Genetics of Usher syndrome

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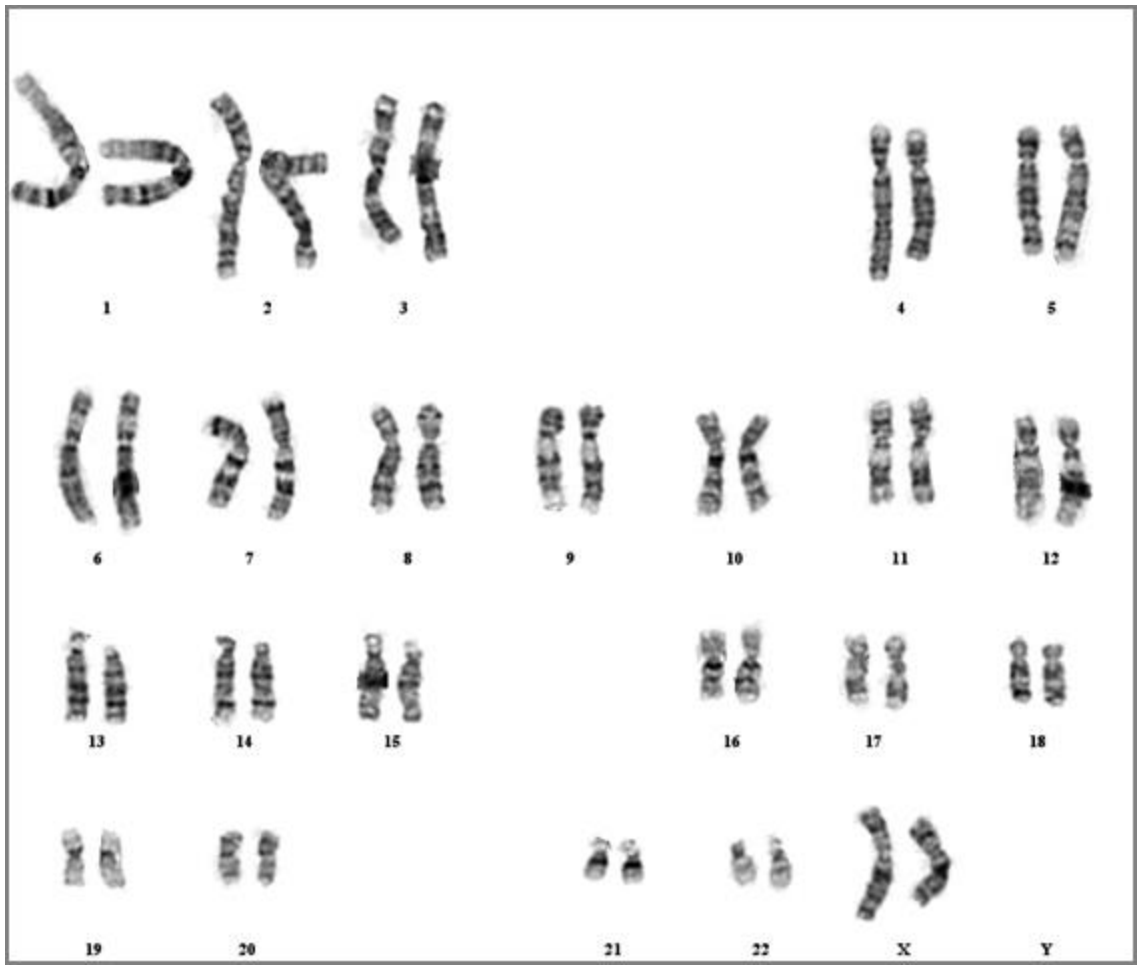
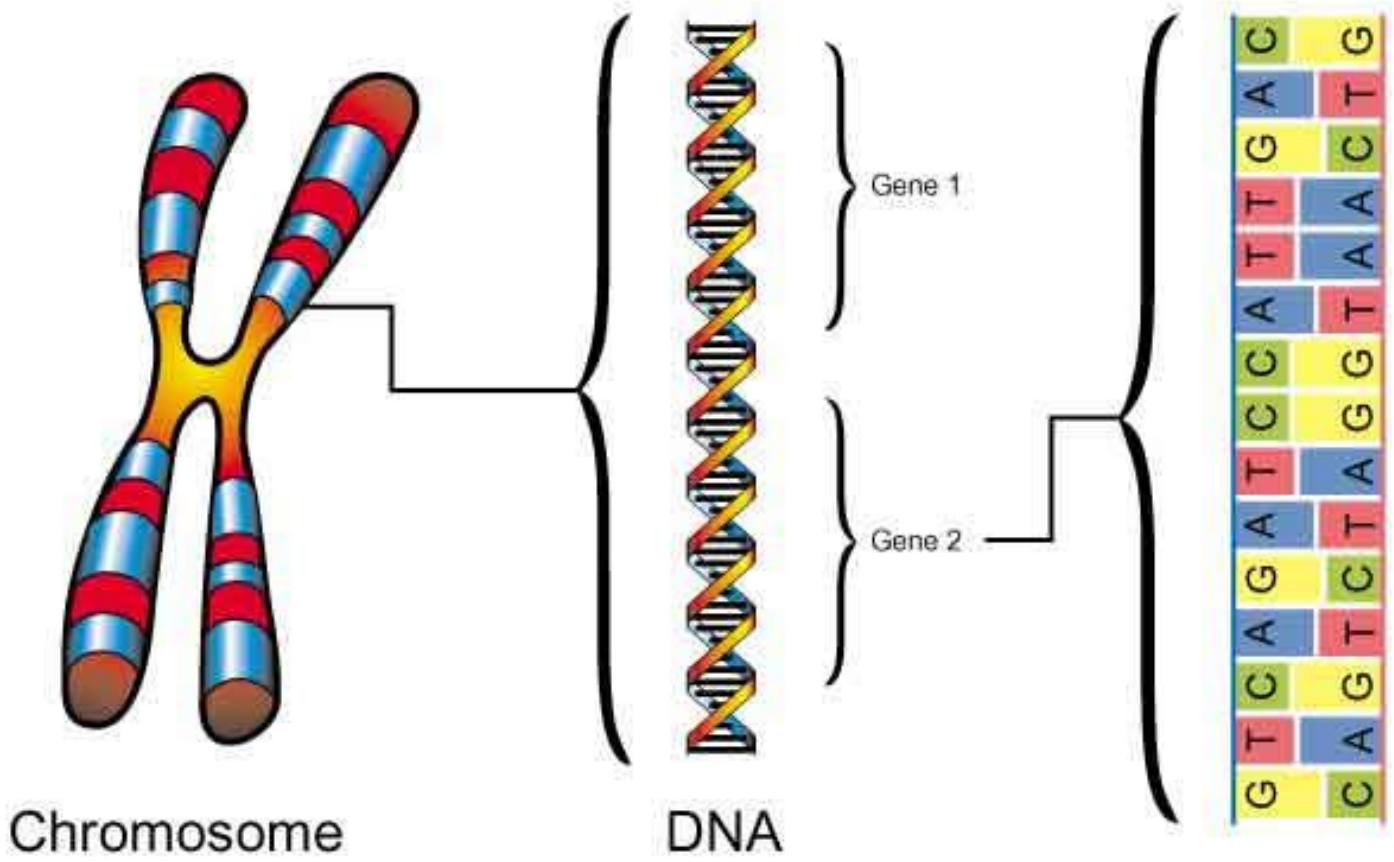
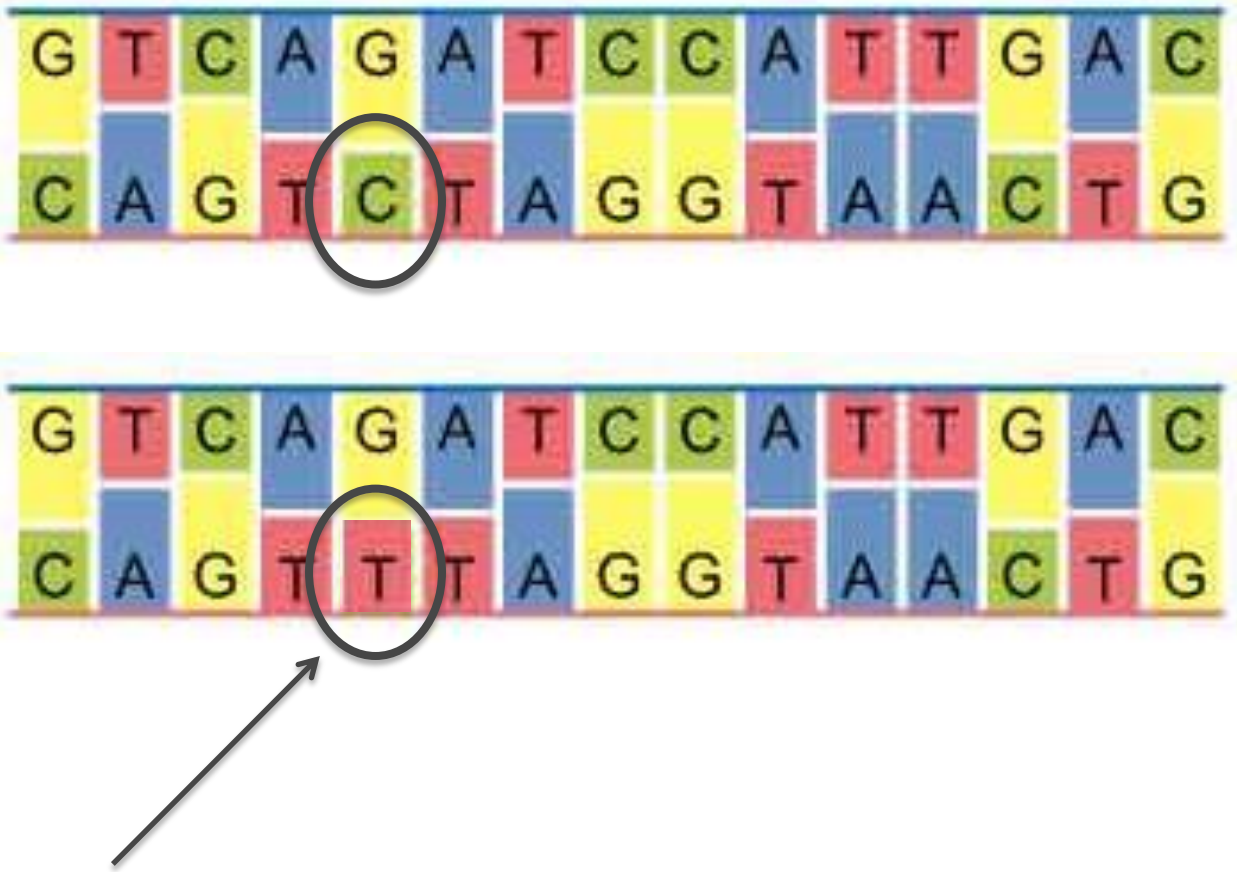
Chromosomes

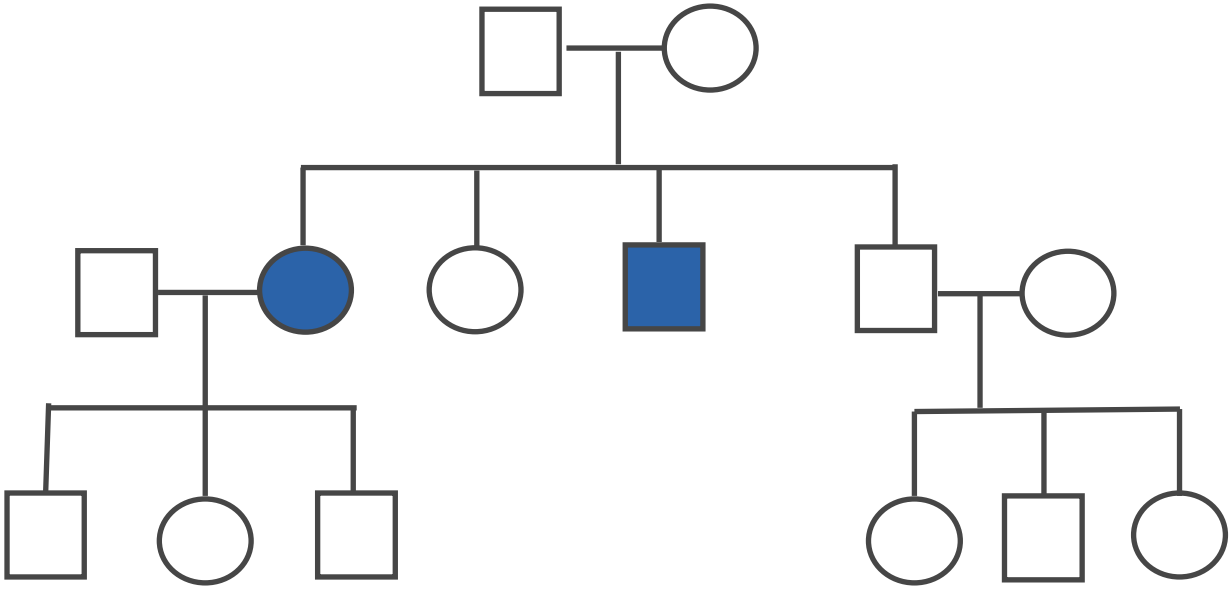
Normal female: 46,XX



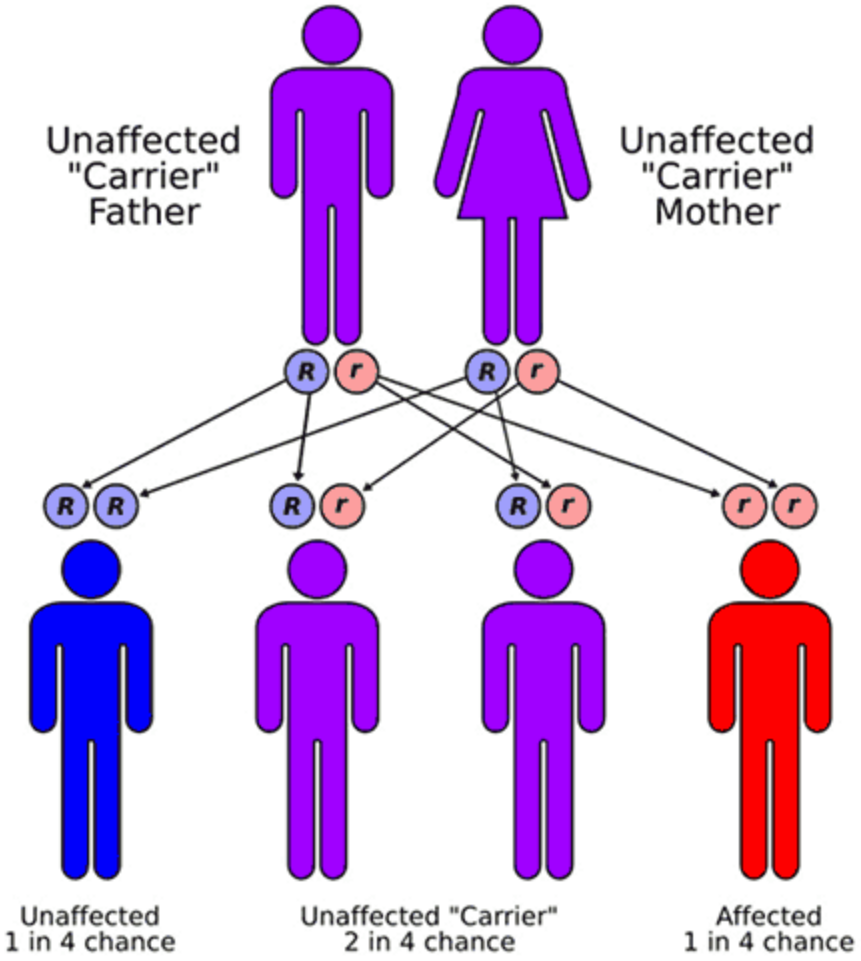

Gene 1
Gene 2
Chromosome
DNA


G T C A G A T C C A T T G A C
C A G T C T A G G T A A C T G
G T C A G A T C C A T T G A C
C A G T T T A G G T A A C T G

Recessive Inheritance

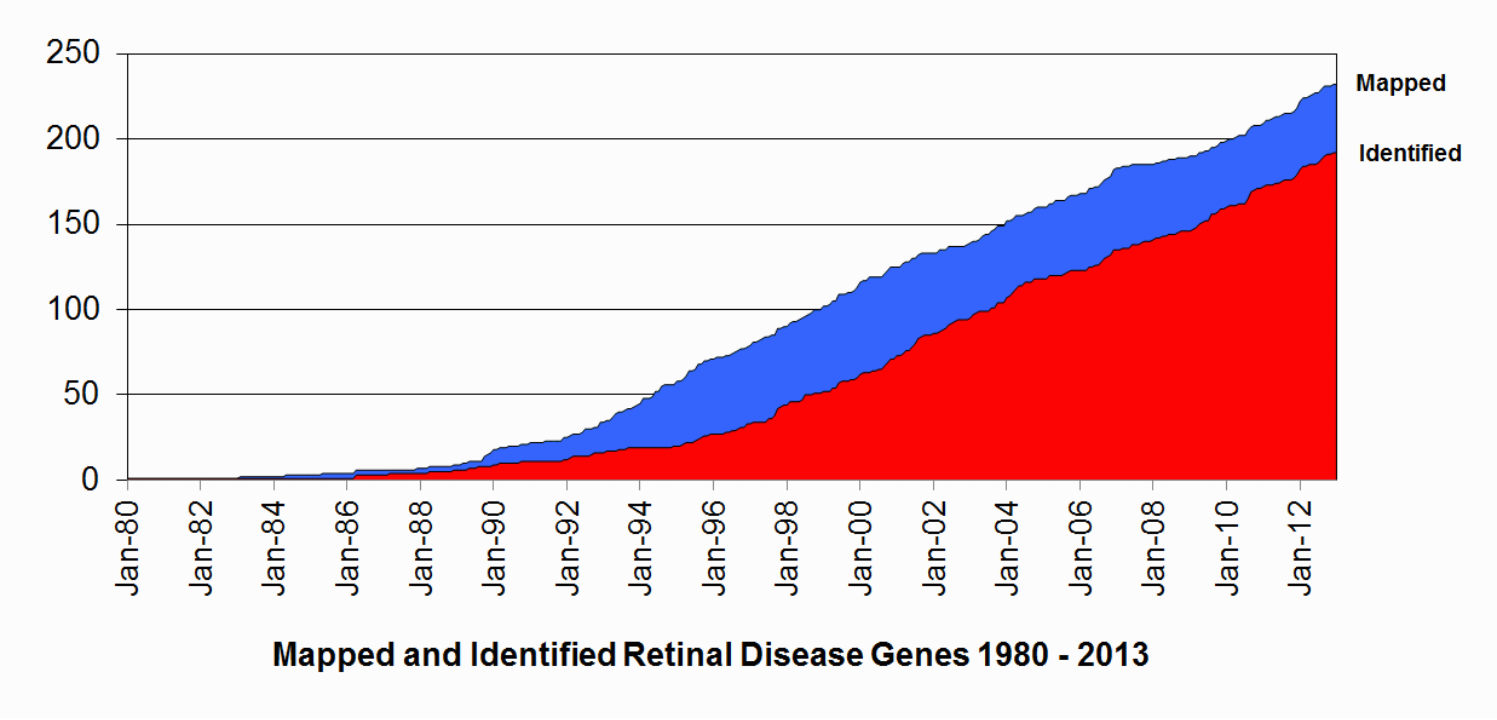


Usher syndrome Inheritance: Autosomal Recessive



Usher syndrome genes

Total # of Genes	Identified Genes
15	12



Mapped and Identified Retinal Disease Genes 1980 - 2013

Usher syndrome type I

Usher syndrome subtype	Gene Name	Relative Incidence
USH1B	*MYO7A*	40-55%
USH1C	*Ush1C*	6-7%
USH1D	*CDH23*	20-35%
USH1E	*Unknown*	Rare
USH1F	*PCDH15*	10-20%
USH1G	*SANS*	~7%

Usher syndrome types II & III

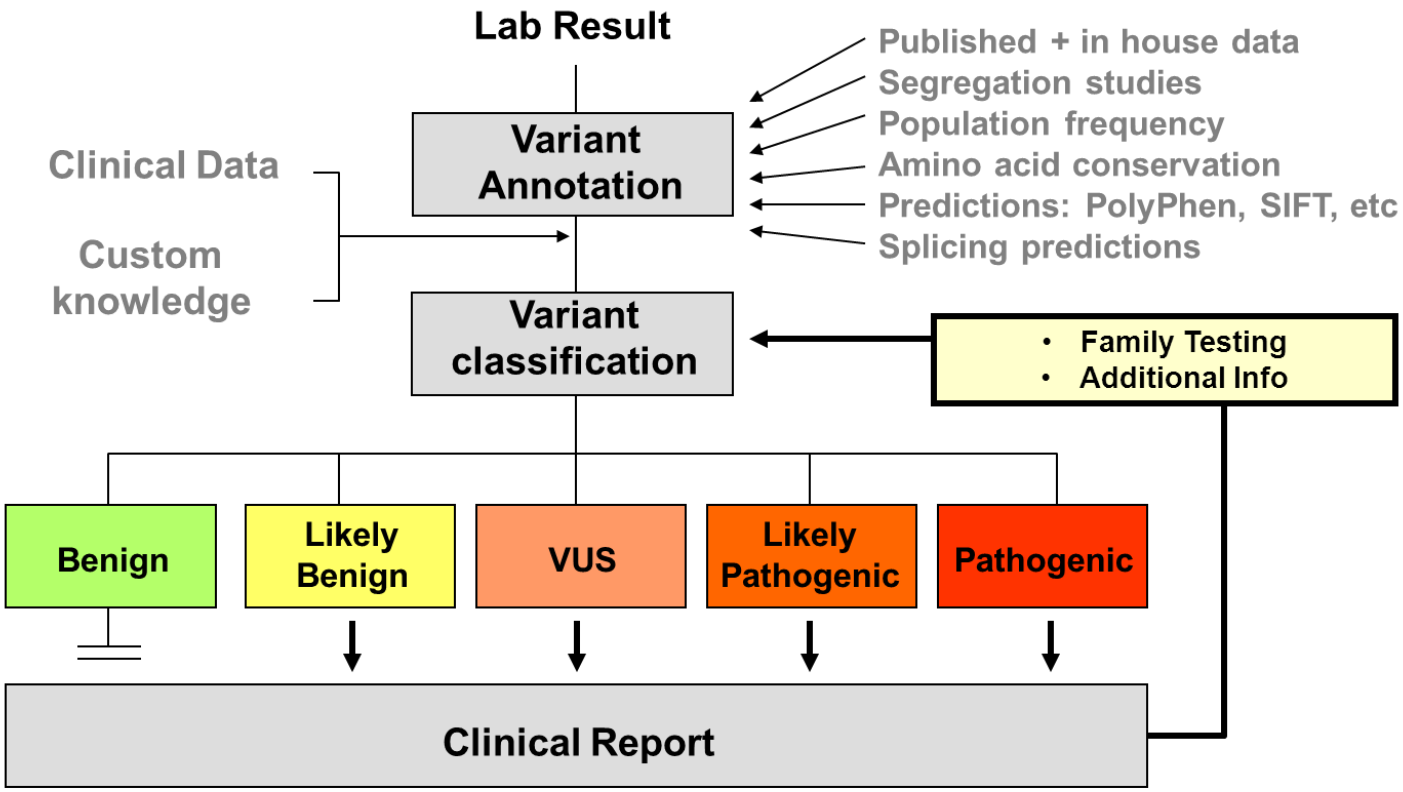
Usher syndrome subtype	Gene Name	Relative Incidence
USH2A	*Ush2A*	~80%
USH2C	*VLGR1*	~15%
USH2D	*WHRN*	~5%
USH1E	*Unknown*	Rare

Usher syndrome subtype	Gene Name	Relative Incidence
USH3	*CLRN1*	100%

Genetic testing: Then & Now

- Single gene test
- Genotyping panels, using known (common) mutations
- NGS (Next Generation Sequencing) Panel tests
- Whole Genome Sequencing

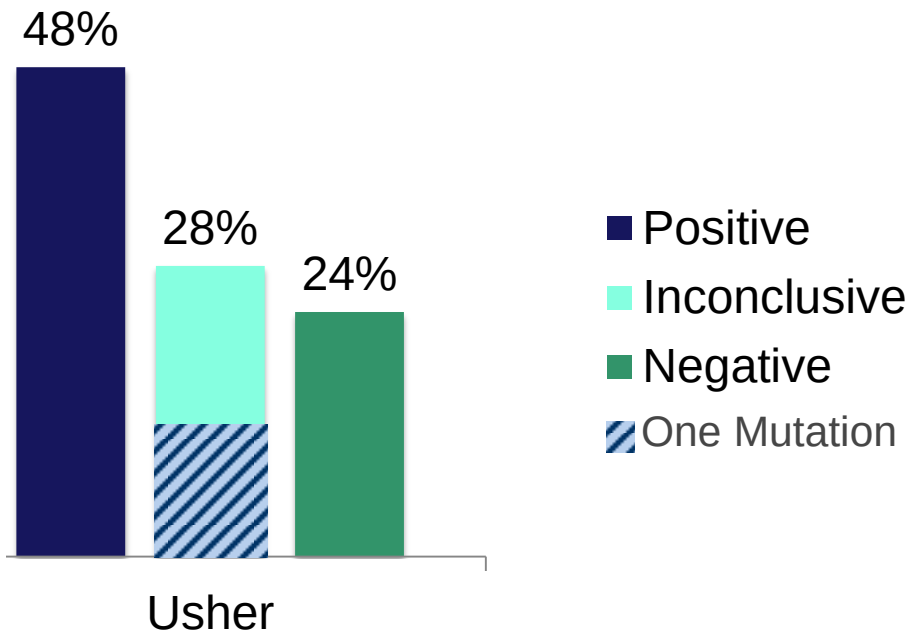
Clinical Annotation



A typical Usher syndrome panel test, using NGS, may identify 50-100 variants per patient.

Further genetic testing complexities…

- Many patients are found with only one mutation by sequencing
- Some of these patients have deletions
- Faugere et al 2010: 8% of Usher cases have larger dels/dups
  - 5 in MYO7A
  - 1 in CDH23
  - 6 in PCDH15
  - 10 in USH2A



Potential Benefits of Genetic Testing

- Clarify uncertain diagnosis
  - Syndromic vs nonsyndromic RP
- Predict disease severity
- Qualify patient for clinical treatment trial
- Enable testing for family members for prenatal/ preimplantation genetic testing
- Aid research
  - Not all cases of Usher syndrome follow the rules
  - Genetic modifiers of disease offer insights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