Unraveling Usher syndrome:
The role of genetic testing

Usher syndrome Family Conference
Seattle, 2016

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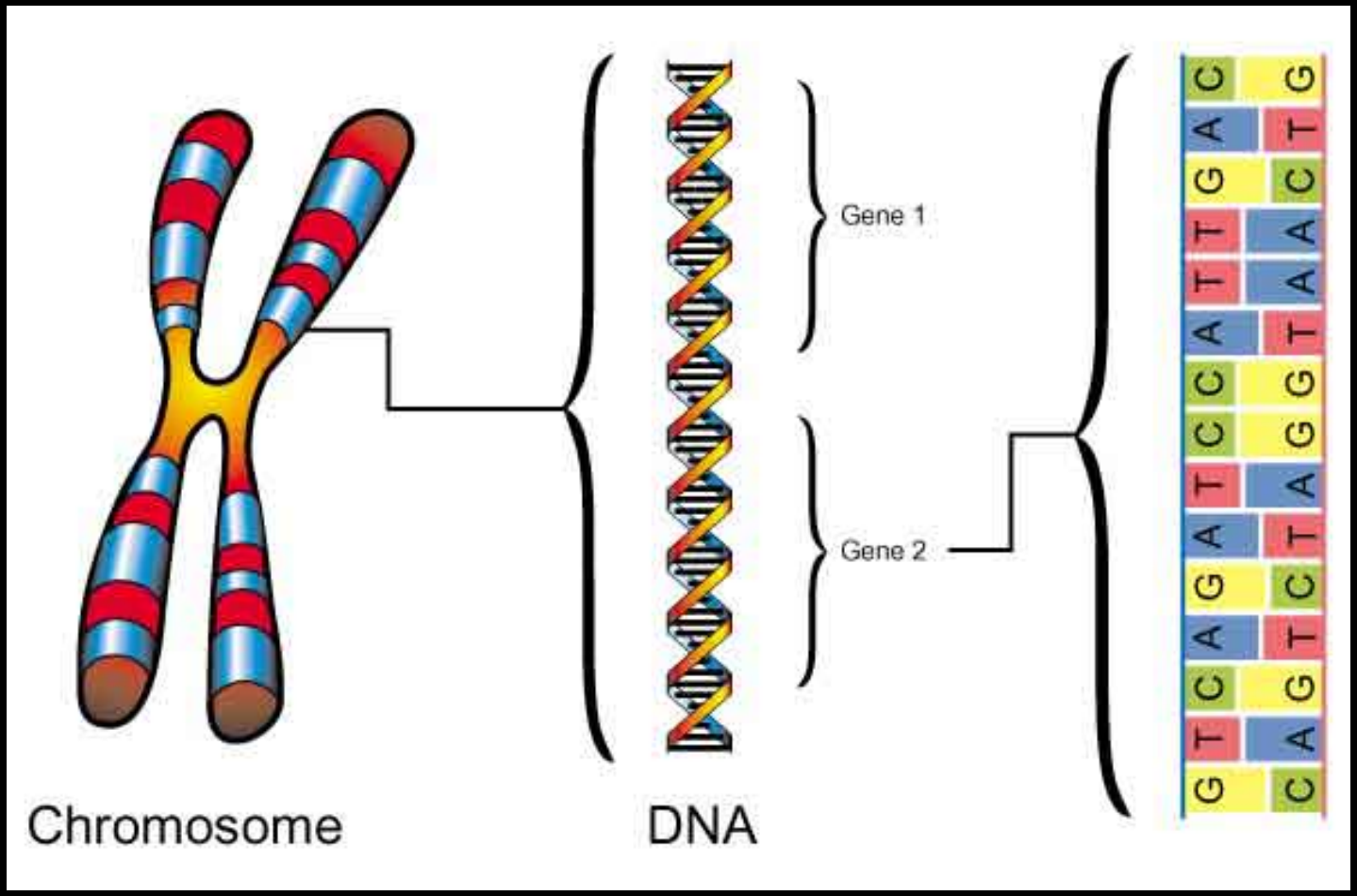
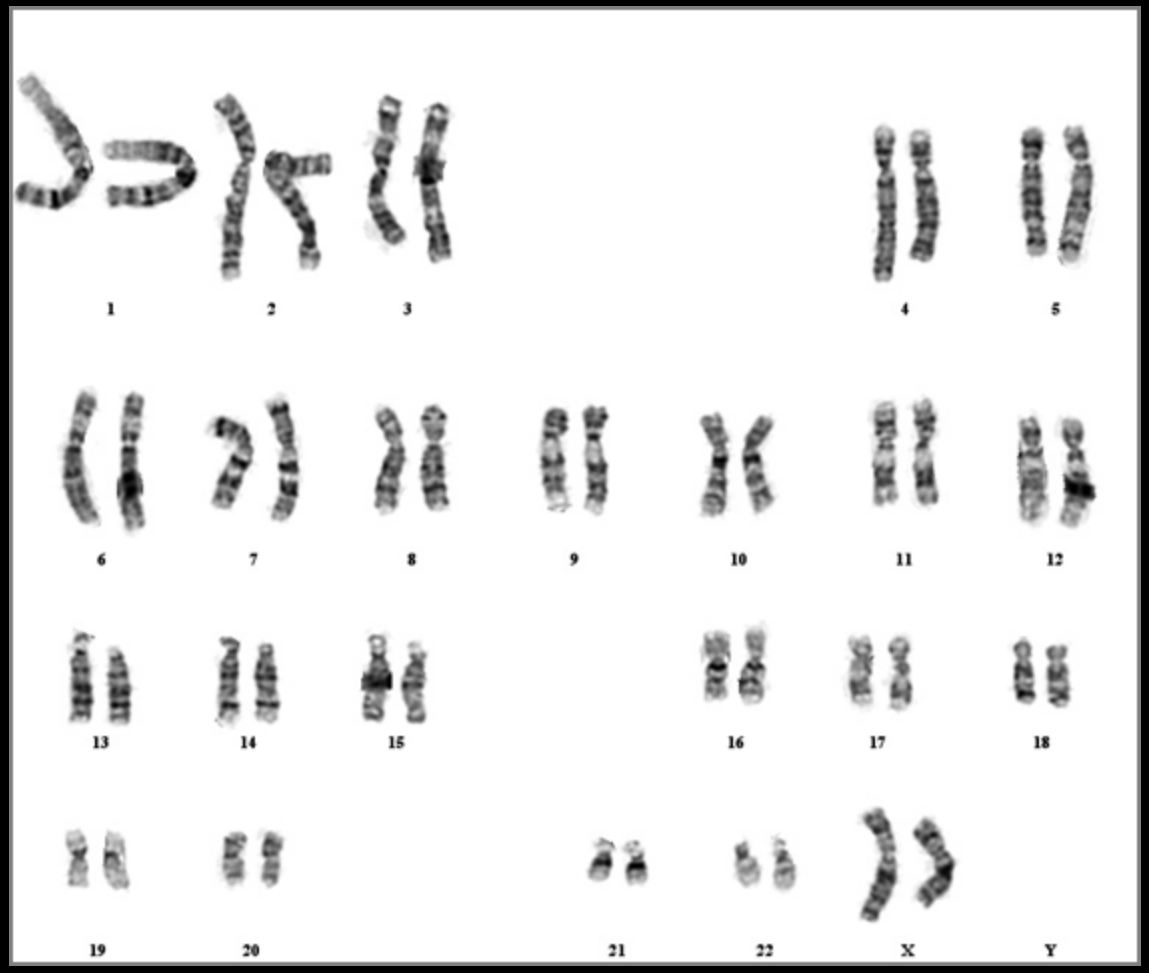
Potential Benefits of Genetic Testing

- Clarify uncertain diagnosis
- Predict disease progression
- Qualify for clinical treatment trial
- Enable testing of family members
- Aid research

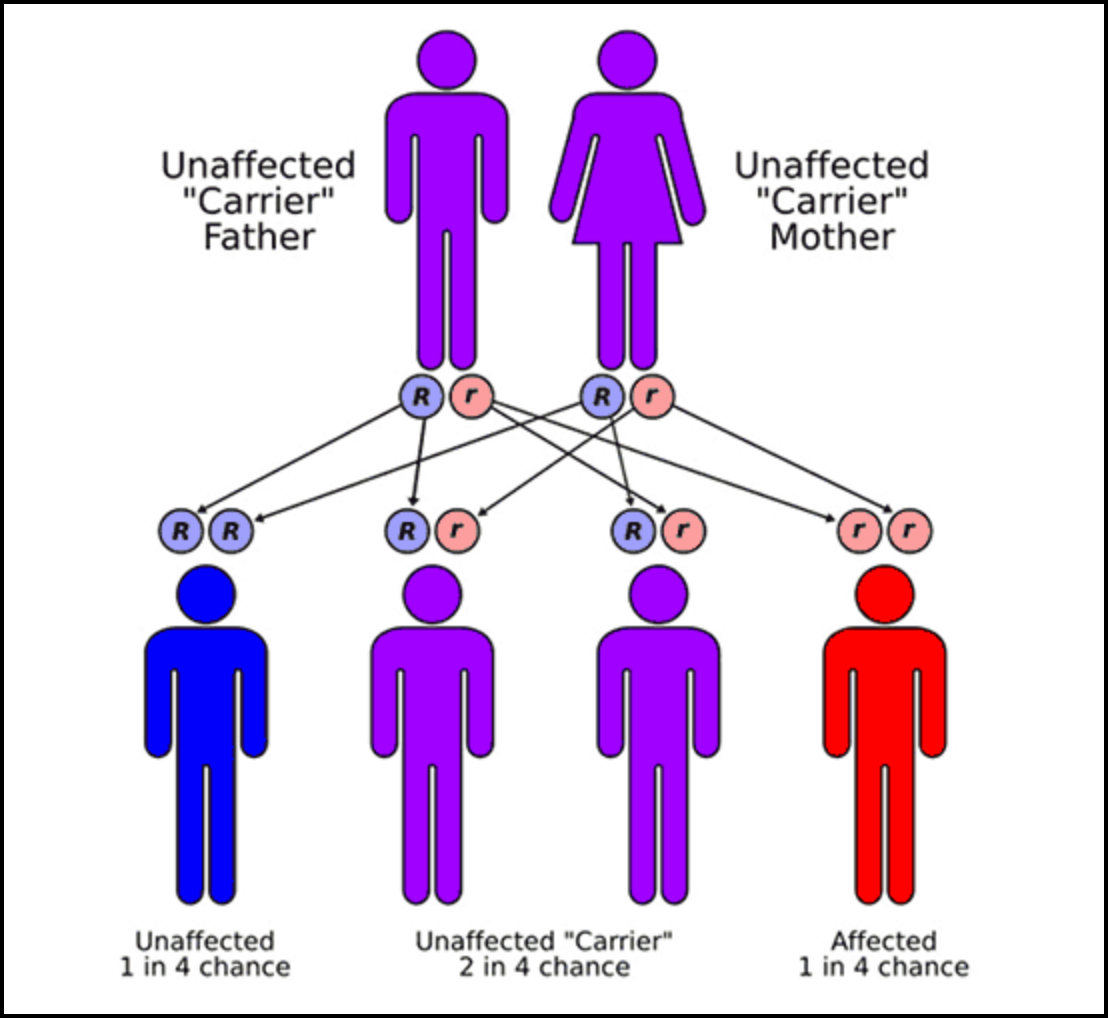

Gene 1
Gene 2
Chromosome
DNA

Chromosomes

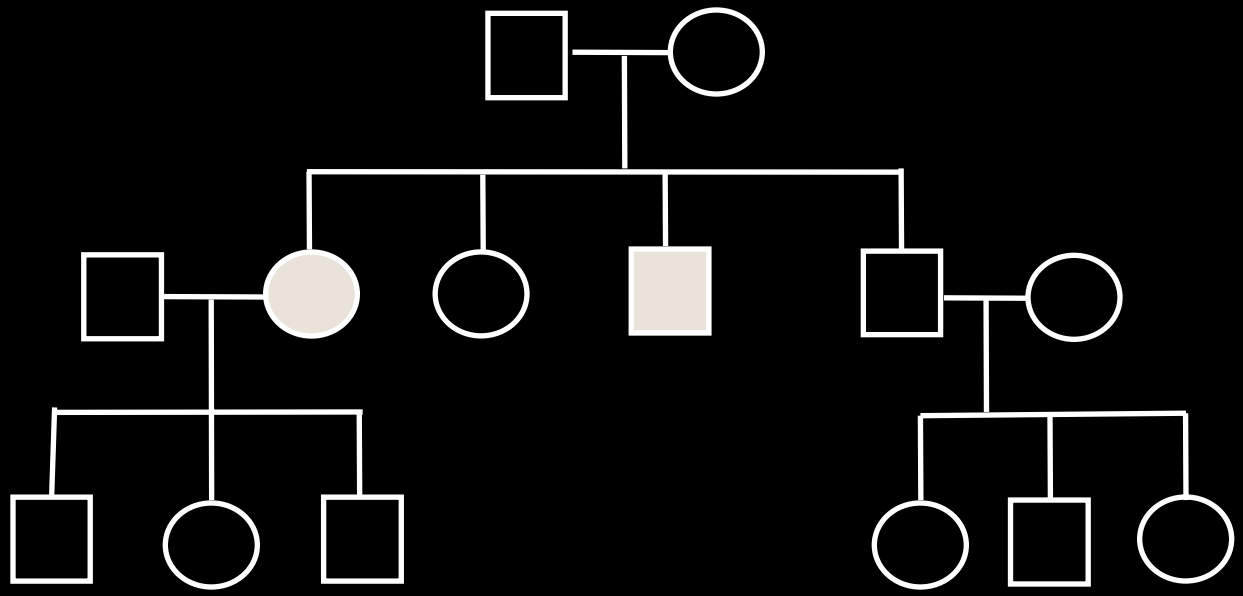
Normal female: 46,XX

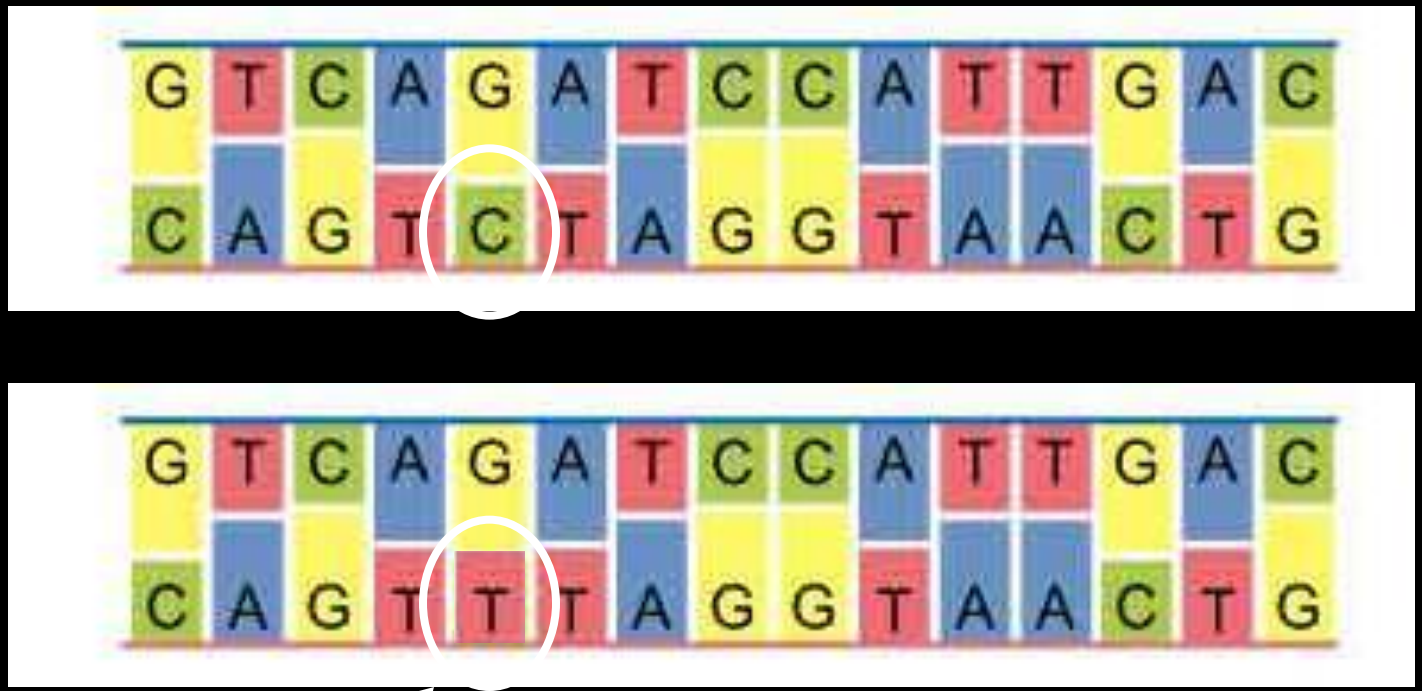


Usher syndrome Inheritance: Autosomal Recessive



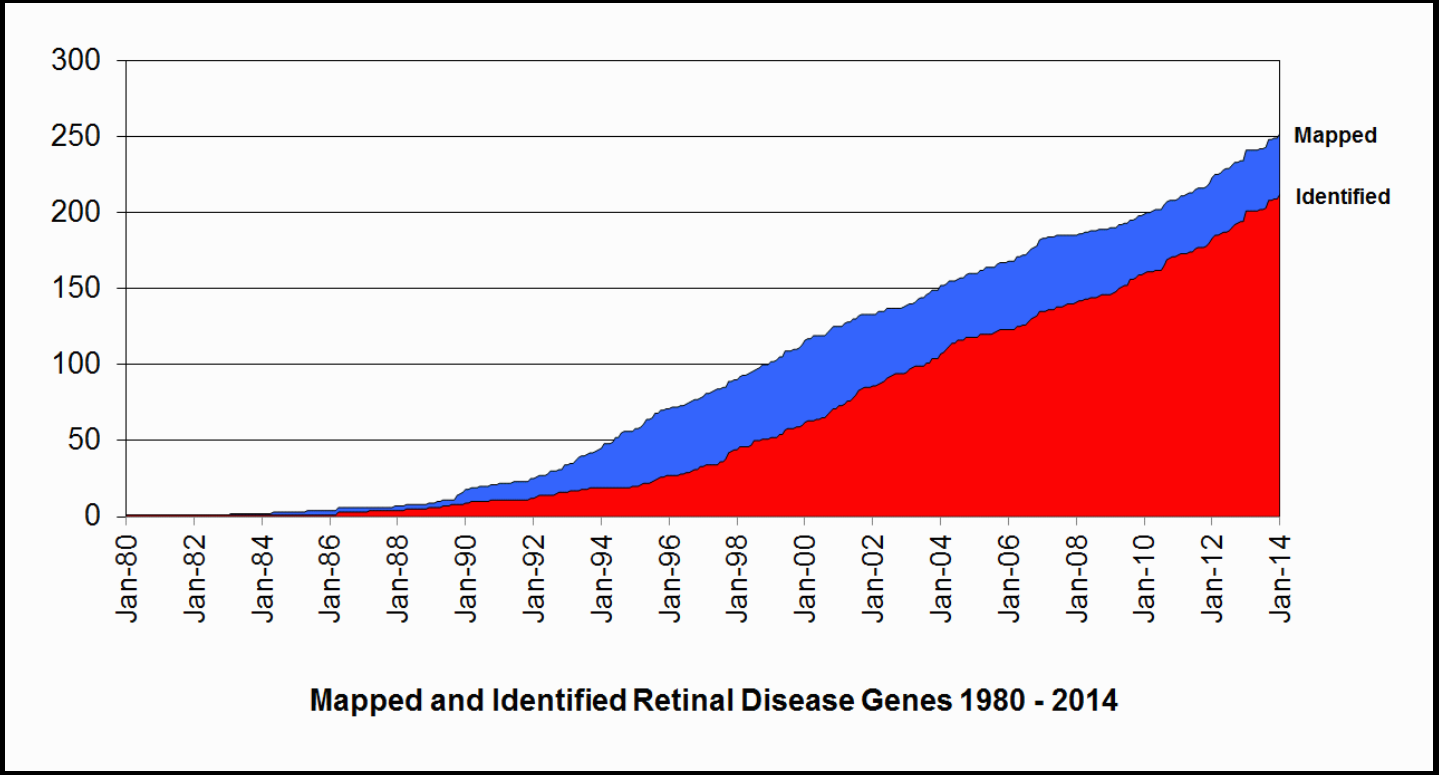
Recessive Inheritance




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

Usher syndrome genes

Total # of Mapped Genes	Identified Genes
15	11 (12? 13?)



Usher syndrome type I

Usher syndrome subtype	Gene Name	Relative Incidence
USH1B	*MYO7A*	50-60%
USH1C	*Ush1C*	6-7%
USH1D	*CDH23*	15-20%
USH1E	*?*	Rare
USH1F	*PCDH15*	10-15%
USH1G	*SANS*	~7%
USH1H	*?*	?
USH1J	*CIB2*	?
USH1K	*?*	?

Usher syndrome types II & III

Usher syndrome subtype	Gene Name	Relative Incidence
USH2A	*Ush2A*	~80%
USH2C	*VLGR1 (GPR98)*	~15%
USH2D	*WHRN*	~5%
USH1E	*Unknown*	Rare

Usher syndrome subtype	Gene Name	Relative Incidence
USH3A	*CLRN1*	>95%
USH3B	*HARS*	Rare

Access Genetic Testing

UNRAVELING USH

AN USHER SYNDROME GENETIC TESTING INITIATIVE

A collaborative effort with Project Usher at the Stephen A. Wynn Institute for Vision Research to ensure everyone with Usher syndrome has access to genetic testing.

Participating in "Unraveling USH"

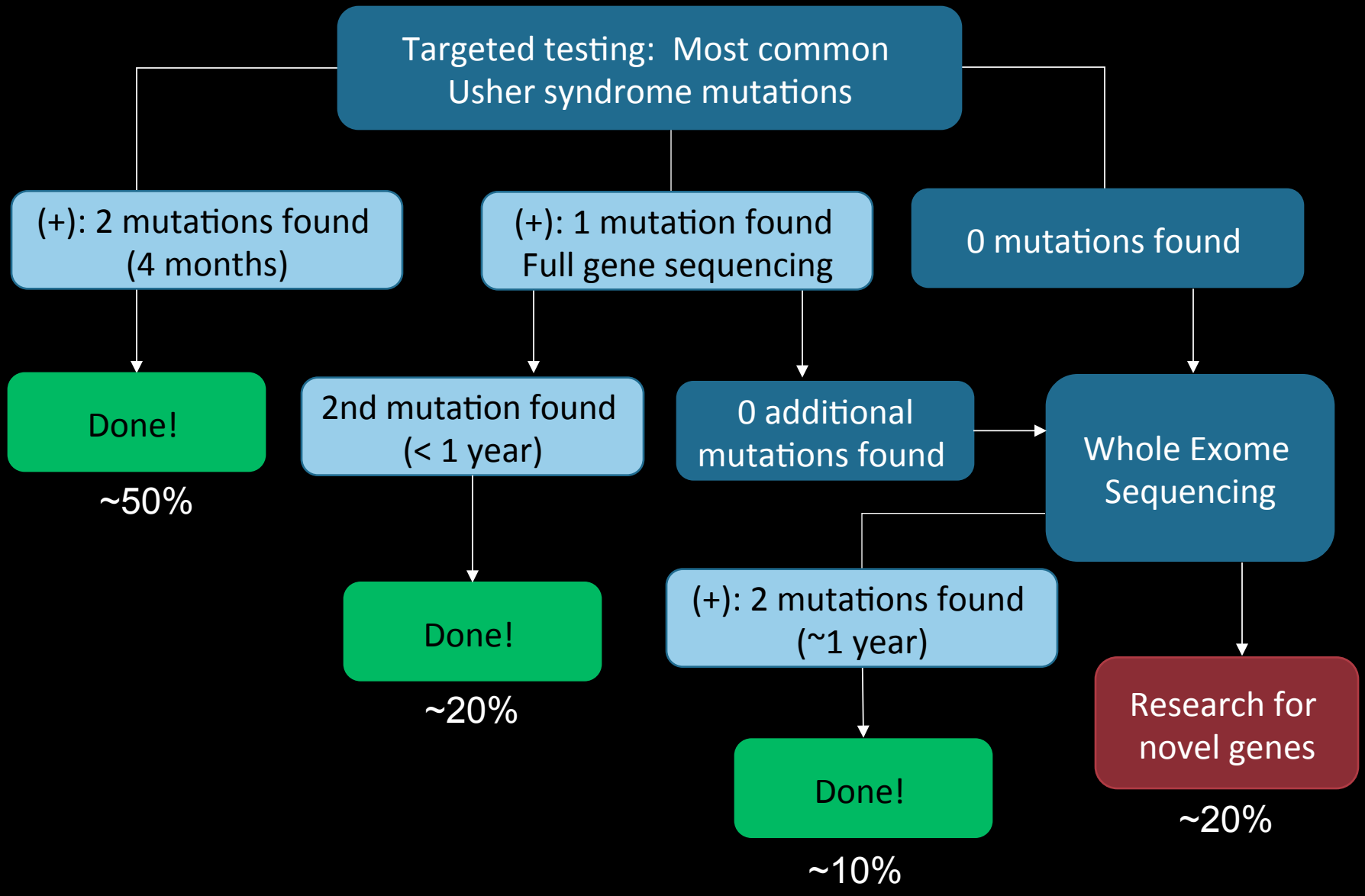
1. Meet with a physician or genetic counselor and ask them to order the test.
2. Work with provider to try to obtain insurance coverage for testing.
3. Add genetic test results to the International Usher syndrome registry.

The Stephen A. Wynn Institute for Vision Research

Project Usher: 5 Goals

- Provide hope
- Provide accurate information
- Find the remaining genes
- Find cures
- Make genetic testing available to all

Genetic Testing Pipeline



Genetic Counseling & Test Coordination

1. Inherited Retinal Dystrophy Expert/ Clinic
   - Usher syndrome coalition (usher-syndrome.org)
   - Foundation Fighting Blindness (blindness.org)

2. Genetic Counselor
   - By phone (informeddna.com)
   - In person (nsgc.org

3. Local physician
   - Resources available at usher-syndrome.org

Clinical Trials: Who Will Benefit?

ClinicalTrials.gov

- Current clinical trials:
  - *MYO7A*
- Upcoming clinical trials:
  - *Ush2A?*
  - *Ush1C?*
  - *CLRN1?*

Is genetic testing necessary for clinical trials that are NOT gene-based?

What can genetic testing research teach us?

Underlying shared pathways

- "Usher syndrome interactome"
- Insights for treatment

Novel genes

- ~80% of patients with Usher syndrome will test (+) for a known "US gene"

Modifiers of disease

- *PDZD7*

What else can genetic testing research teach us?

What is an Usher syndrome gene?

- *ABHD12?*
- *PDZD7?*

What defines Usher syndrome?

- Shared genetic causes/ protein interactions?
- RP + HL +/- vestibular dysfunction, and nothing else?
  - What if a % of patients have Crohn's disease/ IBD and have US from a "Classic" US gene?

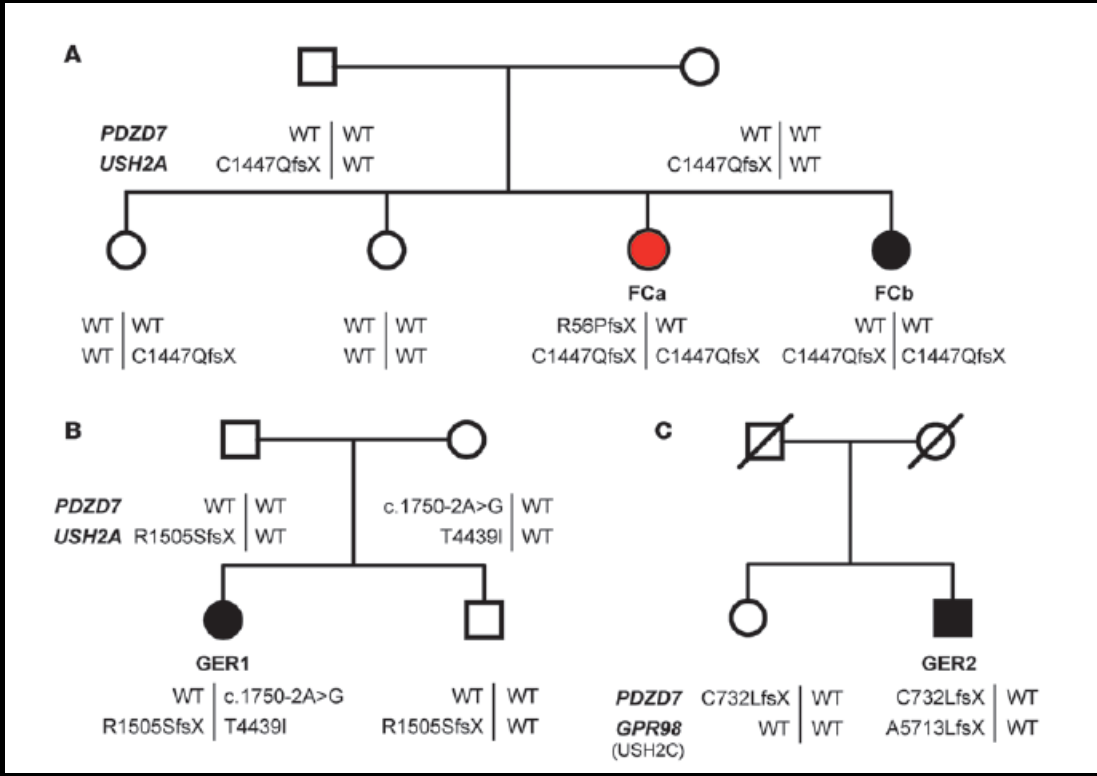

USHER SYNDROME
COALITION


INFORMED DNA
Healthcare, Personalized.

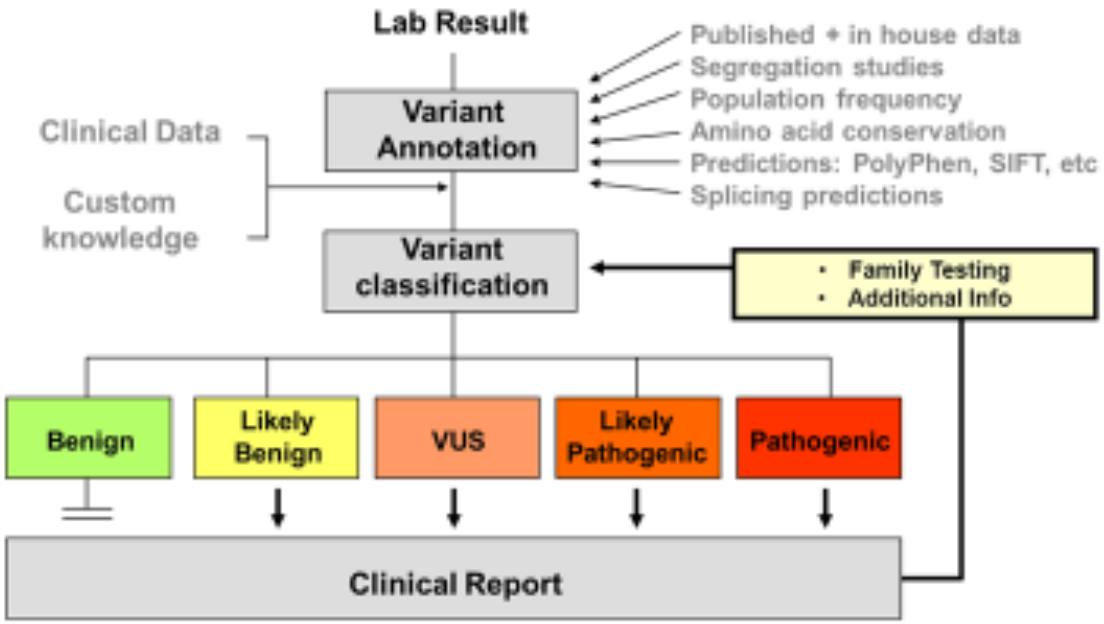
Research article

PDZD7 is a modifier of retinal disease and a contributor to digenic Usher syndrome

Inga Ebermann,[1] Jennifer B. Phillips,[2] Max C. Liebau,[3] Robert K. Koenekoop,[4] Bernhard Schermer,[3,5] Irma Lopez,[4] Ellen Schäfer,[6] Anne-Francoise Roux,[7,8] Claudia Dafinger,[1] Antje Bernd,[9] Eberhart Zrenner,[9] Mireille Claustres,[7,8] Bernardo Blanco,[2] Gudrun Nürnberg,[10] Peter Nürnberg,[5,10] Rebecca Ruland,[1] Monte Westerfield,[2] Thomas Benzing,[3,5] and Hanno J. Bolz[1]



Clinical Annotation



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