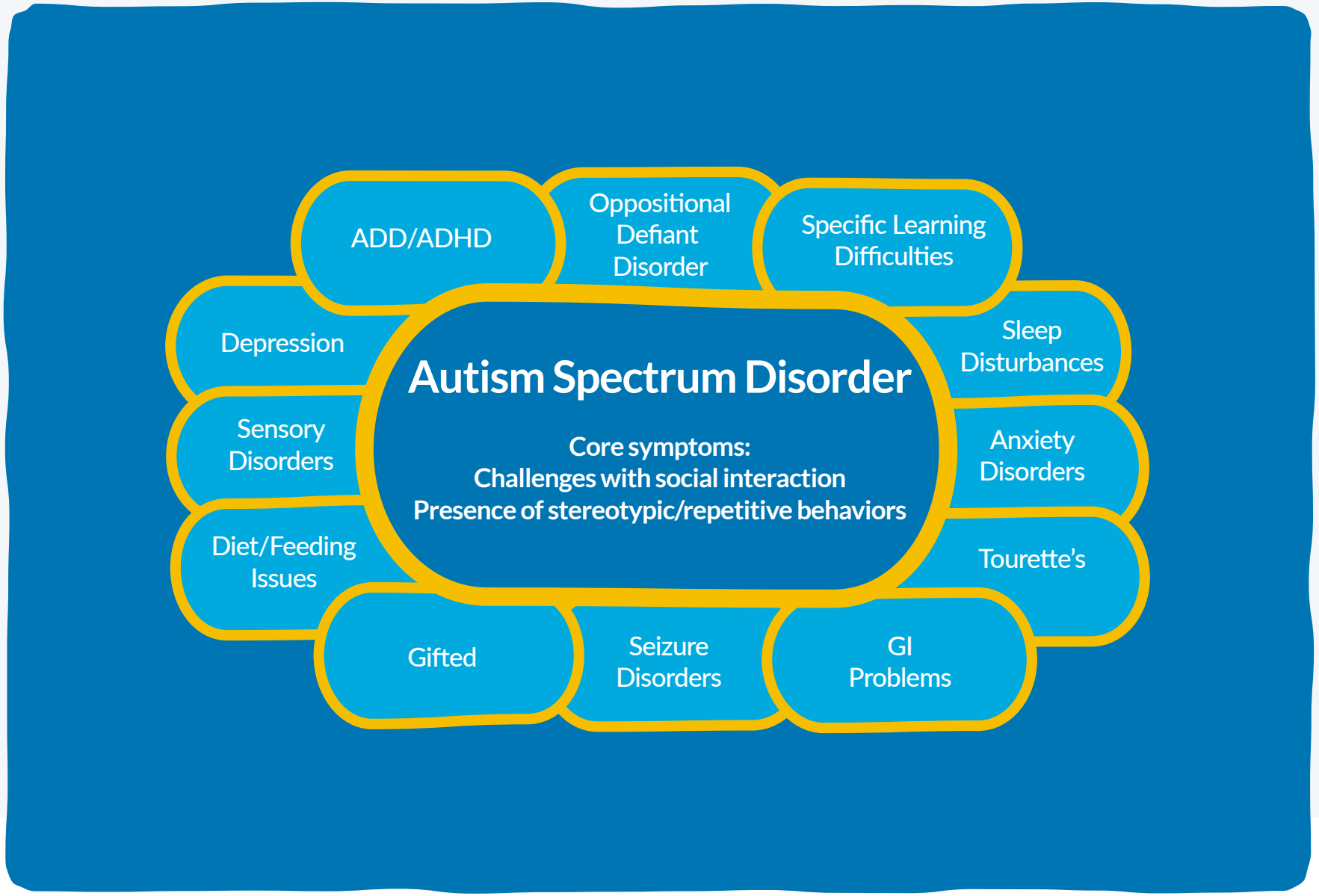
What We Are Learning About Genetics and Autism

Wendy Chung, M.D., Ph.D.
March 26, 2019

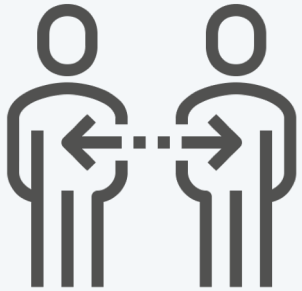
SPARK

What We Know About Autism

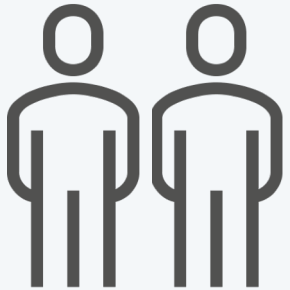
Autism is complex. It is not a single condition, and many individuals have related challenges.



Twin studies in autism research suggest that genes are important to study.



Identical Twins
77%



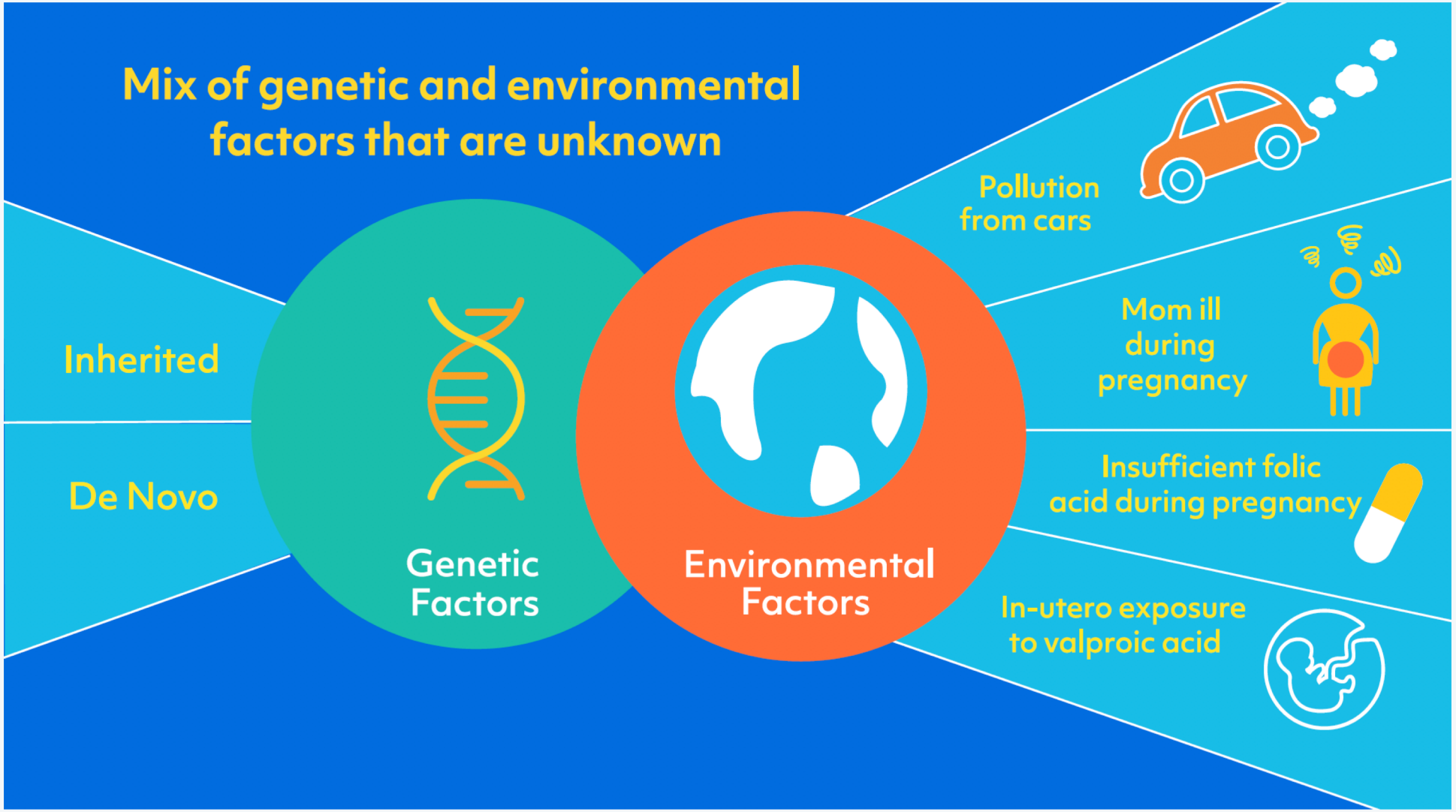
Fraternal Twins
31%

Siblings
20%

General Population
1%

Concordance for autism differs by family relations and is correlated with genetic similarity.

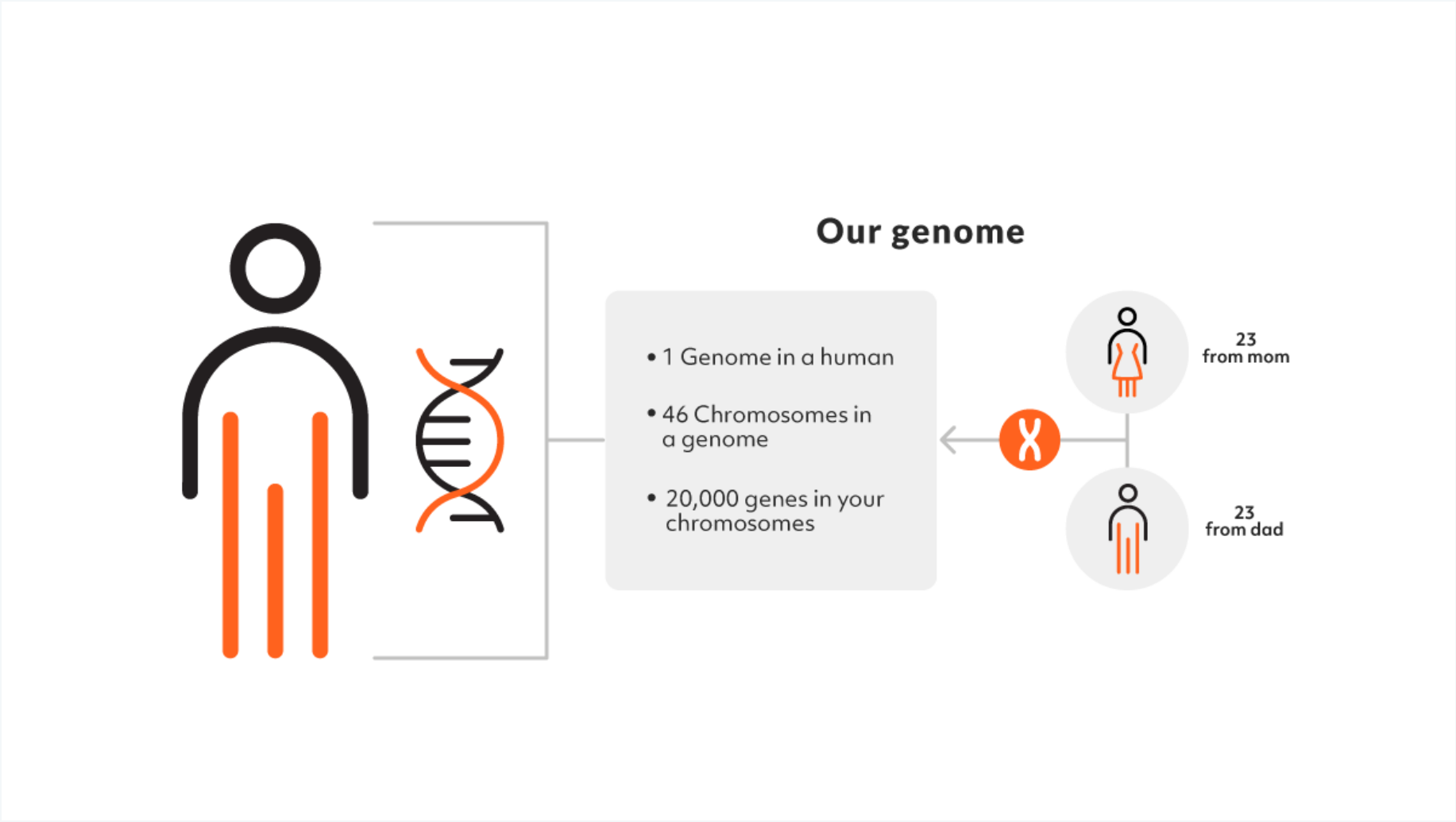
There are many causes of autism, but for most individuals we do not yet know the cause.



SPARK

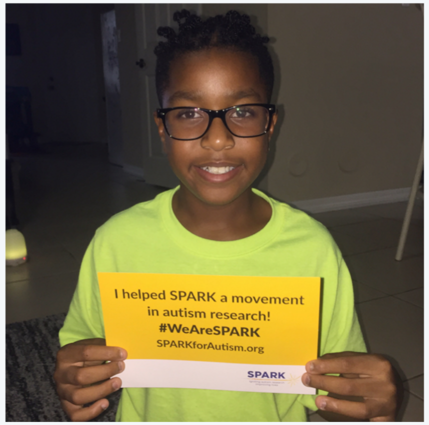
An Overview of Genetics

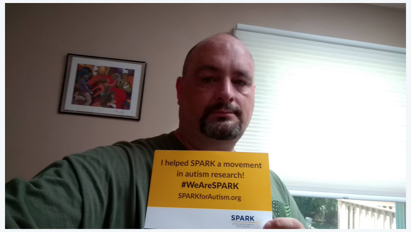
The collection of all your DNA is your genome and codes for the instructions for your body in 20,000 genes.

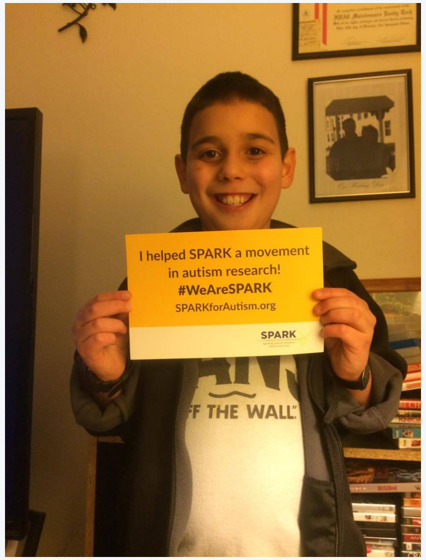


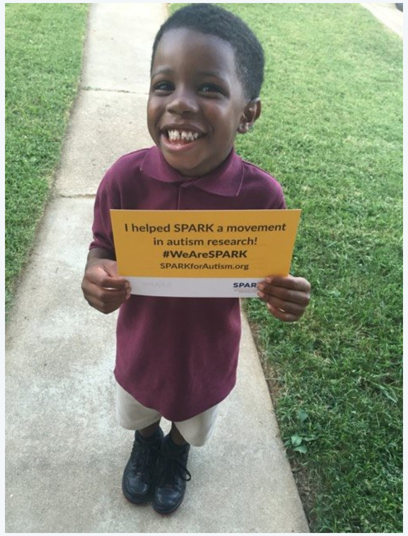
SPARK

We are all different, and some of these differences are coded in our genes.

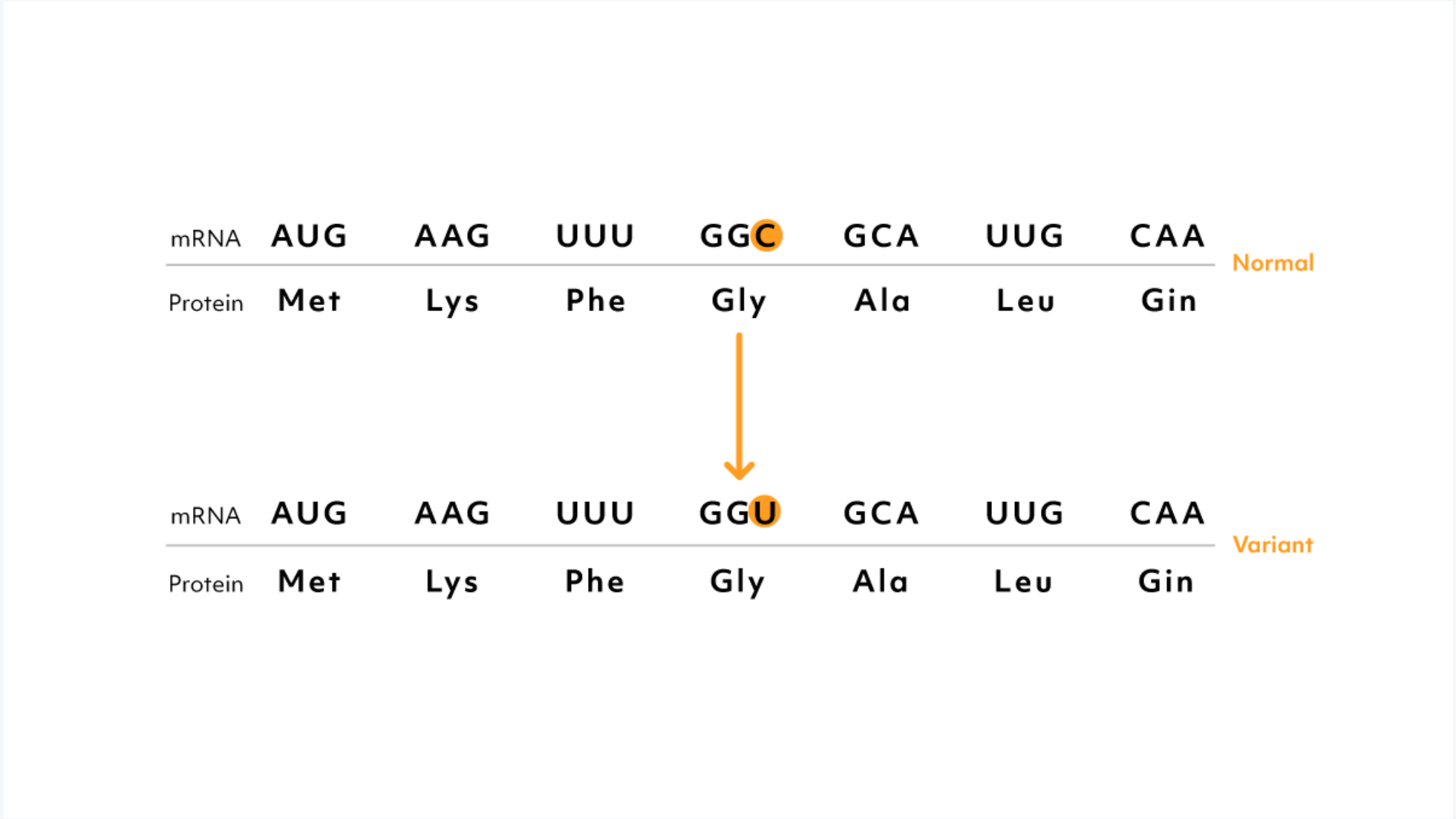




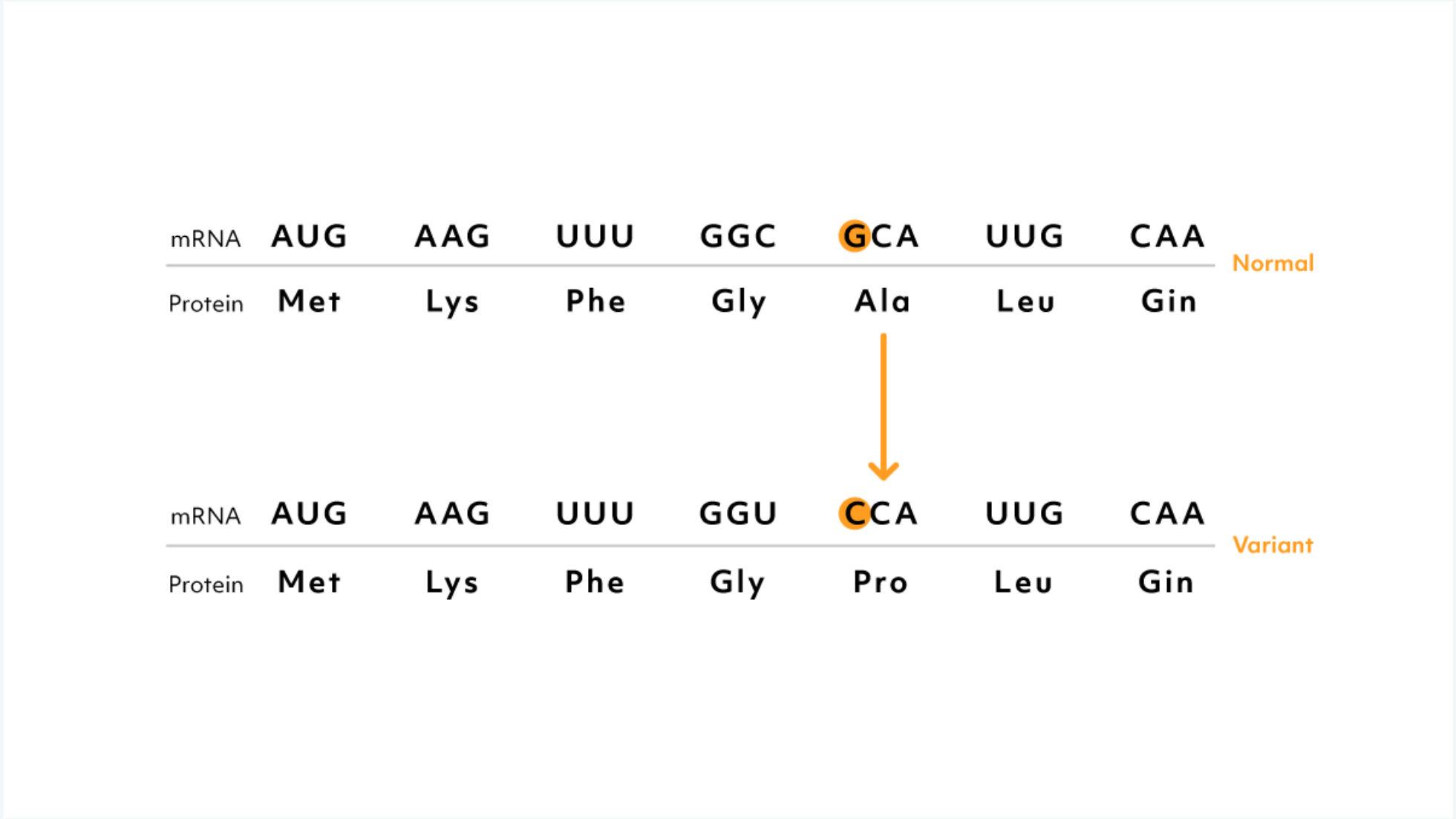




Silent Variant

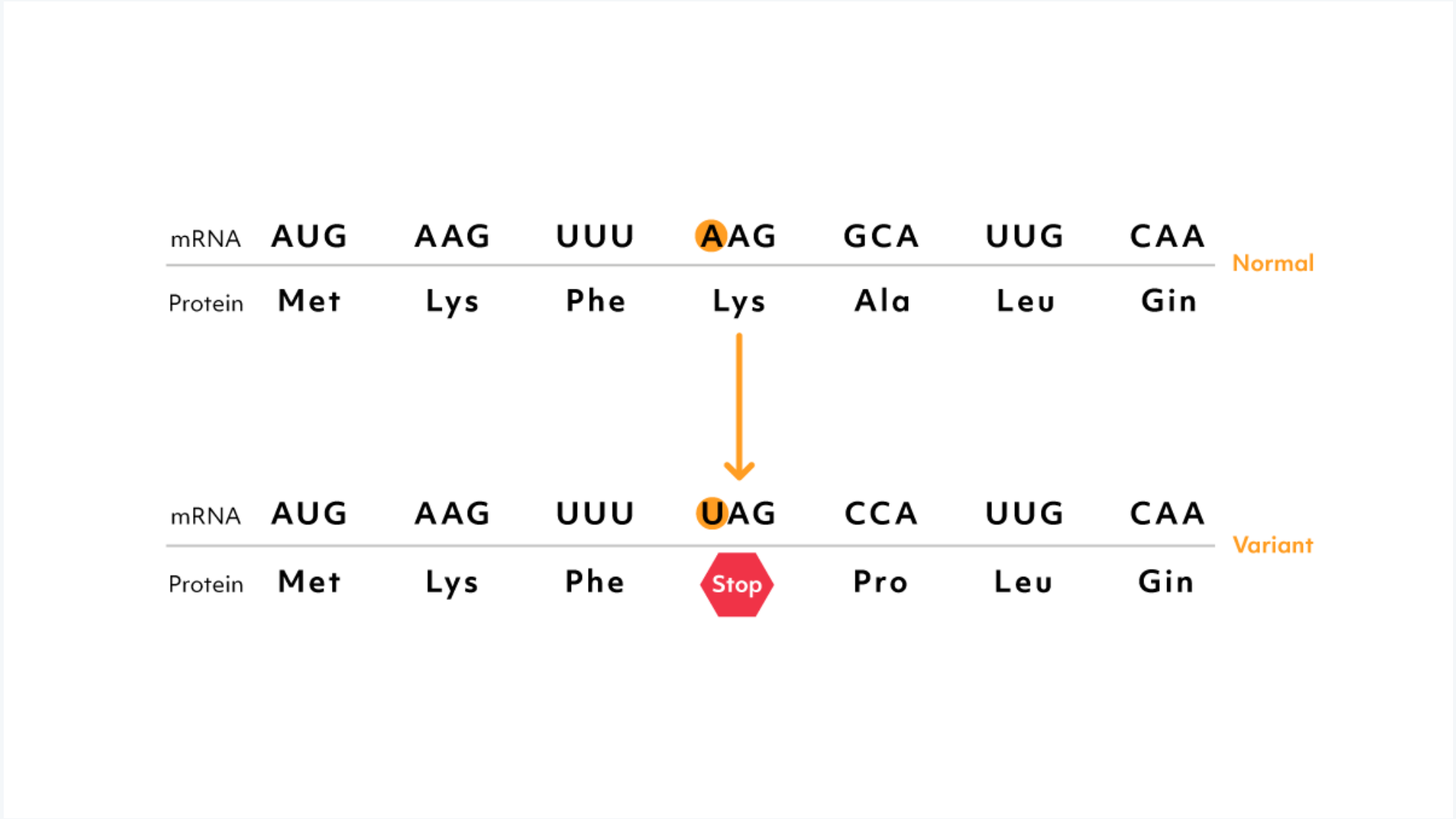


Missense Variant



SPARK

Nonsense Variant



SPARK

Our genes are encoded in pieces called exons.

wpod?am fkw cu.gjhklf four sjckfo qu score

and void m$%d jkkk yp@mvjckd fkkseo

cbqw.oiwjfm du seven years ago dllfkk*wqm

fkkd xmmenfyruuci our skkdj$fmvjkjdfk&%wo

qppalfdkkf qaq.d eiidty forefathers brought jjd

qpoooekfjk vbzxx dsg forth a

The exons are separated by DNA of unclear function.

wpod?am fkw cu.gjhklf four sjckfo qu score

and void m$%d jkkk yp@mvjckd fkkseo

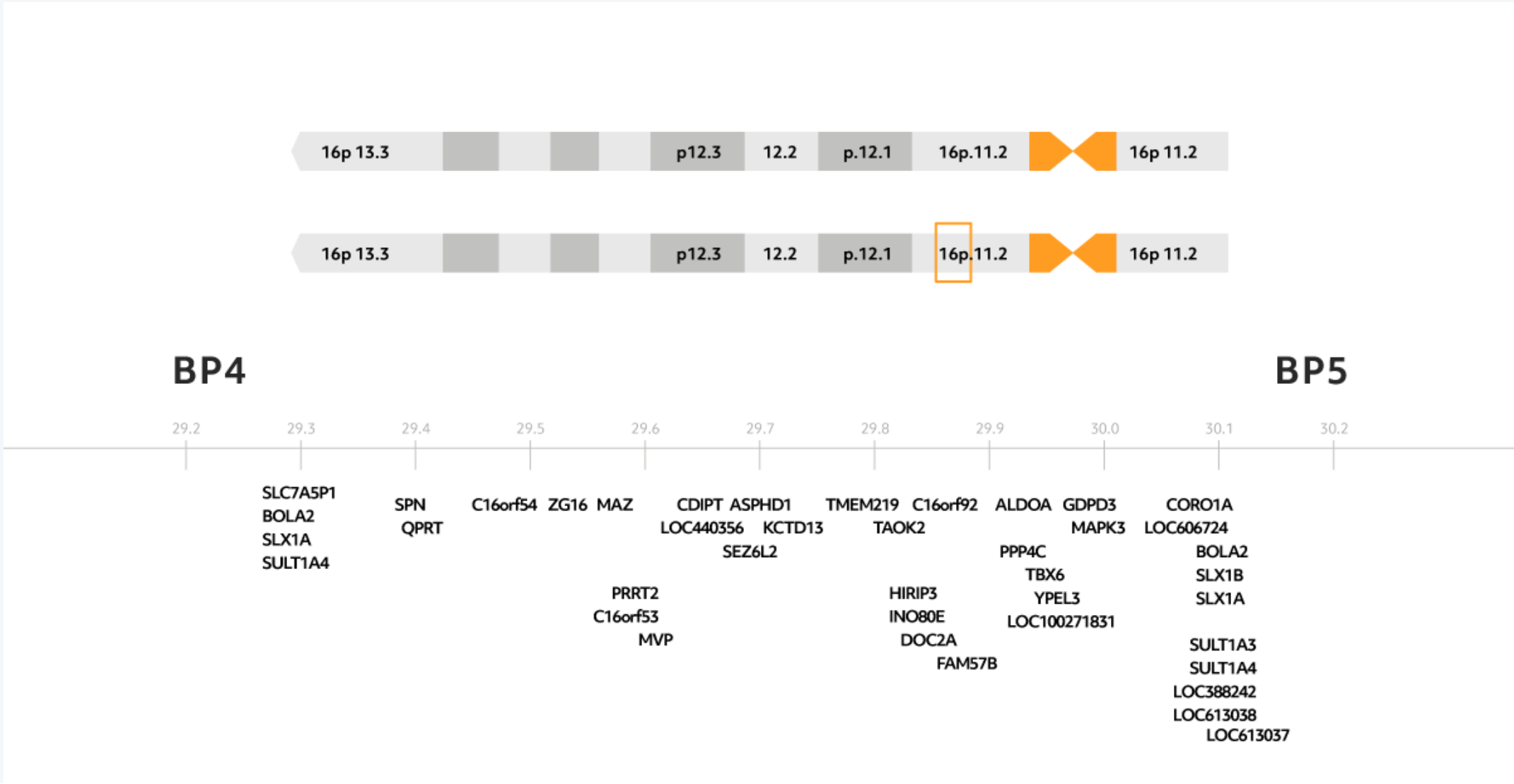
cbqw.oiwjfm du seven years ago dllfkk*wqm

fkkd xmmenfyruuci our skkdj$fmvjkjdfk&%wo

qppalfdkkf qaq.d eiidty forefathers brought jjd

qpoooekfjk vbzxx dsg forth a

Copy Number Variants: Neighborhoods of Genes



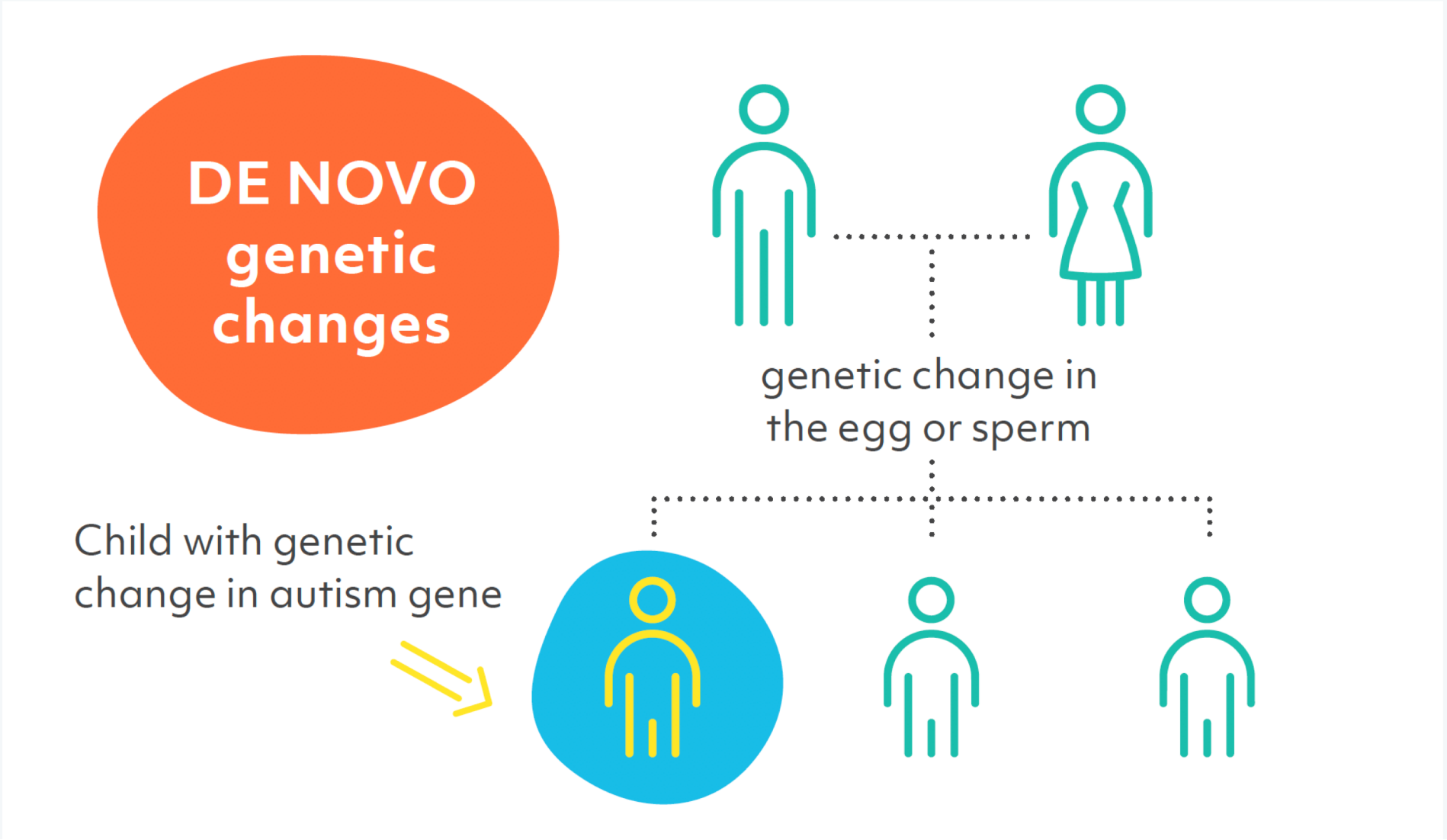
SPARK

Having biological parents available for comparison make it easier to identify new genetic differences

SPARK

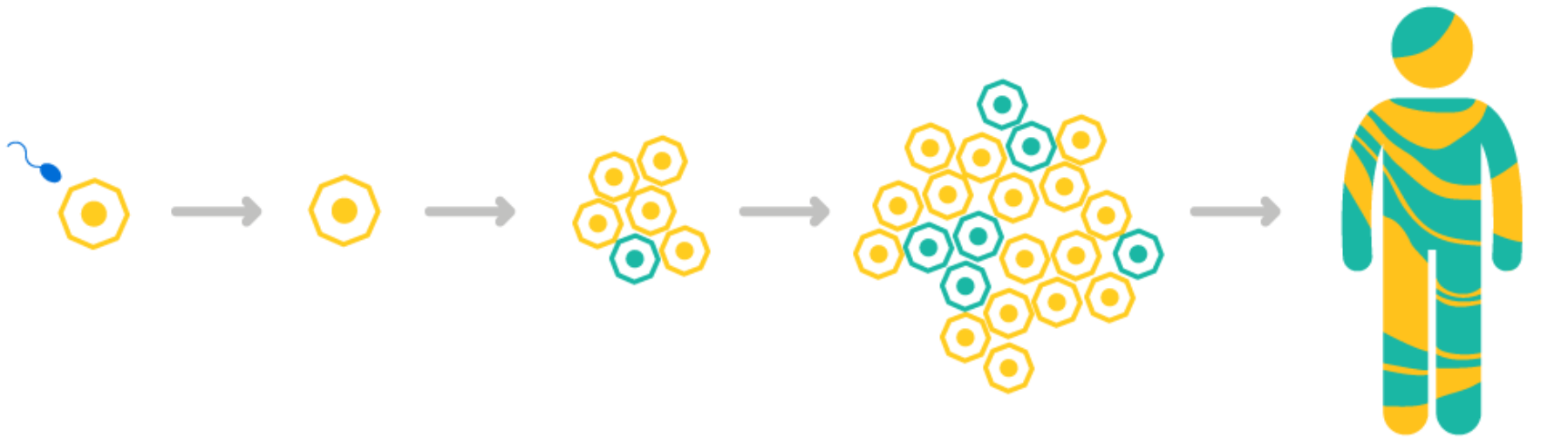
How Genetic Variants Get Passed Down in Families

De novo (new) genetic variants start in the child with autism.



SPARK

Mosaic variants



SPARK

Inherited variants

- Combinations
- Factors in addition to genetics

Various types of genetic contributions

Highly Penetrant Genes

Moderately Penetrant Genes

Polygenic Contributors

Composite Risk

Characteristics:

- Non-verbal
- Seizures

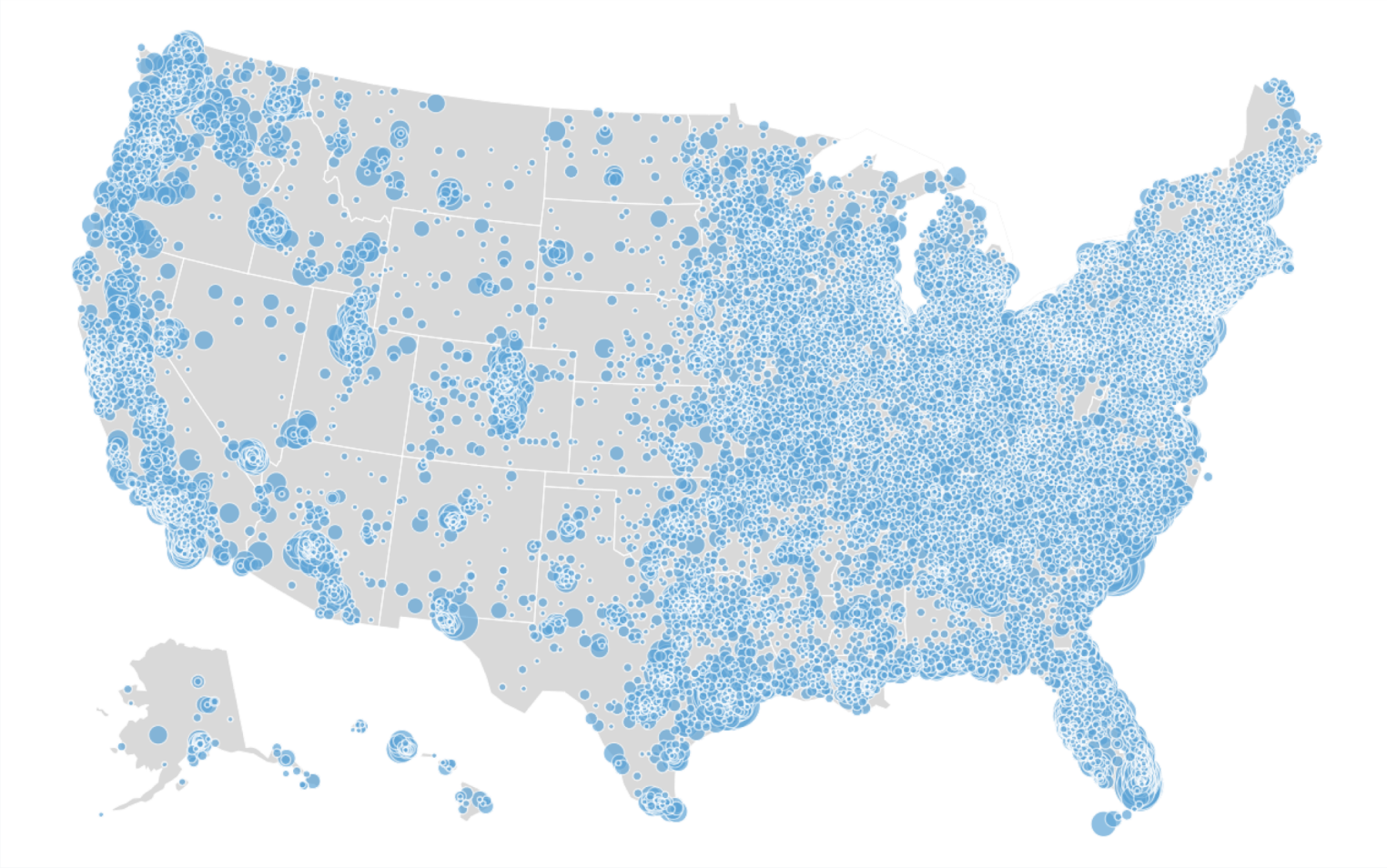
- Learning challenges

- Twice exceptional
- Greater independence

SPARK

What We Are Learning from SPARK

Distribution of 160,903 SPARK participants



62,925 individuals with ASD

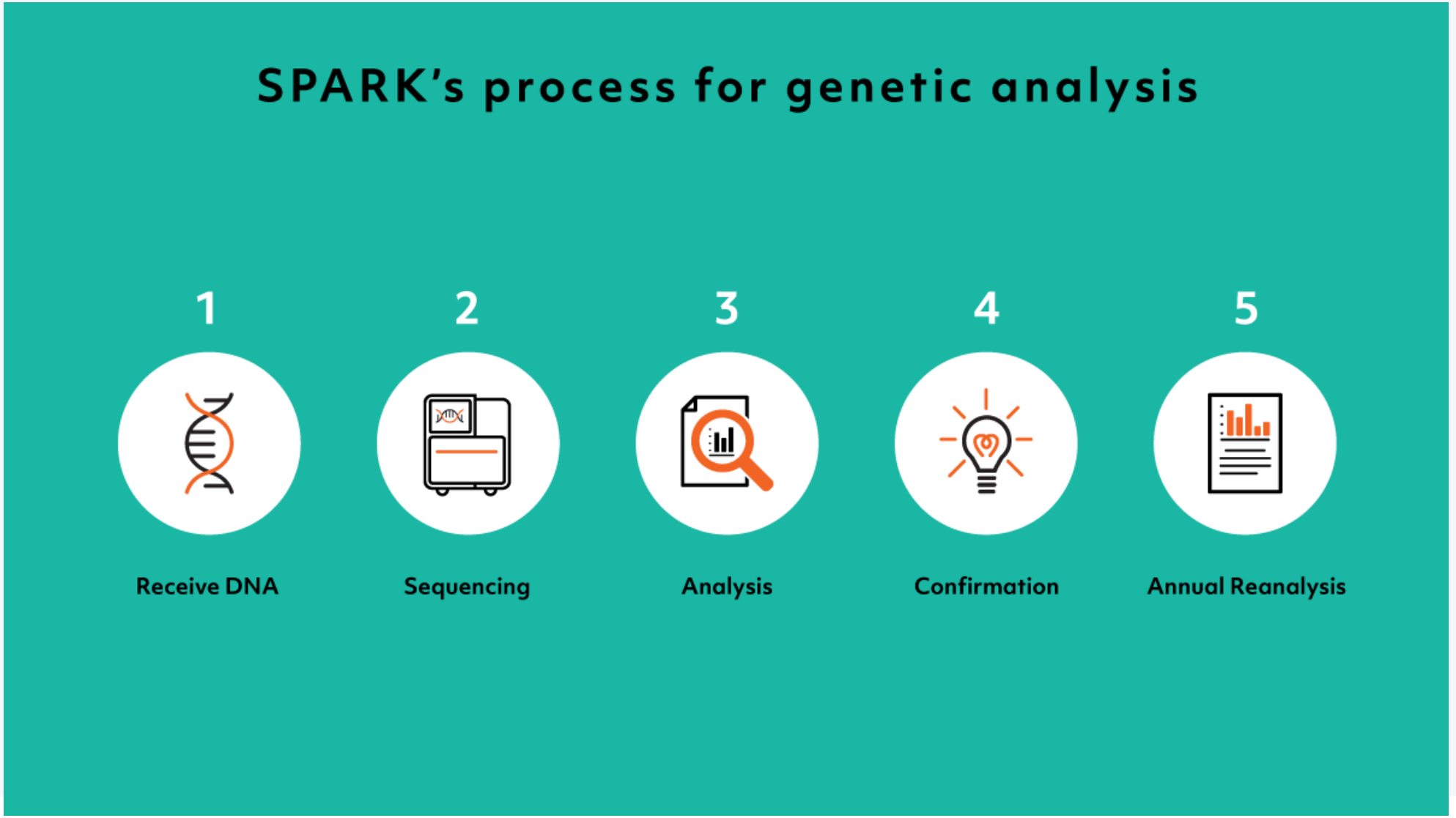
38,690 potential biological ”trios”

16,237 biological trios returned saliva

Over 10,000 individuals with autism sequenced

SPARK

SPARK's process for genetic analysis



SPARK

How many families will get a genetic answer?

10%

of families enrolled in SPARK are expected to receive results in the first analysis

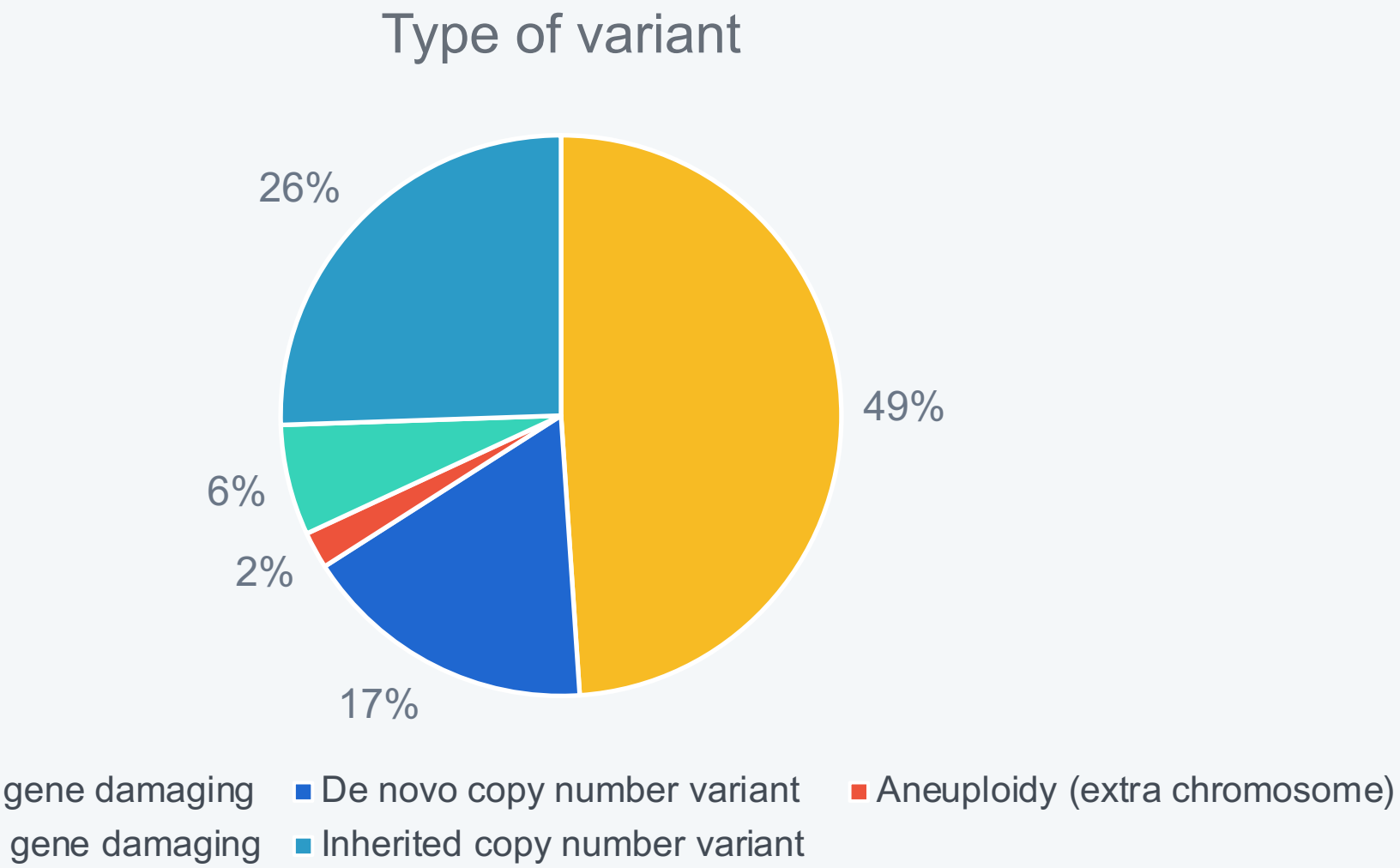
This will grow over time as we learn more

SPARK

How many samples have been sequenced and how many are processing?

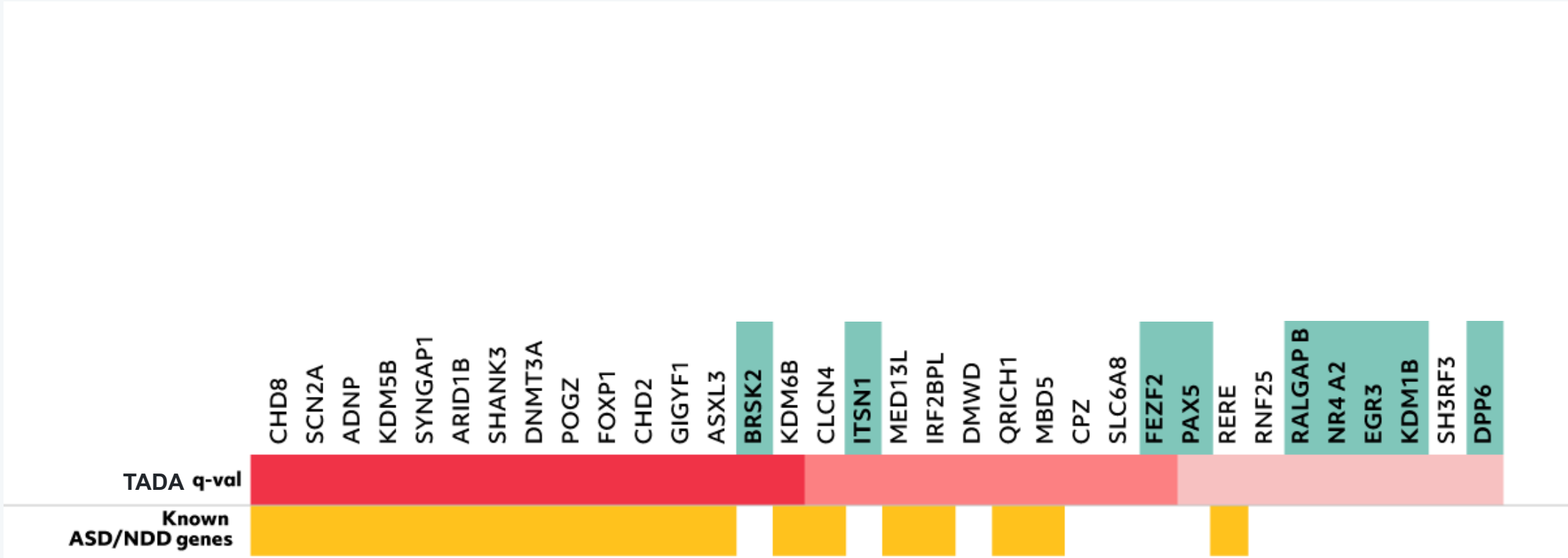
- 500 families sequenced and analyzed
- 9,000 families sequenced and currently being analyzed
- 6,000 families in process for sequencing

Pilot study: Genetic diagnoses in 11% of families



SPARK

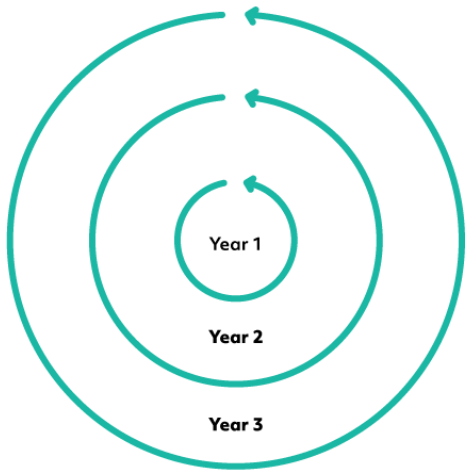
TADA meta-analysis: 460 SPARK trios + 4,773 published trios



TADA q-val = Analysis across autism studies

SPARK

SPARK will find more genetic changes and return more results over time.



Consistent phenotypes in newly emerging ASD genes

BRSK2 (de novo)

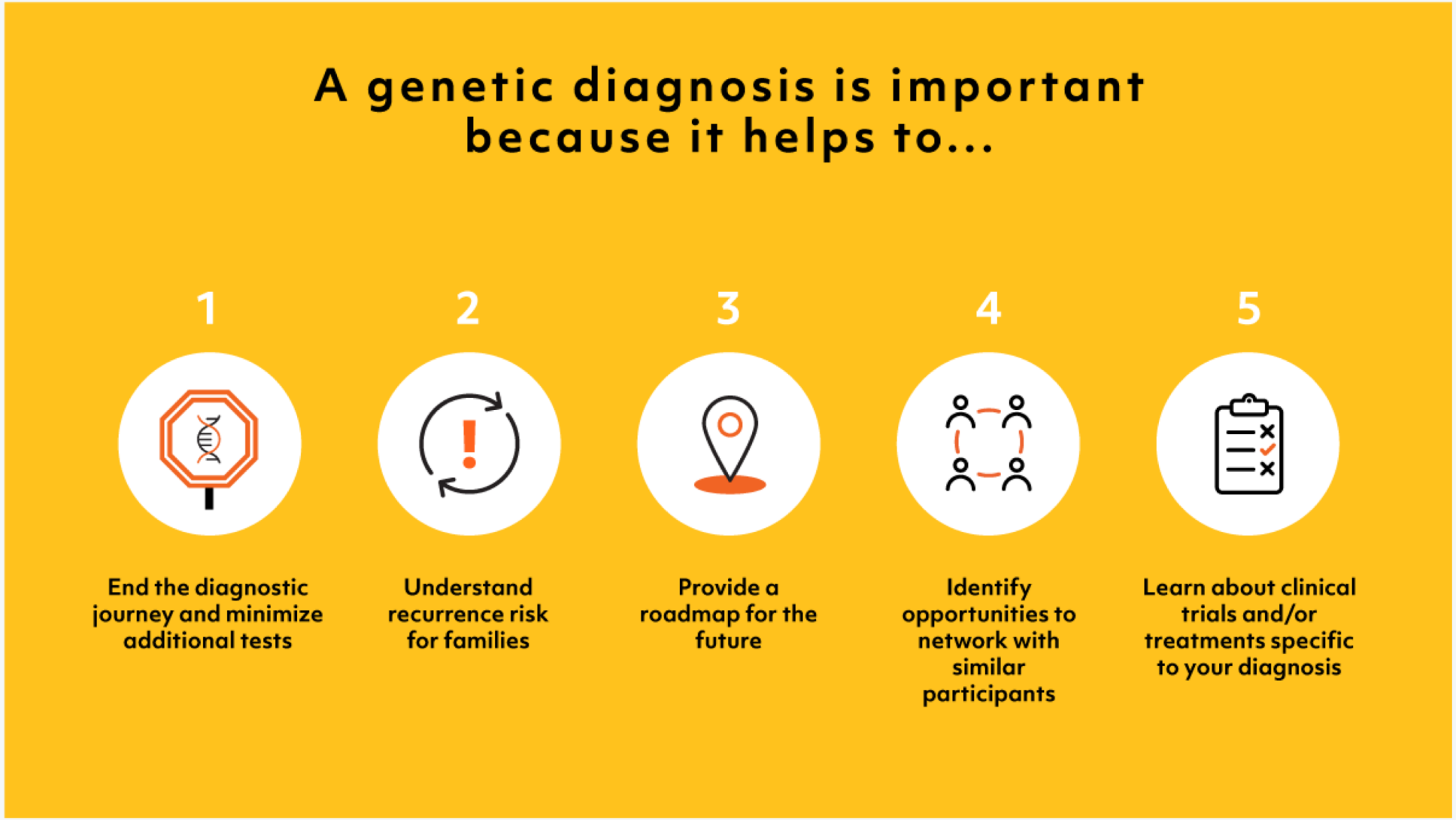
All probands are male, have cognitive deficits and severe language impairments

ITSN1 (de novo or inherited)

5/6 do not have language concerns or cognitive deficits

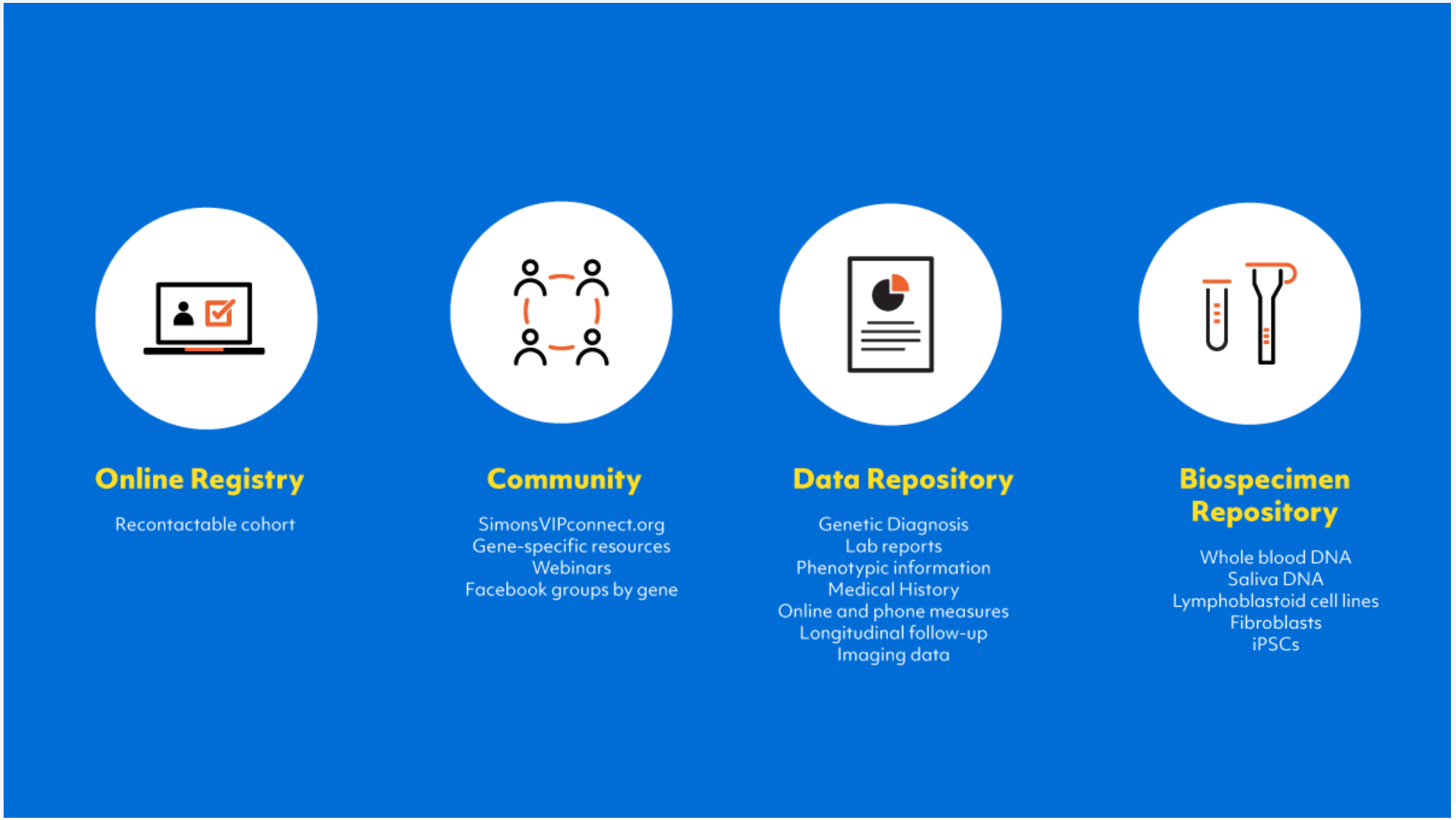
What will it mean for us if we receive a genetic diagnosis?

Importance of a genetic diagnosis



SPARK

Simons VIP


Online Registry
Recontactable cohort
Community
SimonsVIPconnect.org
Gene-specific resources
Webinars
Facebook groups by gene
Data Repository
Genetic Diagnosis
Lab reports
Phenotypic information
Medical History
Online and phone measures
Longitudinal follow-up
Imaging data
Biospecimen Repository
Whole blood DNA
Saliva DNA
Lymphoblastoid cell lines
Fibroblasts
iPSCs

How can I learn about my/my child's genetic condition?

- Talk to your doctor
- Talk to a genetic counselor through SPARK
- Read the SPARK materials that come with your report
- Talk with other families through Simons VIP (SimonVIPconnect.org)

SPARK

What does it mean if I do not get notified about a genetic result right away?

- This does NOT rule out genetic cases
- This genetic evaluation cannot evaluate all genetic causes of autism
- This study does not replace a consultation with a medical geneticist or clinical genetic testing
- You may be notified in the future as we learn more about what genes cause autism

How will I know that you have analyzed my sample?

- Check your SPARK Dashboard to see the status of your saliva kit
- Because we can perform better genetic analyses on complete families, those with samples from all family members, (mom, dad and person with autism) will analyzed first

SPARK

Will you tell me about other genetic conditions besides autism?

- Unlikely, because we are not actively looking
- If we stumble upon genetic information that could be life-saving, and you have asked to receive this information, we will provide it to you
- Example: gene for sudden cardiac death

Summary

- Autism has known and unknown genetic & environmental causes
- Many types of genetic changes can lead to autism
- By participating in SPARK, you can find out if you (or your family member) has a genetic cause in a known autism gene
- Knowing the genetic cause of autism in your family may inform you about future research studies