



Learning Objectives

September 20, 2024

- **Describe variant analysis and classification at a high level**
- **Define basic genetic terms and concepts as they relate to a genetic test report**
- **Navigate the major elements of a genetic test report.**
- **Discuss challenges and solutions to implementing genomic medicine in a NICU setting**



Genetic Glossaries

<https://www.genome.gov/genetics-glossary>

A glossary with short videos and figures for each term.
From the National Human Genome Research Institute at the NIH.

<https://mymds.bham.ac.uk/genetics/glossary.htm>

A comprehensive, yet concise glossary from the University of Birmingham in the UK. Printable; seven pages.

<https://www.cancer.gov/publications/dictionaries/genetics-dictionary/expand/A>

A glossary with audio pronunciation of terms from NCI at the NIH.

<https://jamanetwork.com/journals/jama/fullarticle/1677346>

A concise, three page printable glossary from JAMA. Not as comprehensive as the other glossaries on this slide.



Variant Interpretation

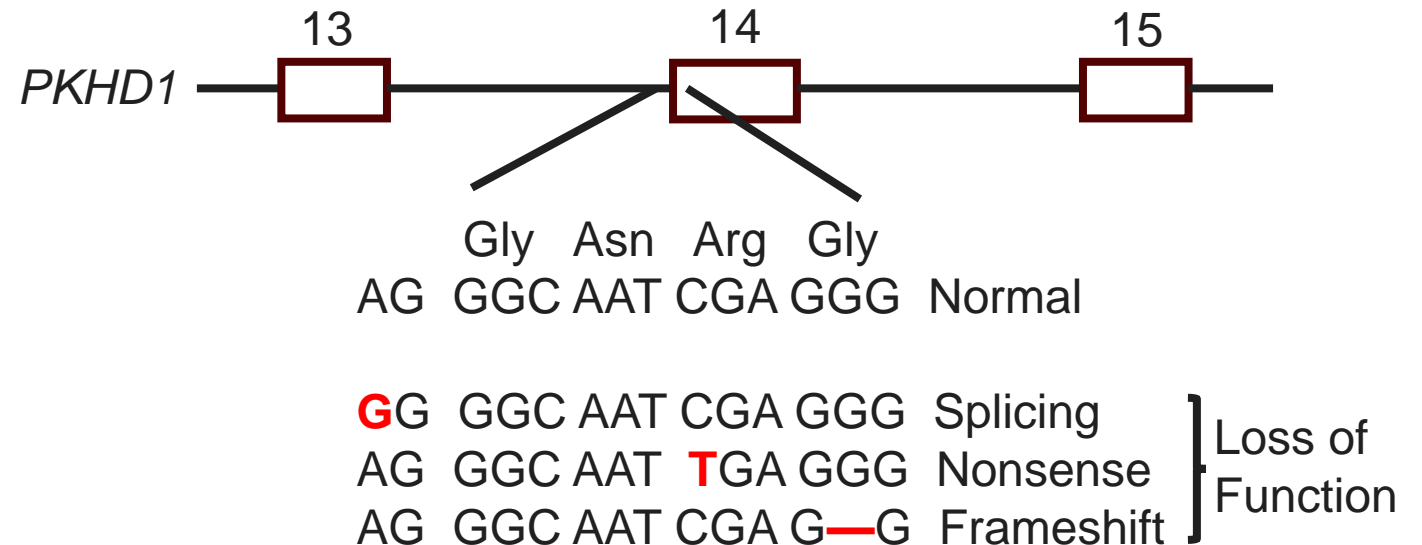
Jim Weber

September 20, 2024

Average Numbers of *de novo* Mutations per Generation in Live Births

Mutation Type	Numbers
Tandem Repeats	1,000 ??
Nucleotide Substitutions	90
Short (≤ 50 bp deletions or insertions)	8
Short (≤ 50 bp) Indels (deletions plus insertions)	0.5 ??
Structural Variants (> 50 bp deletions or insertions)	0.2 ??
Aneuploidies	0.003
Balanced Translocations	0.001 ??

DNA Sequence Variants (Variants) are defined as any and all differences between the patient's sequence and the human reference sequence.





Variant Interpretation

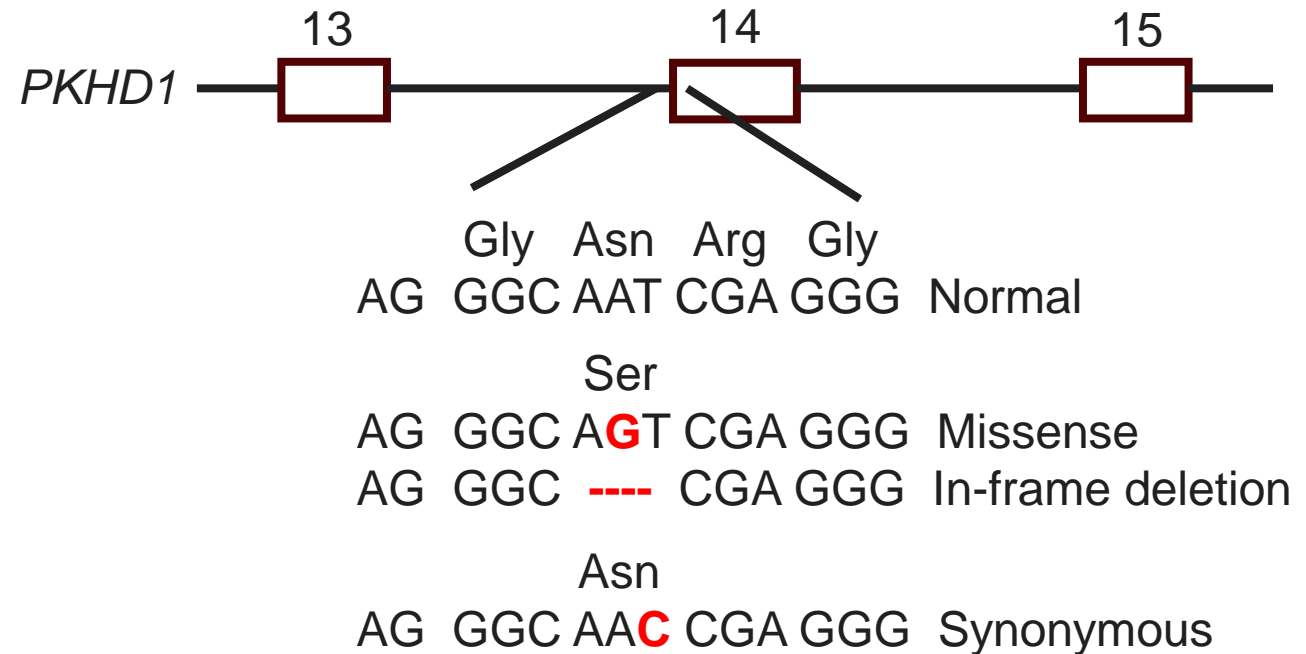
Jim Weber

September 20, 2024

Average Numbers of *de novo* Mutations per Generation in Live Births

Mutation Type	Numbers
Tandem Repeats	1,000 ??
Nucleotide Substitutions	90
Short (≤ 50 bp deletions or insertions)	8
Short (≤ 50 bp) Indels (deletions plus insertions)	0.5 ??
Structural Variants (> 50 bp deletions or insertions)	0.2 ??
Aneuploidies	0.003
Balanced Translocations	0.001 ??

DNA Sequence Variants (Variants) are defined as any and all differences between the patient's sequence and the human reference sequence.





Average Numbers of Variants by Interpretation Category

Interpretation	Exome	Genome
Pathogenic	2	3
Likely Pathogenic	2	3
Uncertain	100	5,000
Likely Benign	200	10,000
Benign	25,000	3M

Interpretation Guidelines: 2008, 2015, 2024??
ACMG (American College of Medical Genetics)
AMP (Association for Molecular Pathology)

Pathogenic, Likely Pathogenic: “a healthcare provider can use the molecular testing information in clinical decision making.”

Uncertain: “should not be used in clinical decision making.”

Likely Benign, Benign: “healthcare provider can conclude that it is not the (primary) cause of the patient’s disorder.”

PubMed IDs: 25741868, 18414213



	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Population Data	MAF is too high for disorder <i>BA1/BS1</i> OR observation in controls inconsistent with disease penetrance <i>BS2</i>			Absent in population databases <i>PM2</i>	Prevalence in affecteds statistically increased over controls <i>PS4</i>	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact on gene /gene product <i>BP4</i> Missense in gene where only truncating cause disease <i>BP1</i> Silent variant with non predicted splice impact <i>BP7</i>	Multiple lines of computational evidence support a deleterious effect on the gene /gene product <i>PP3</i>	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before <i>PM5</i> Protein length changing variant <i>PM4</i>	Same amino acid change as an established pathogenic variant <i>PS1</i>	Predicted null variant in a gene where LOF is a known mechanism of disease <i>PVS1</i>
Functional Data	Well-established functional studies show no deleterious effect <i>BS3</i>		Missense in gene with low rate of benign missense variants and path. missenses common <i>PP2</i>	Mutational hot spot or well-studied functional domain without benign variation <i>PM1</i>	Well-established functional studies show a deleterious effect <i>PS3</i>	
Segregation Data	Non-segregation with disease <i>BS4</i>		Co-segregation with disease in multiple affected family members <i>PP1</i>	Increased segregation data →		
De novo Data				<i>De novo</i> (without paternity & maternity confirmed) <i>PM6</i>	<i>De novo</i> (paternity & maternity confirmed) <i>PS2</i>	
Allelic Data		Observed in <i>trans</i> with a dominant variant <i>BP2</i> Observed in <i>cis</i> with a pathogenic variant <i>BP2</i>		For recessive disorders, detected in <i>trans</i> with a pathogenic variant <i>PM3</i>		
Other Database		Reputable source w/out shared data = benign <i>BP6</i>	Reputable source = pathogenic <i>PP5</i>			
Other Data		Found in case with an alternate cause <i>BP5</i>	Patient's phenotype or FH highly specific for gene <i>PP4</i>			

To be interpreted as pathogenic a variant must be:

Rare (< 0.5% population frequency)

Either have been found in other affected individuals or be similar in type to different pathogenic variants reported in other affected individuals.

ClinVar Search ClinVar by gene symbols, location, HGVS expressions, c-dot, p-dot, conditions, and more
[Advanced](#) [He](#)

Home About Access Help Submit Statistics FTP

i We've updated the ClinVar website to better support classifications of somatic variants!
Read more about changes to the website in our [web release notes](#); more information about somatic variants in ClinVar is available on [GitHub](#).

```
ACTGATGGTATGGGGCCAAGAGATATATCT  
CAGGTACGGCTGTCATCACTTAGACCTCAC  
CAGGGCTGGGCATAAAAGTCAGGGCAGAGC  
CCATGGTGCATCTGACTCCTGAGGAGAAGT  
GCAGGTTGGTATCAAGGTTACAAGACAGGT  
GGCACTGACTCTCTCTGCCTATTGGTCTAT
```

ClinVar

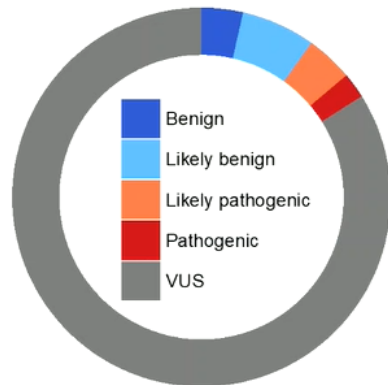
ClinVar aggregates information about genomic variation and its relationship to human health.



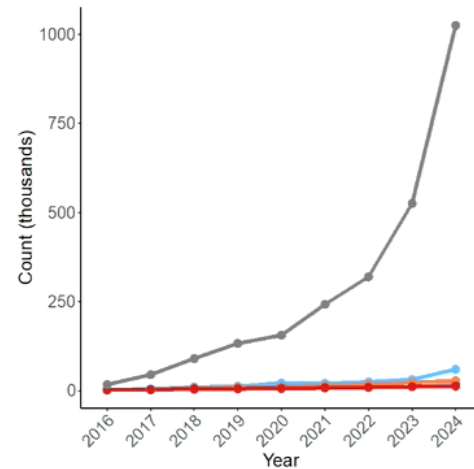
Heidi Rehm Harvard

Most missense variants in clinical genetics databases have unknown significance

ClinVar missense variants



N = 1,153,802



Shawn Fayer
Landrum et al. 2014, *NAR*

These results should be interpreted in context of clinical findings, family history and other laboratory data.





Penetrance

Penetrance will often depend upon:

- How “affected” is defined
- Genotype
- Age
- Sex
- Ancestry

Penetrance is defined as the fraction of individuals with a specific variant (or variants in the case of recessive disease) who are affected.

Penetrance Values for LOF Pathogenic Variants in *BRCA1*

Disorder/Group	Penetrance
Breast Cancer, Women, to age 70	65%
Breast Cancer, Women, to age 40	13%
Ovarian Cancer, Women, to age 70	39%
Breast Cancer, Men, to age 70	0.2%

References: PMID 12677558, 35077220

References

ACMG Guidelines

Richards et al. Genetics in Medicine 2008 PMID:18414213

Richards et al. Genetics in Medicine 2015 PMID:25741868

ClinVar

Landrum et al. Nucleic Acids Res. 2020 PMID:31777943

Penetrance

Wright et al. Nature Genetics 2024 PMID:39075210

Antoniou et al. American Journal of Human Genetics 2003 PMID: 12677558

Li et al. Journal of Clinical Oncology 2022 PMID: 35077220

