Mendelian Genomics: Solving the Unsolved

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The Forefront of Genomics®

Whole exome sequencing transformed Mendelian gene discovery

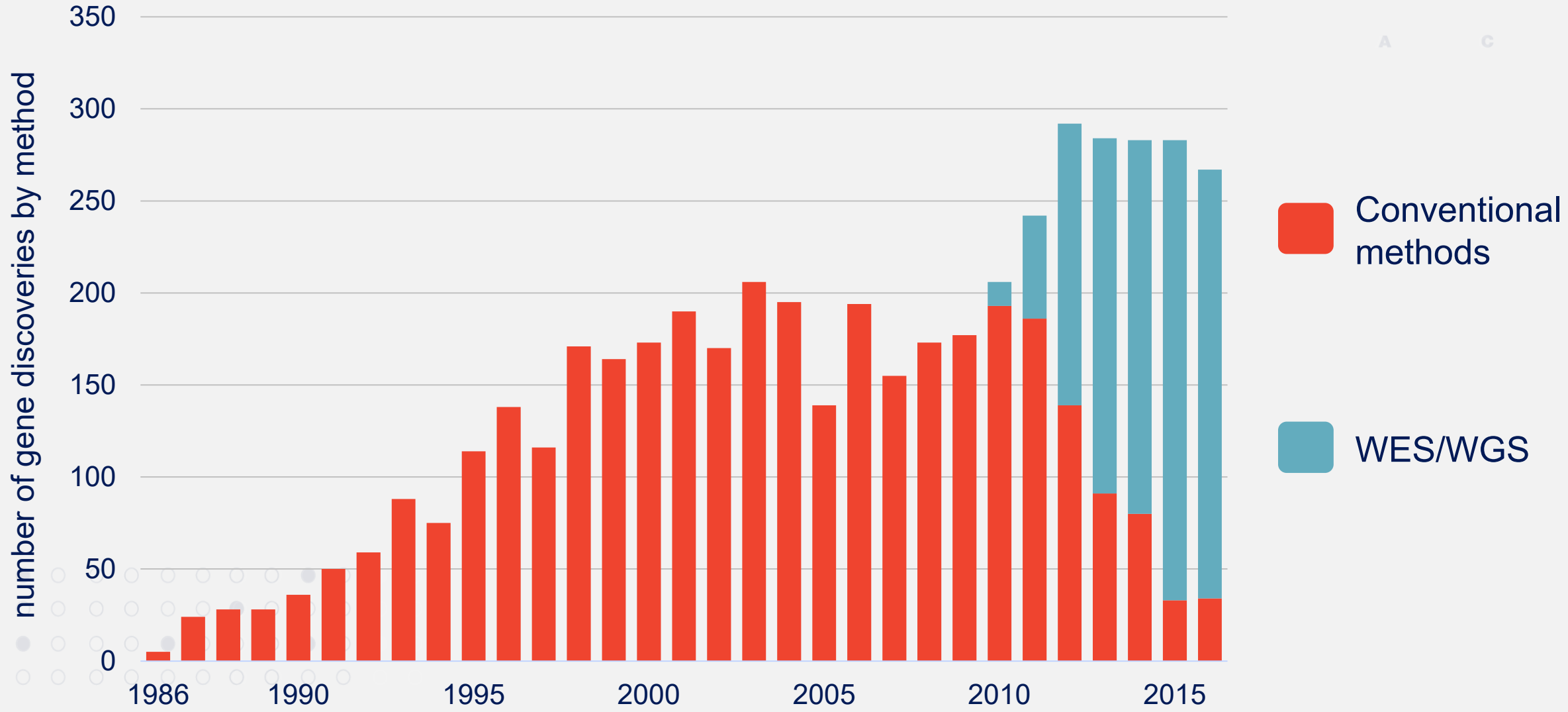

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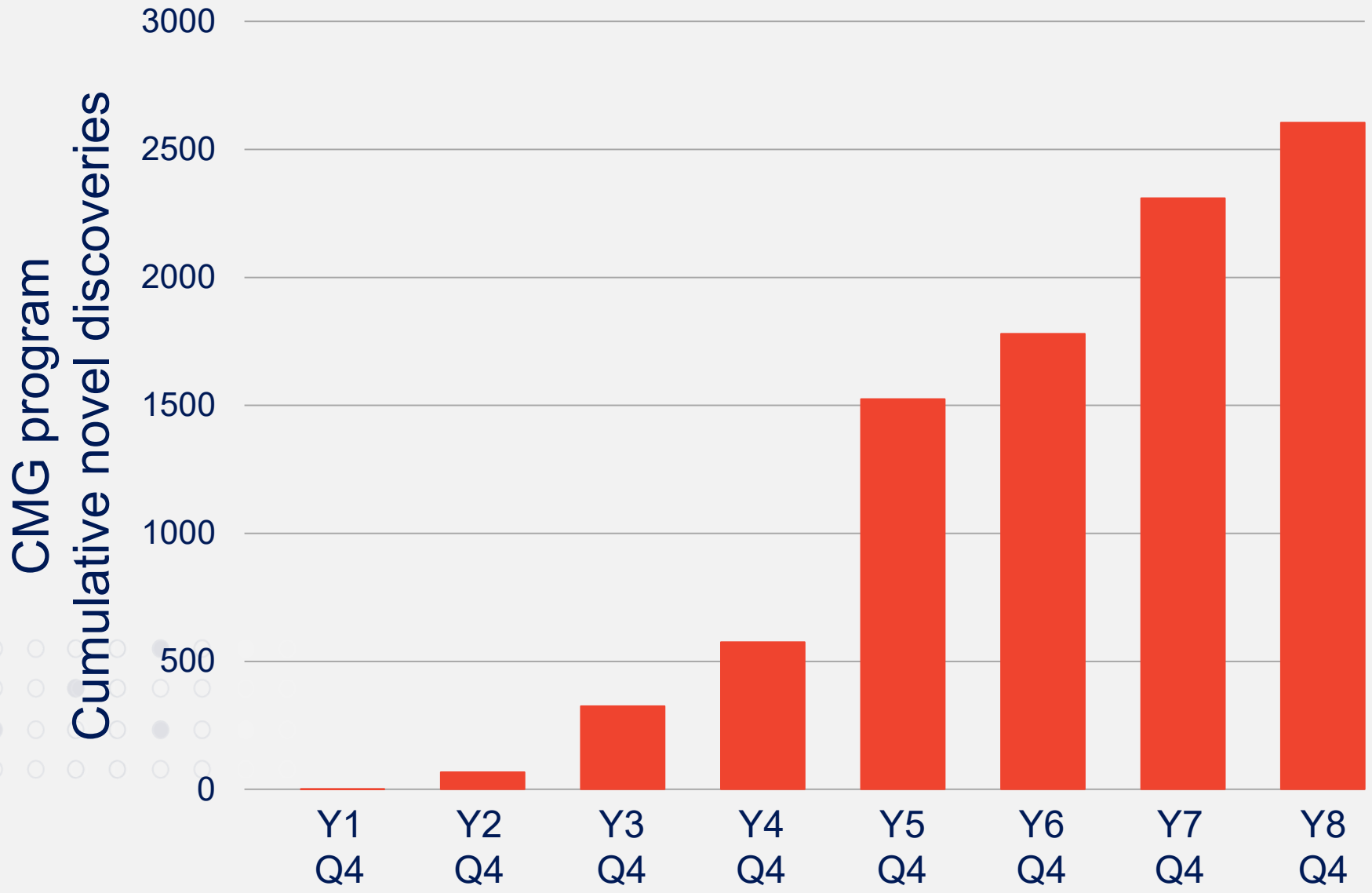
chart recreated from Chong et al., 2015 and Bamshad et al., 2019

What is the “forefront” of Mendelian Genomics?

We have not yet reached a plateau



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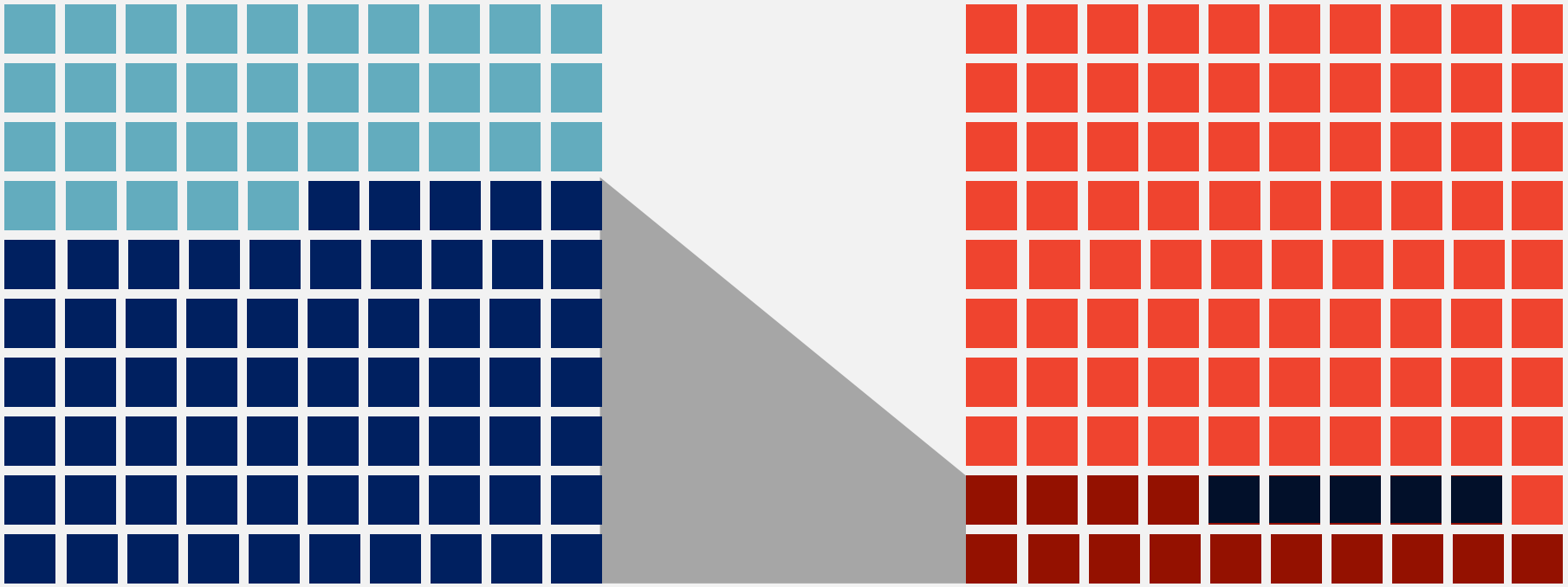
There is a lot left to discover



65% of Mendelian phenotypes have a known genetic basis

19% of human genes are associated at least one Mendelian phenotype

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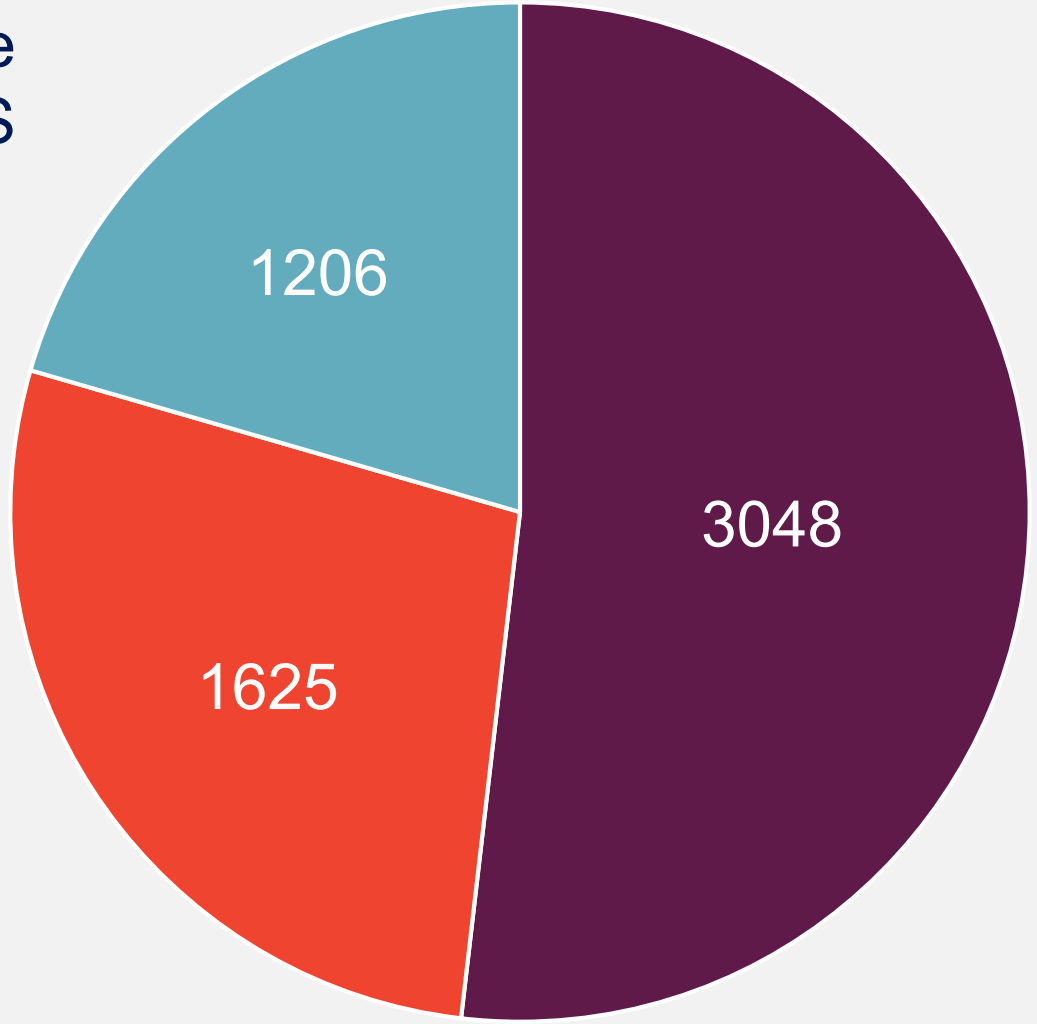
from GSP coordinating center - mendelian.org

A substantial proportion of cases are not solved by WES

no candidate identified by WES



tier 1
i.e. CONCLUSIVE

(multiple kindreds or linkage + additional experimental evidence)

tier 2
i.e. SUGGESTIVE

(one kindred, no additional evidence)

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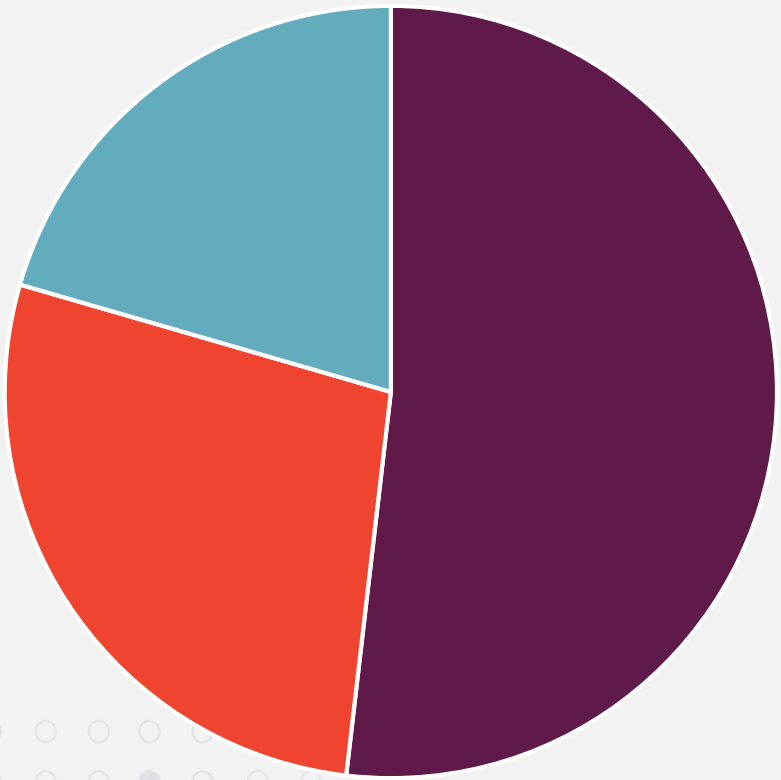
The Forefront of Mendelian Genomics?



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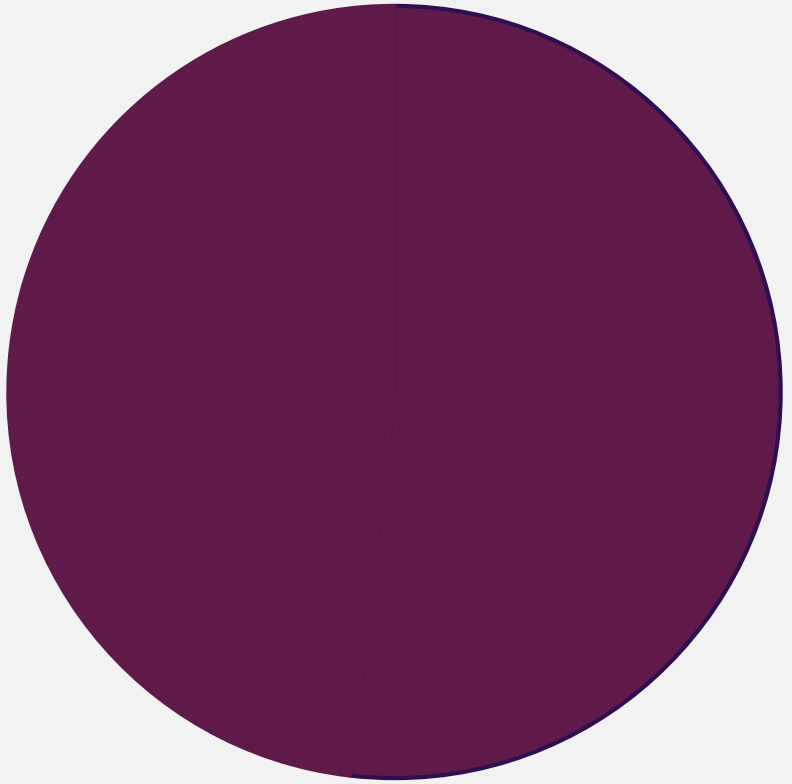

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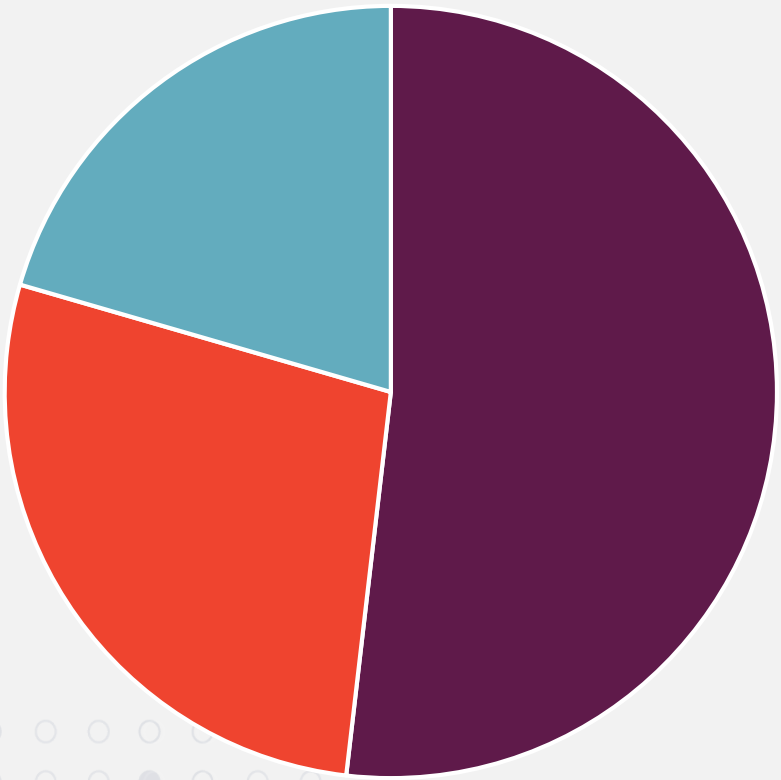
What is needed?



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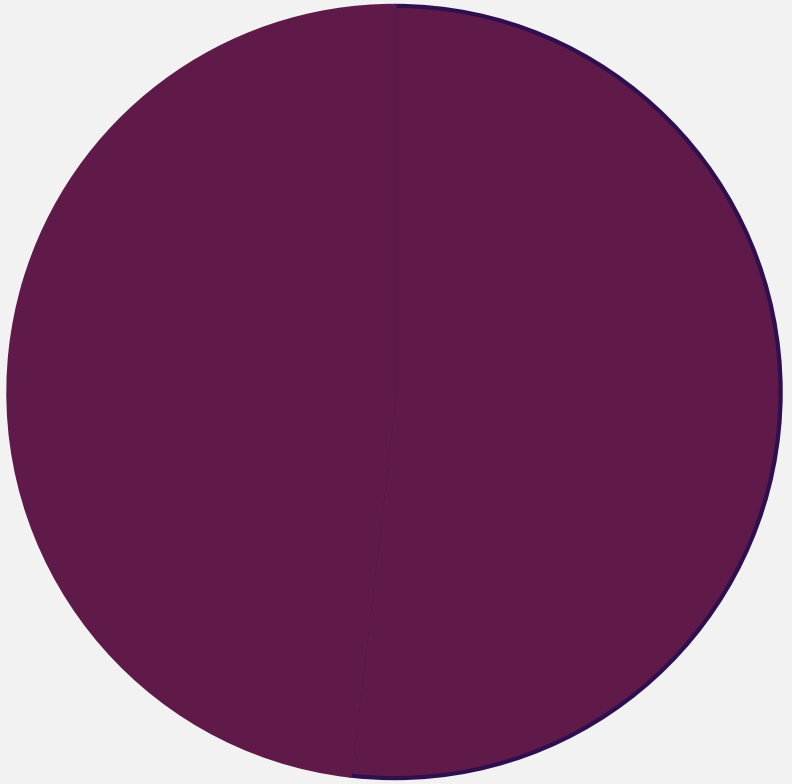

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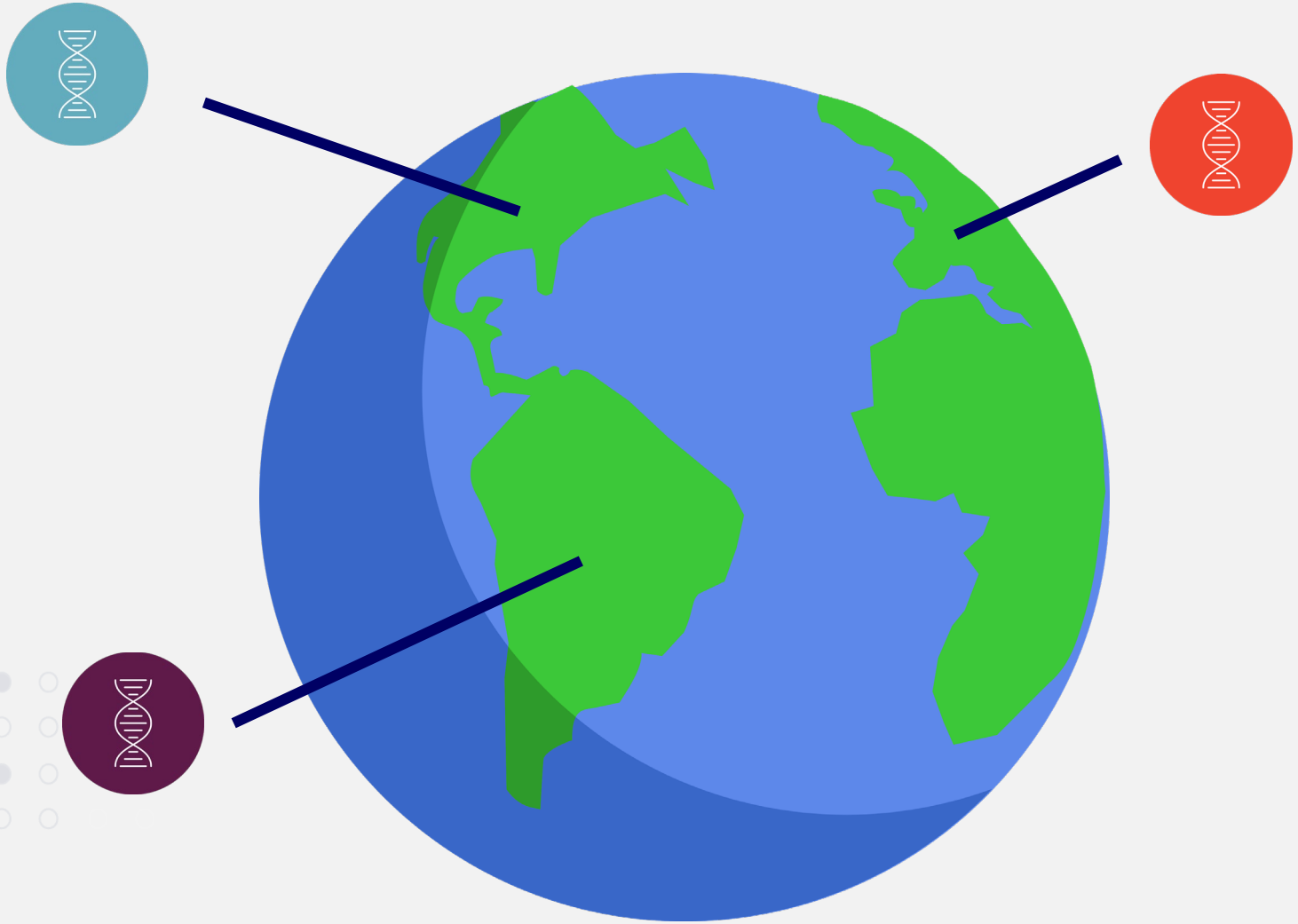
The case for data sharing



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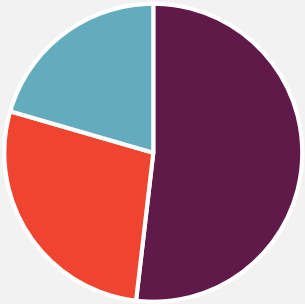
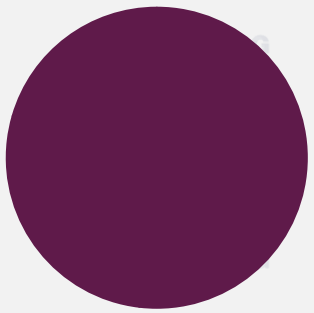
Functional follow up can move candidates from tier 2 to tier 1

- Does this variant actually impact protein function?
- Does it make biological sense?
- Does it lead to a similar phenotype in a model organism?

What does WES miss? How do we sort through it?

- Use more/different sequencing
  - WGS
  - RNA-seq or methylation analysis
- Develop high-throughput ways to prioritize non-coding variants

A Mendelian genomics program to get from  to 

- Continued novel discovery
- Greater emphasis on solving cases that aren't easily solved by WES
- Allow for follow-up on candidate variants
- High priority on data sharing
- Collaboration within the consortium
- Involve the broader research community

Two RFAs:
Mendelian Genomics Centers
Data Coordination Center

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Mendelian Genomics Centers

- Use sequencing to identify novel gene/phenotype associations underlying Mendelian conditions
- Develop scalable approaches for functional follow-up
- Prioritize samples with detailed phenotype info, that have been consented for broad research use
- Work together as a consortium to move towards Tier 1
  - Unsolved cases
  - Variant interpretation
  - Best practices for functional validation
- Engage and empower the broader research community through outreach/education

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Data Coordination Center

- Ensure that complete, quality controlled data from the MGCs is made available to the community
    - deposited in AnVIL, ClinVar, Matchmaker Exchange, etc.
- Track collaborations and samples in the pipeline of the MGCs
- Create infrastructure to share sequence and phenotype data from unsolved cases
- Logistical coordination
- Oversee the Mendelian Genomics Opportunity Fund
    - flexible funding for outside investigators
    - validation studies, annotation or analysis, other opportunities

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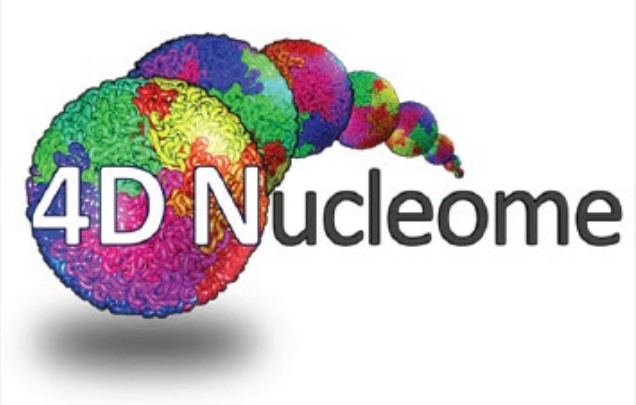
Opportunity Funds?

- Allows funding of small projects within a more rapid timeline than traditional grant mechanisms
- Provides flexibility to address current and emerging areas of need
- Funds are administered as subaward through the DCC
- DCC coordinates application intake and review
- Applications are peer-reviewed by a review panel
- Examples of programs that have used Opportunity Funds:

Undiagnosed Diseases Network



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Proposed funding levels for the Mendelian Genomics Program

	FY21	FY22	FY23	FY24	FY25	5 yr. total
MGCs (3-4)	$9 M	$9 M	$9 M	$9 M	$9 M	$45 M
DCC **Opp. funds**	$2.25 M (0)	$3 M ($750K)	$3 M ($750K)	$3 M ($750K)	$3.75 M ($750K)	$15 M ($3 M)
total	$11.25 M	$12 M	$12 M	$12 M	$12.75 M	$60 M

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Discussion and questions

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