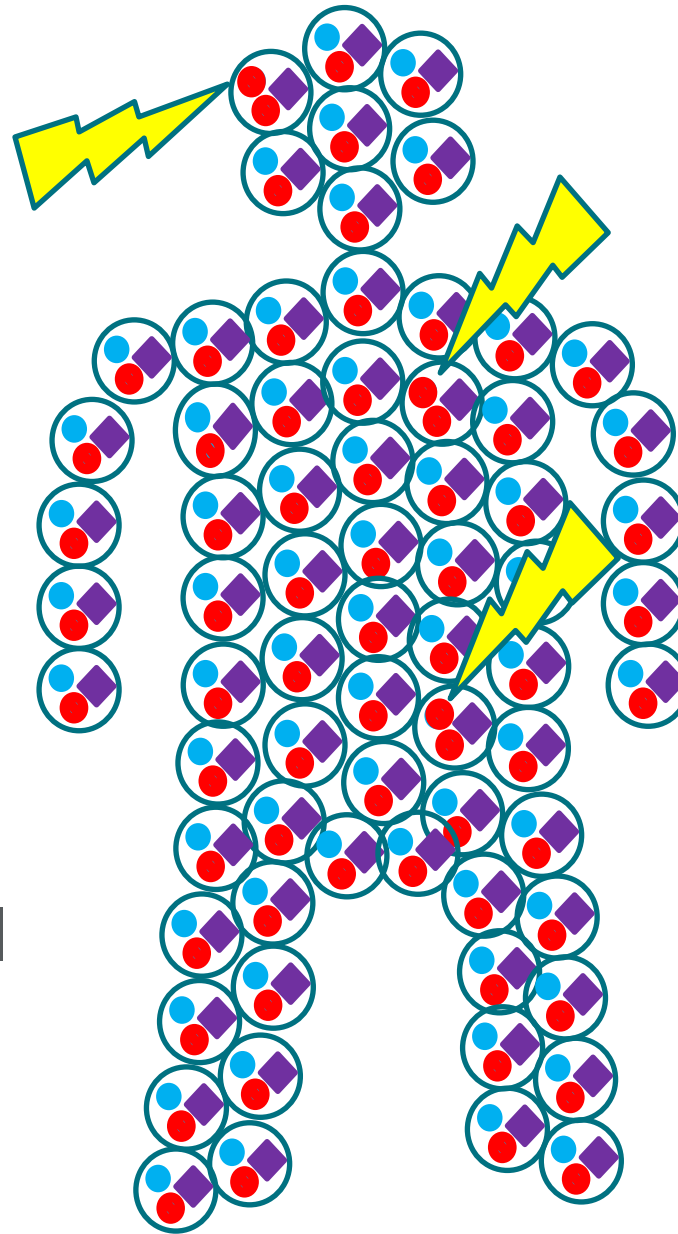
Random /
Environmental
Mutations are all
second hits



Person
with
TSC

Why mTOR
Inhibitors can
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TSC

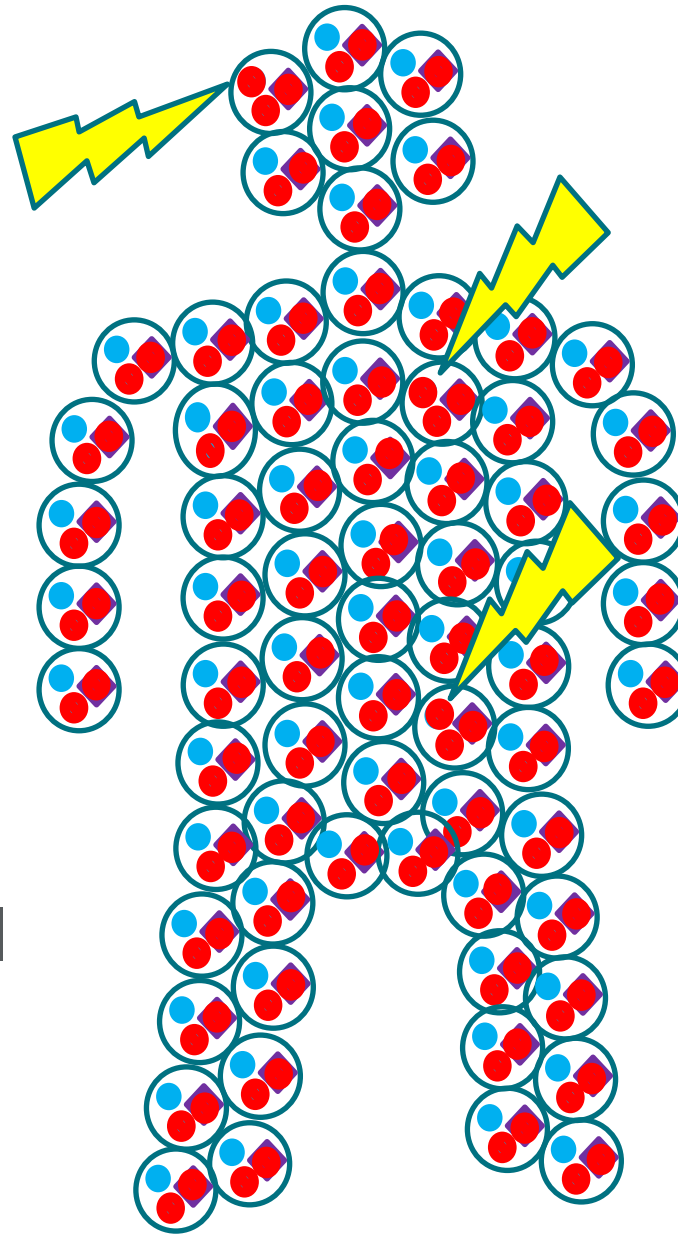
Random /
Environmental
Mutations are all
second hits



Person
with
TSC

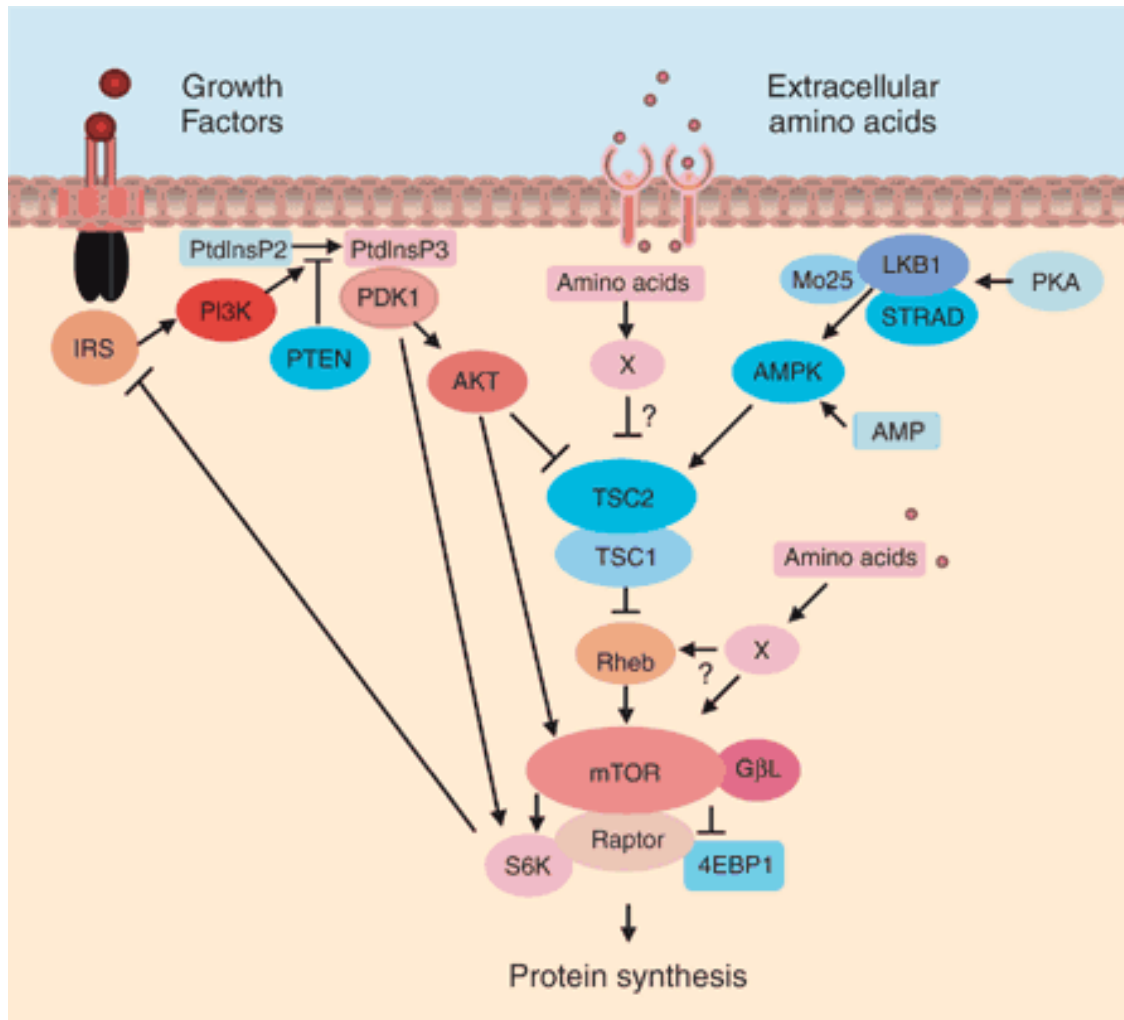
Why mTOR
Inhibitors can
be affective
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TSC

Random /
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Mutations are all
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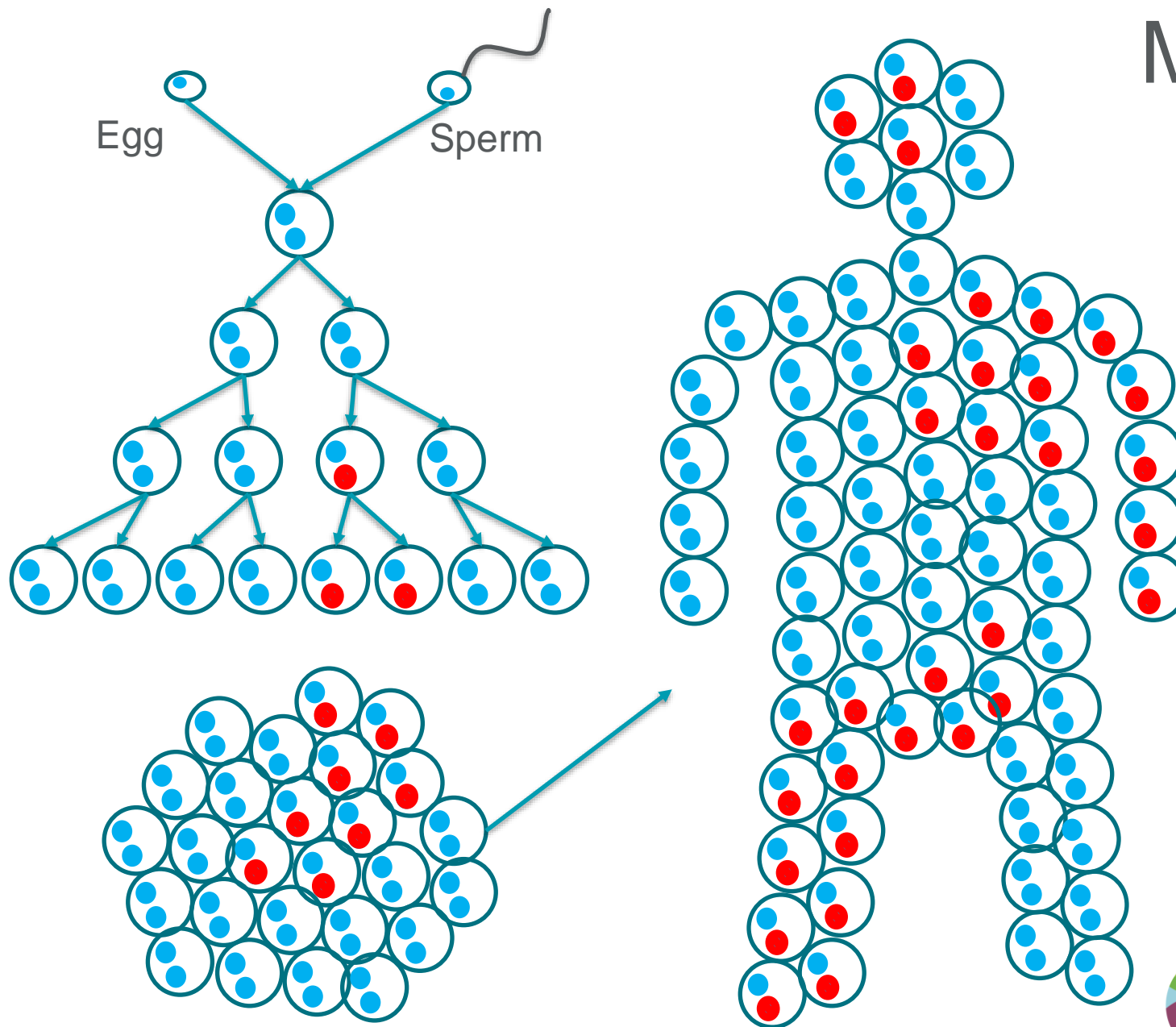


Person
with
TSC

mTOR pathway



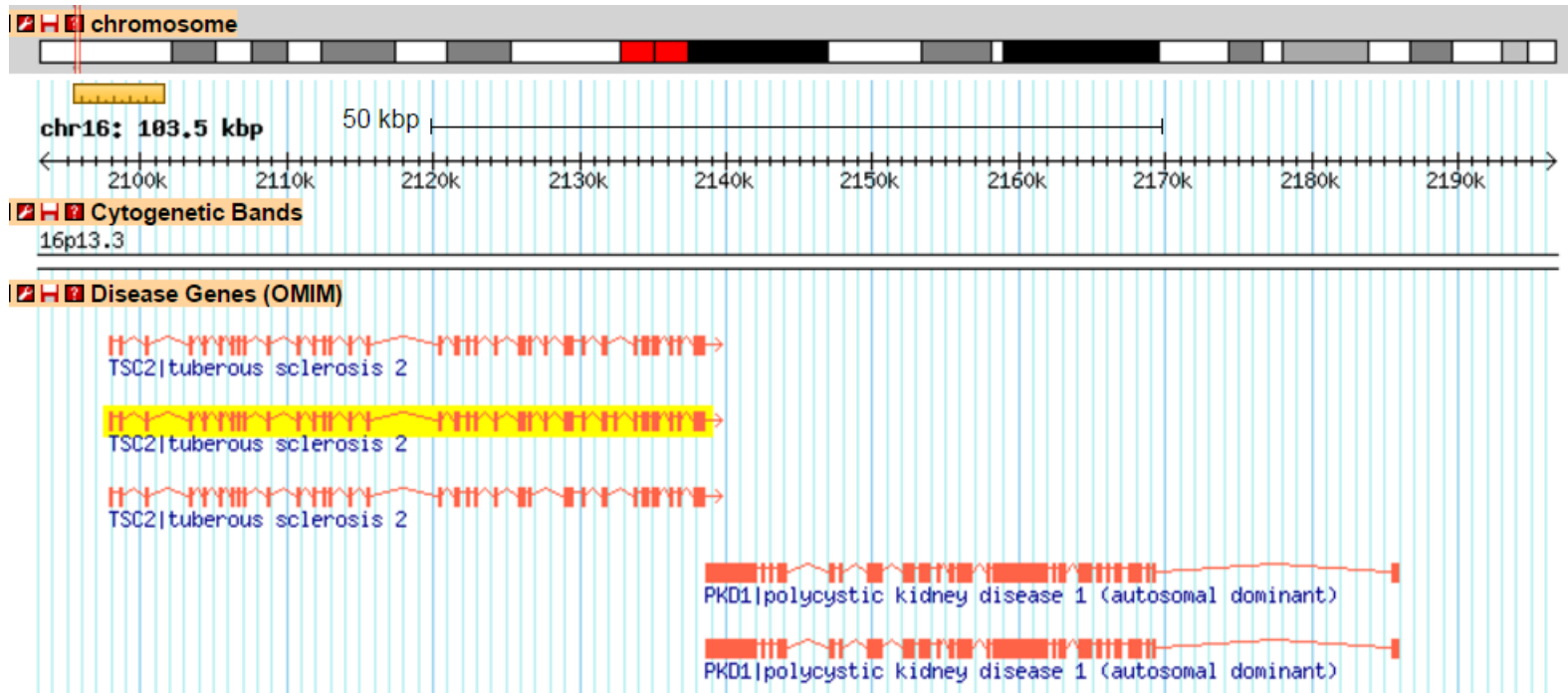
Mosaic TSC



Variable expression

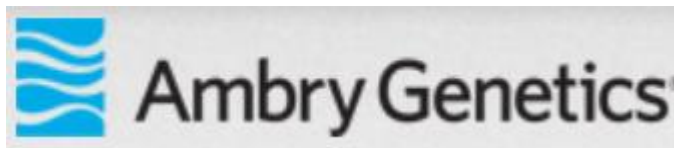
- Huge spectrum of severity
- Between families and within families
- TSC1 vs TSC2

Contiguous Gene Deletion



TSC + polycystic kidney disease

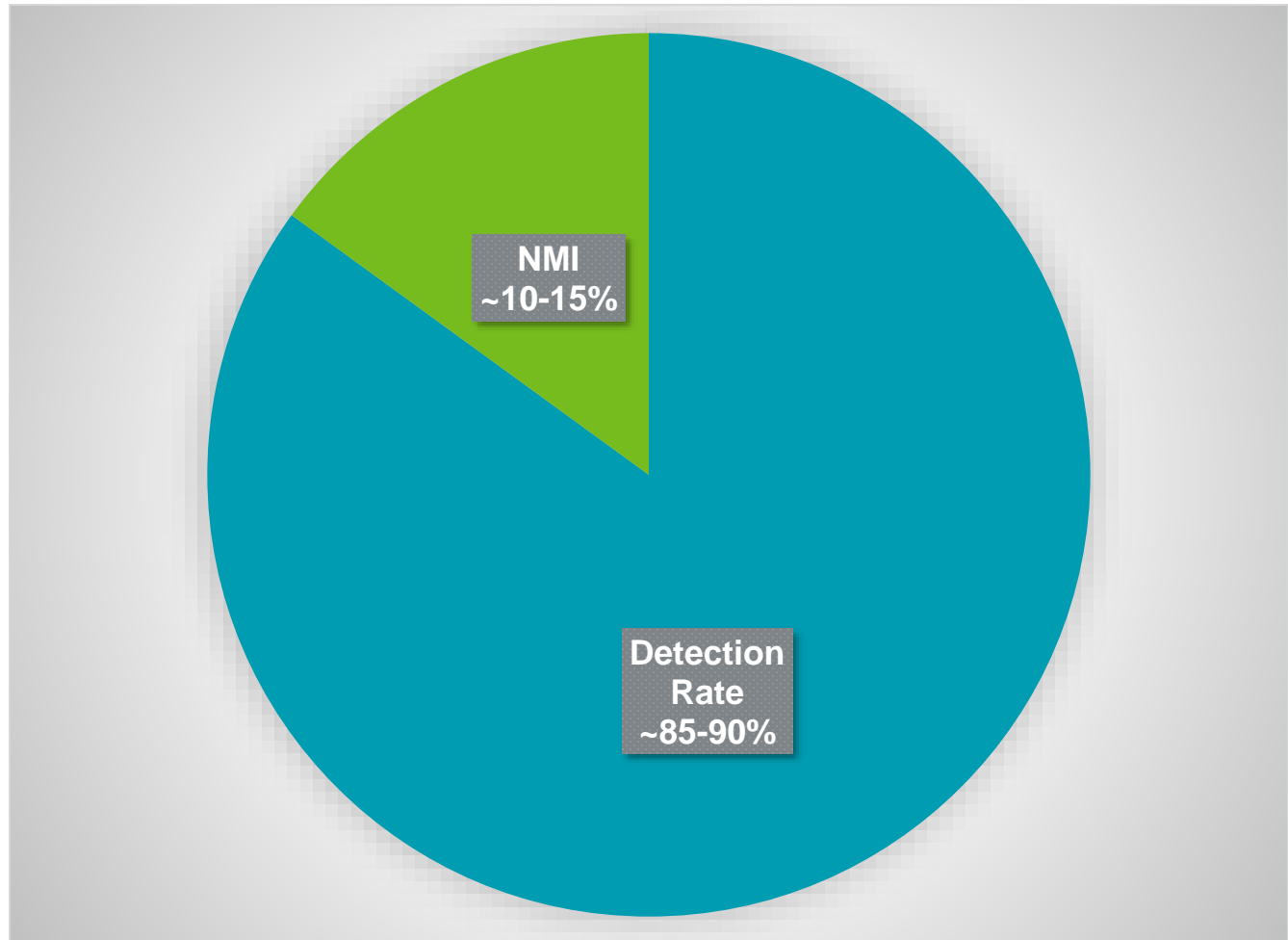
Clinical Genetic Testing



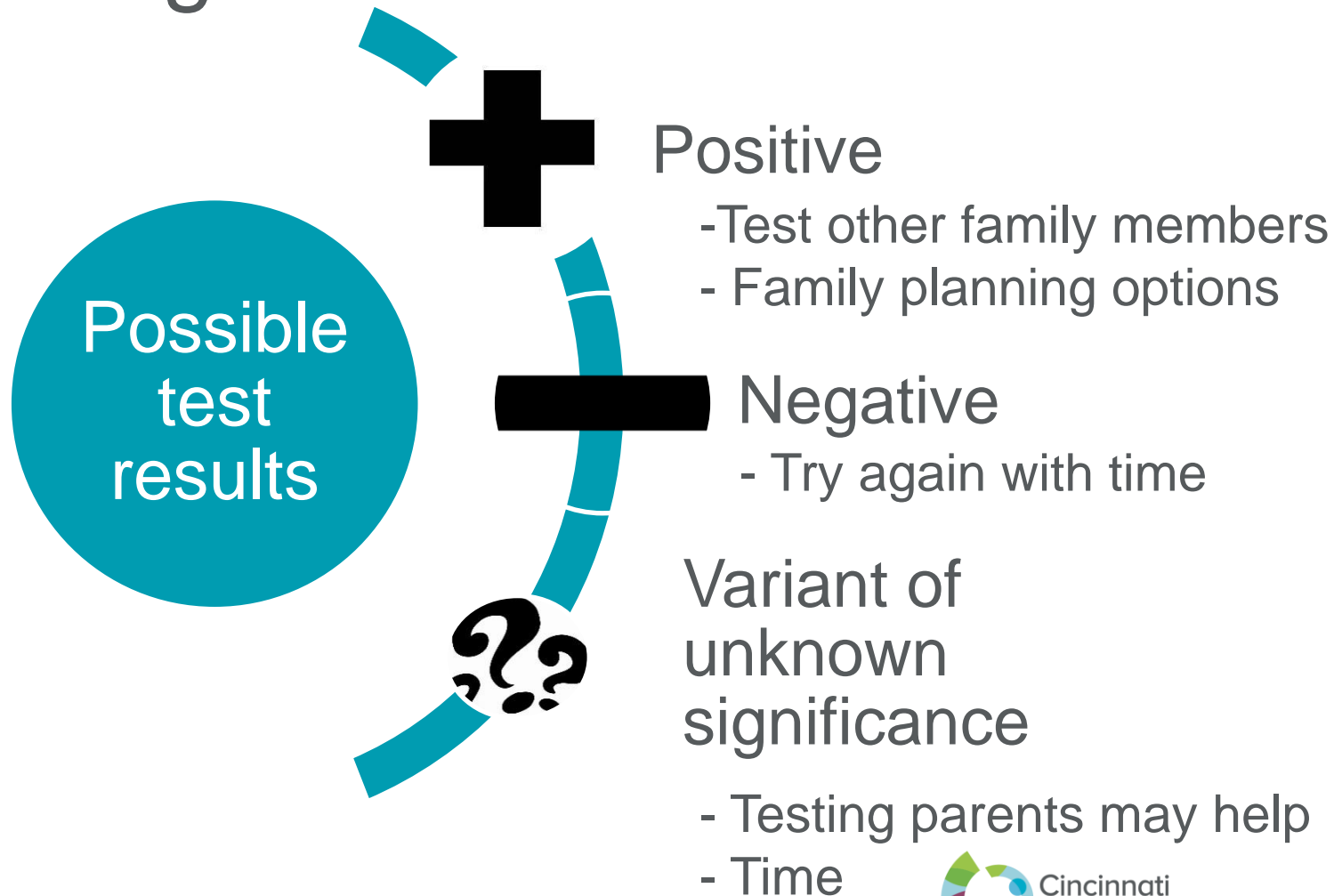
Not all genetic testing is created equal

- Sanger sequencing
 - Older
 - Not reliable under ~20% mosaicism
- Next Generation Sequencing (NGS)
 - Can have a low depth read similar to Sanger
 - Can have a much higher depth read enabling it to find mosaicism under 1%
- When getting deletion data from NGS data, possibility to miss small deletions
- Different labs will analyze different areas around the genes that may or not be relevant

Current clinical genetic testing: Sequencing and deletion analysis of TSC1 and TSC2



Results of Clinical Genetic Testing



GeneTherapy in TSC

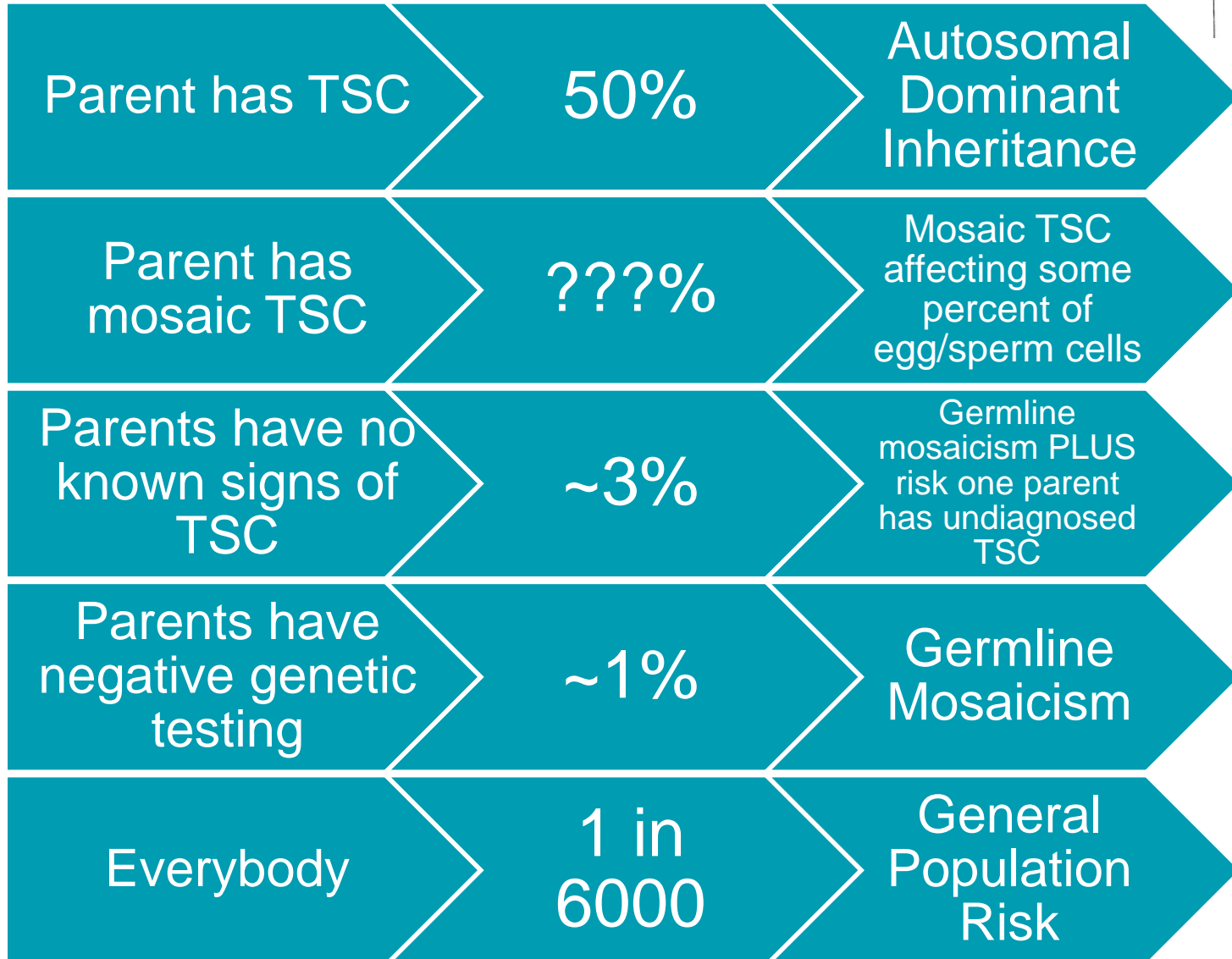


TSC is **ALWAYS** genetic

Sometimes it is **INHERITED**

Other times it is **sporadic**

TSC Recurrence Risk



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Thank you to my patients
and coworkers



Thank you to my patients
and coworkers



QUESTIONS?