PARTNERS HEALTHCARE | FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

Data Sharing to Support Test Interpretation

Heidi L. Rehm, PhD, FACMG
Associate Professor of Pathology, BWH/Harvard Medical School
Director, Laboratory for Molecular Medicine

Disclosures

- *I direct a non-profit fee-for-service diagnostic laboratory that performs clinical testing for hearing loss*
- *I receive NIH funding to support the ClinGen project*

The OtoGenome Test: 70 gene targeted panel on the NGS platform

ACTG1
ATP6V1
BSND
CCDC50
CLDN1
COCH
COL11A2
CRYM
DFNA5
DIAPH1
ESPN
ESRRB
BOR *EYA1*
EYA4
GIPC3
GJB2
GJB3
GJB6

GPSM2
GRHL2
GRXCR1
HGF
ILDR1
KCNE1 JLNS
KCNQ1
KCNQ4
LHFPL5
LOXHD1
LRTOMT
MARVELD2
MIR96
MSRB3
MTRNR1
MTTS1
MYH14
MYH9
MYO15A

MYO1A
MYO3A
MYO6
OTOA
DFNB59 AN
OTOF
POU3F4
POU4F3
PRPS1
RDX
SERPINB6
SLC17A8
SLC26A4 Pendred
STRC
TECTA
TIMM8A
TJP2
TMC1
TMIE
TMPRSS3

CDH23 USHER
CLRN1
DFNB31
GPR98
MYO7A
PCDH15
USH1C
USH1G
USH2A
TPRN
TRIOBP
WFS1 Wolfram

NGS Usher subpanel also available (9 Usher genes)

Rare variation is common in the general population

Particularly in the Usher syndrome genes

Total variants from ESP and dbSNP	**7737**
Classified as Benign	291
Classified as Likely Benign	2578
Unclassified due to low frequency	4813

ACMG Lab QA Committee on the Interpretation of Sequence Variants

ACMG
Sue Richards (chair), Heidi Rehm (co-chair)
Sherri Bale, David Bick, Soma Das, Wayne Grody, Madhuri Hegde, Elaine Spector

AMP
Julie Gastier-Foster, Elaine Lyon

CAP
Nazneen Aziz, Karl Voelkerding

ACMG
American College of Medical Genetics and Genomics

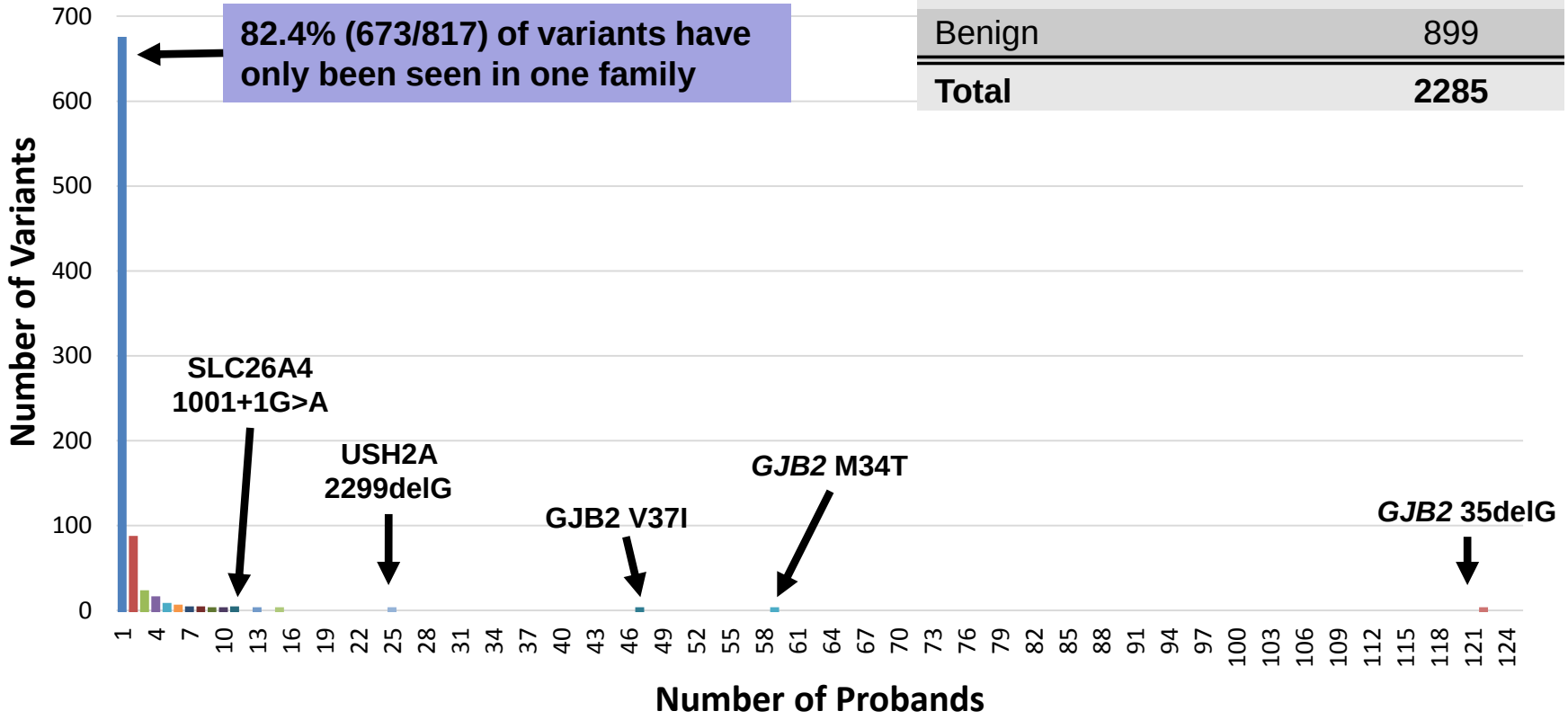
AMP Association for Molecular Pathology

cap

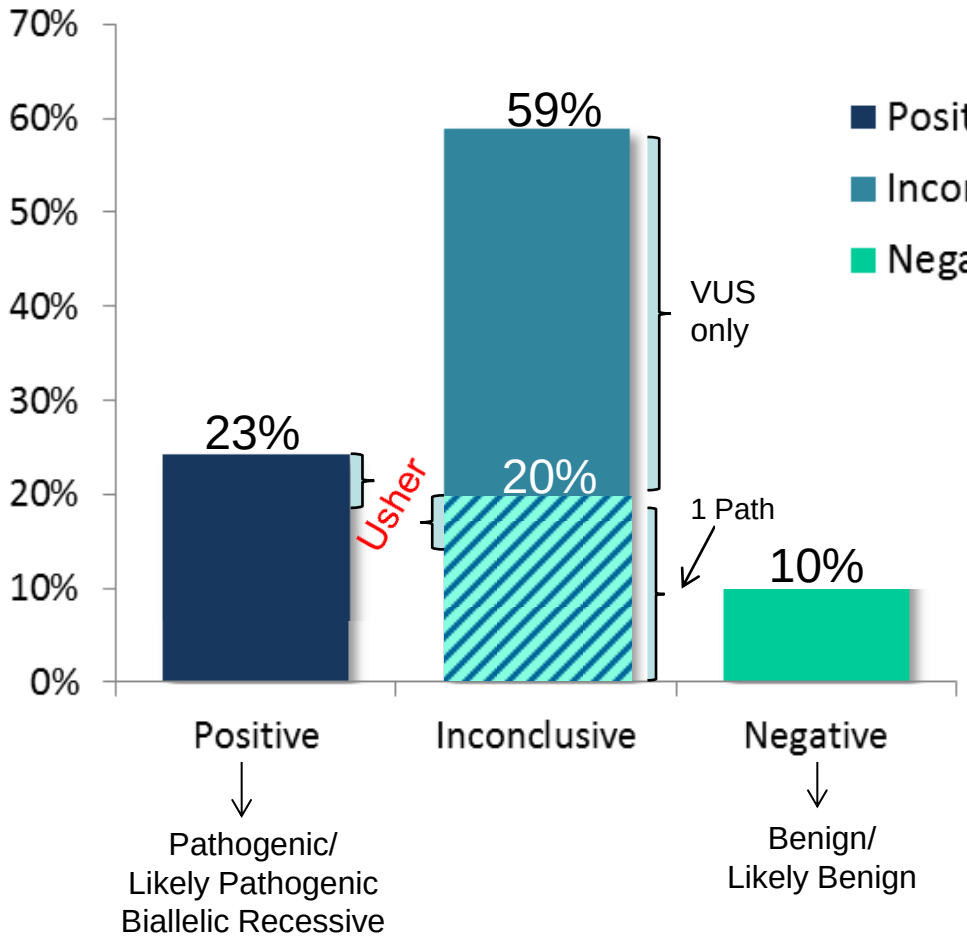
Hearing loss variants in over 3000 cases

817 variants

Reported Variant Classification	
Pathogenic	223
Likely Pathogenic	121
Unknown Significance	462
Likely Benign	580
Benign	899
Total	**2285**

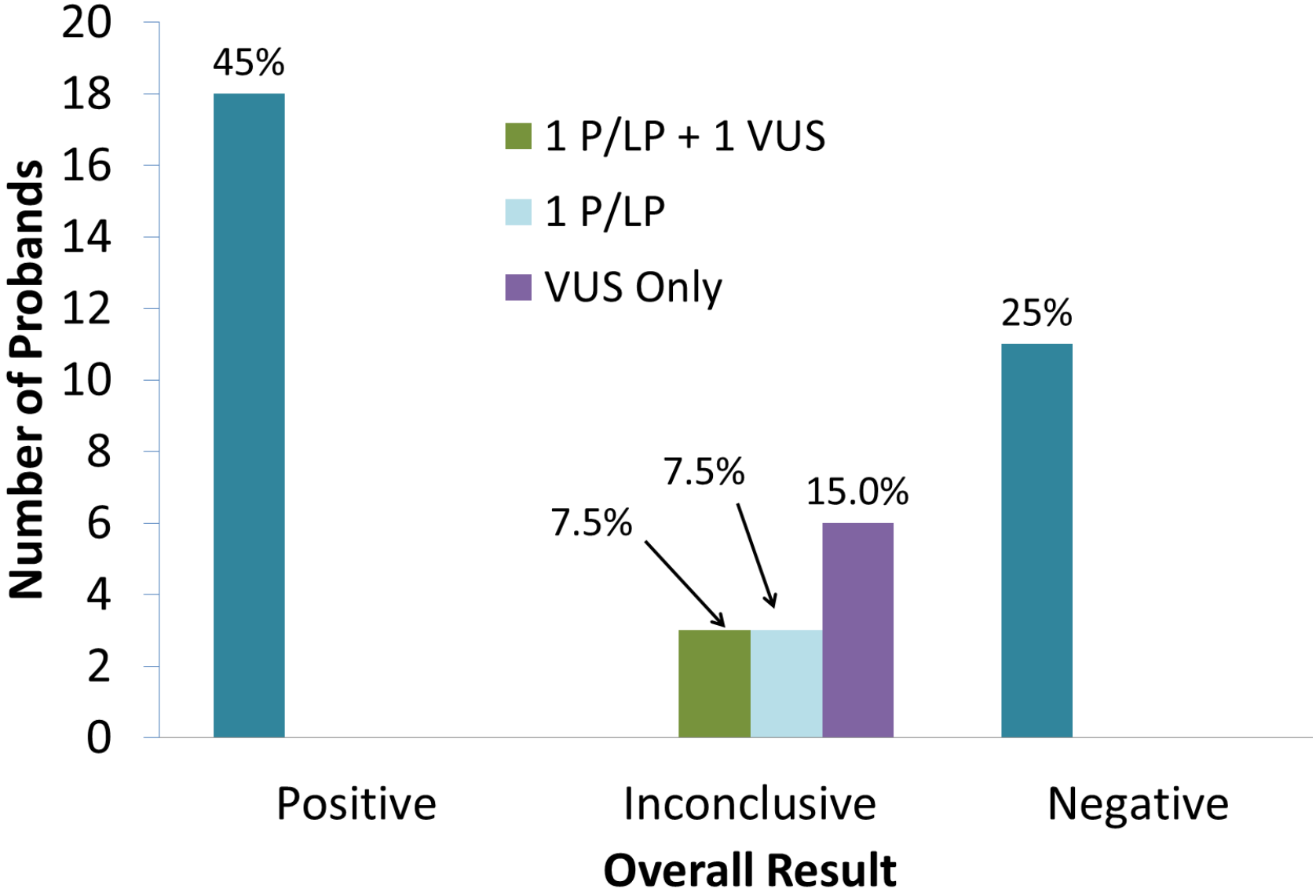


OtoGenome Detection Rates



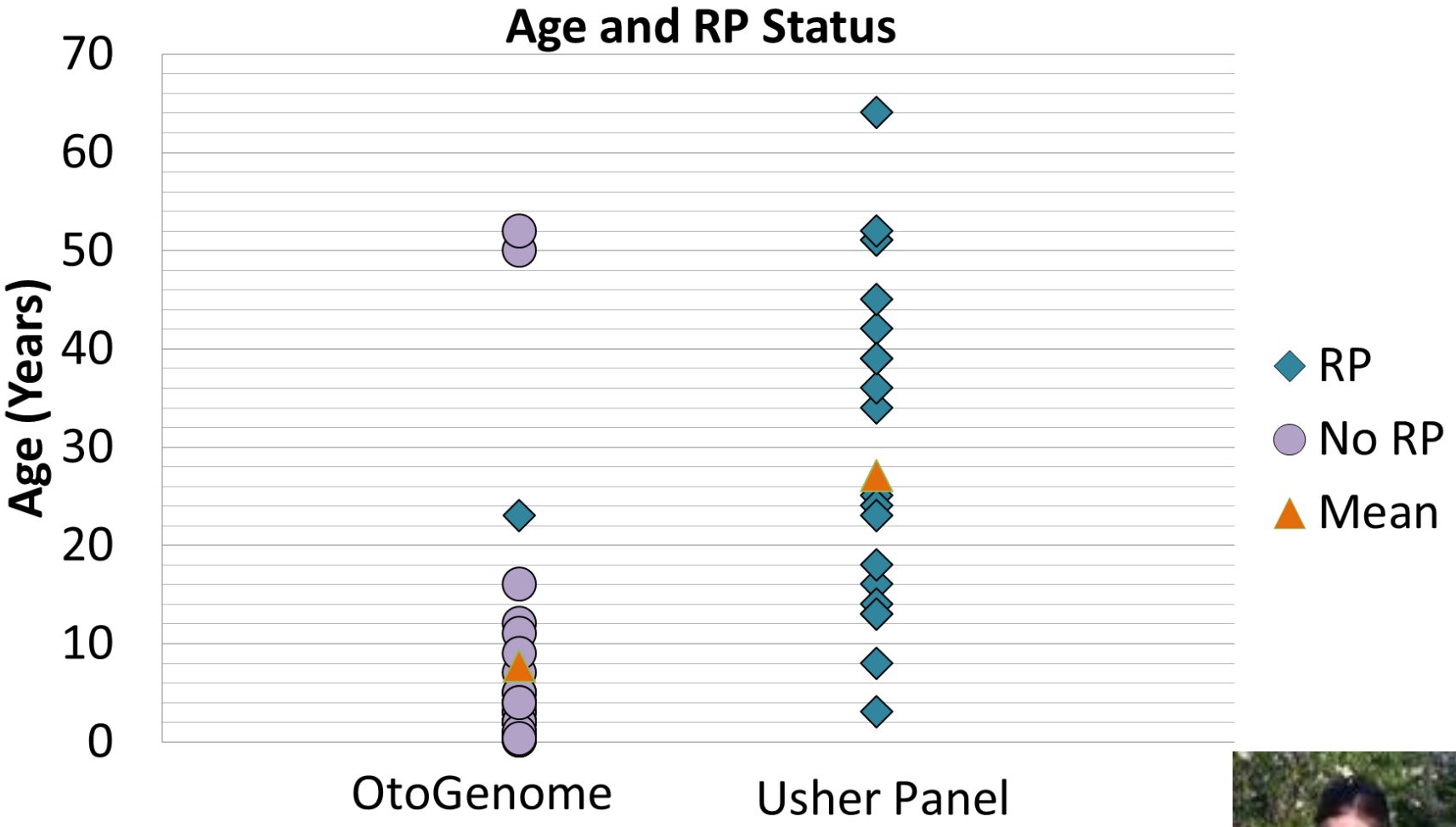
~7% of cases have pathogenic variants in Usher genes, most unaware of their risk for RP

Detection Rate for Usher Panel



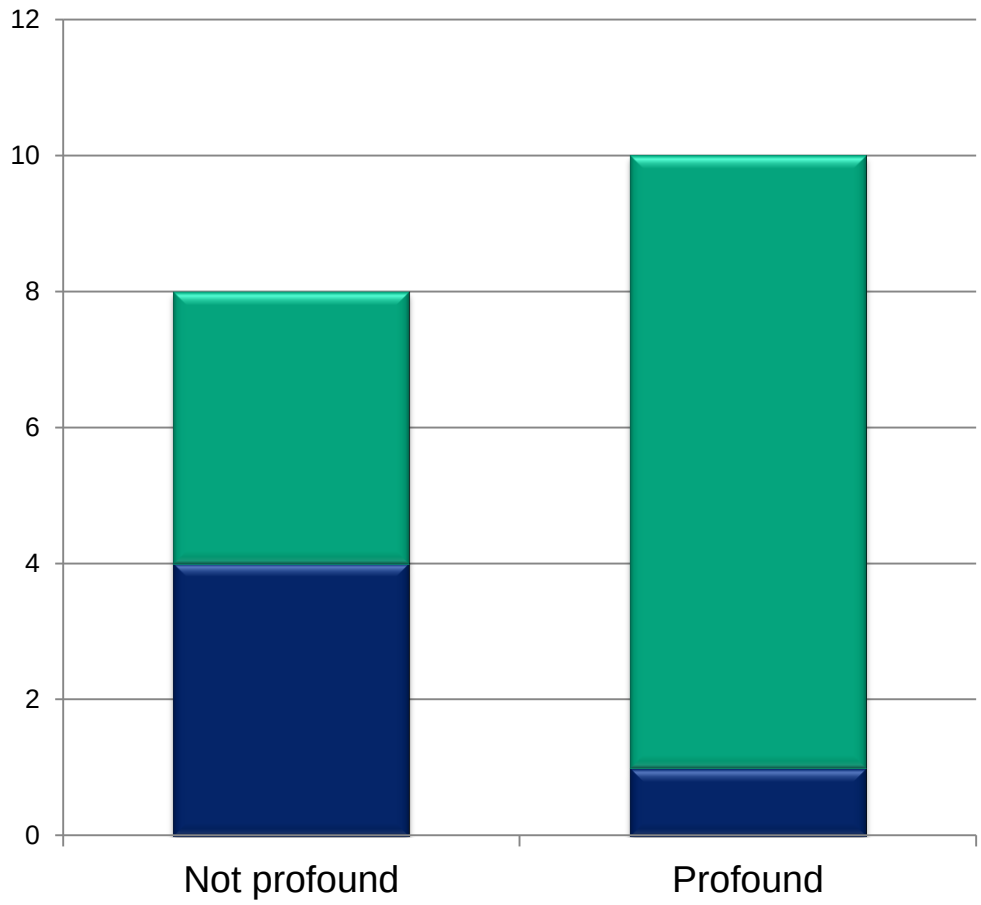
Courtesy of Andrea Muirhead

Age of Testing and Presence of RP



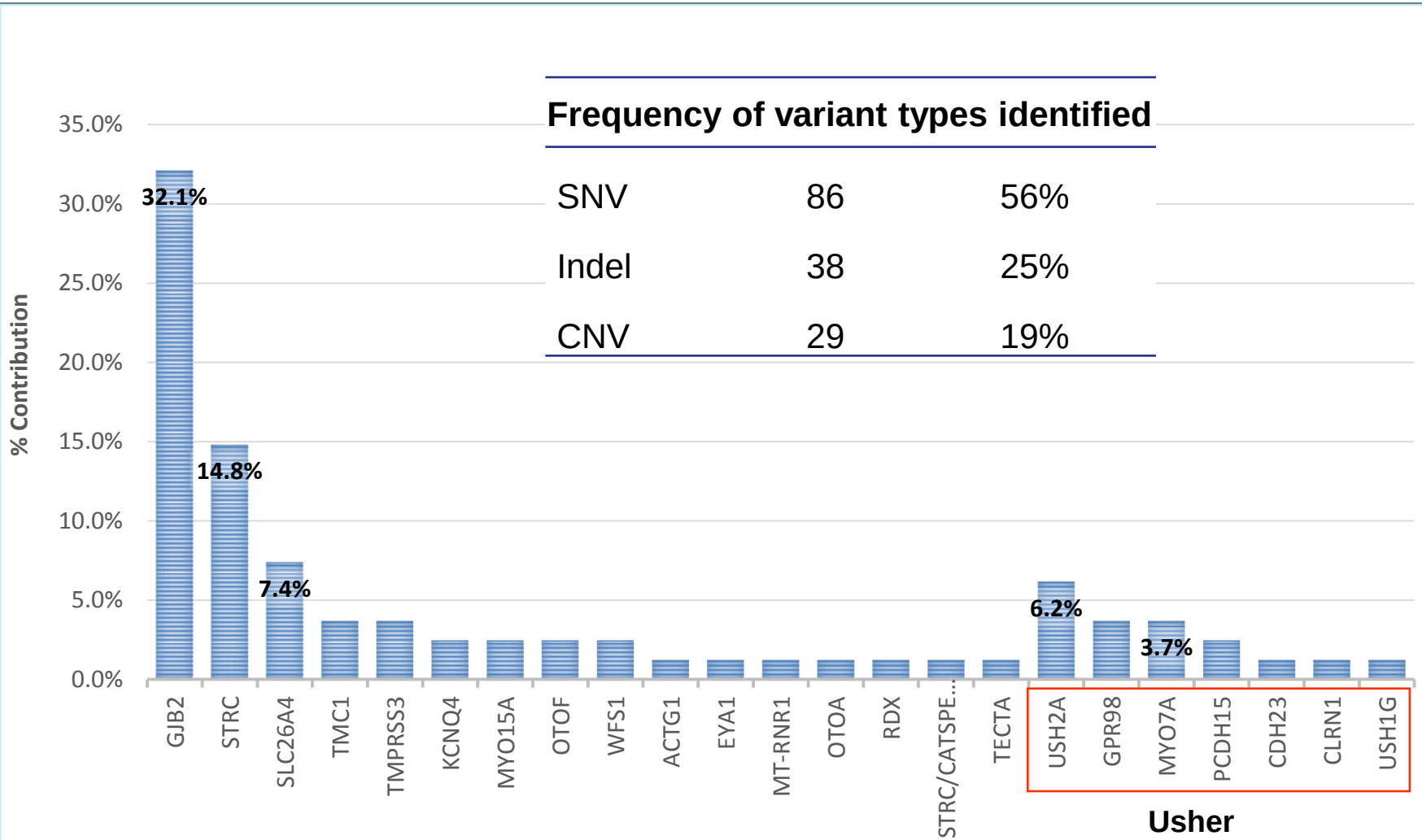
Courtesy of Andrea Muirhead

Hearing Loss Severity with USH1 Gene Mutations



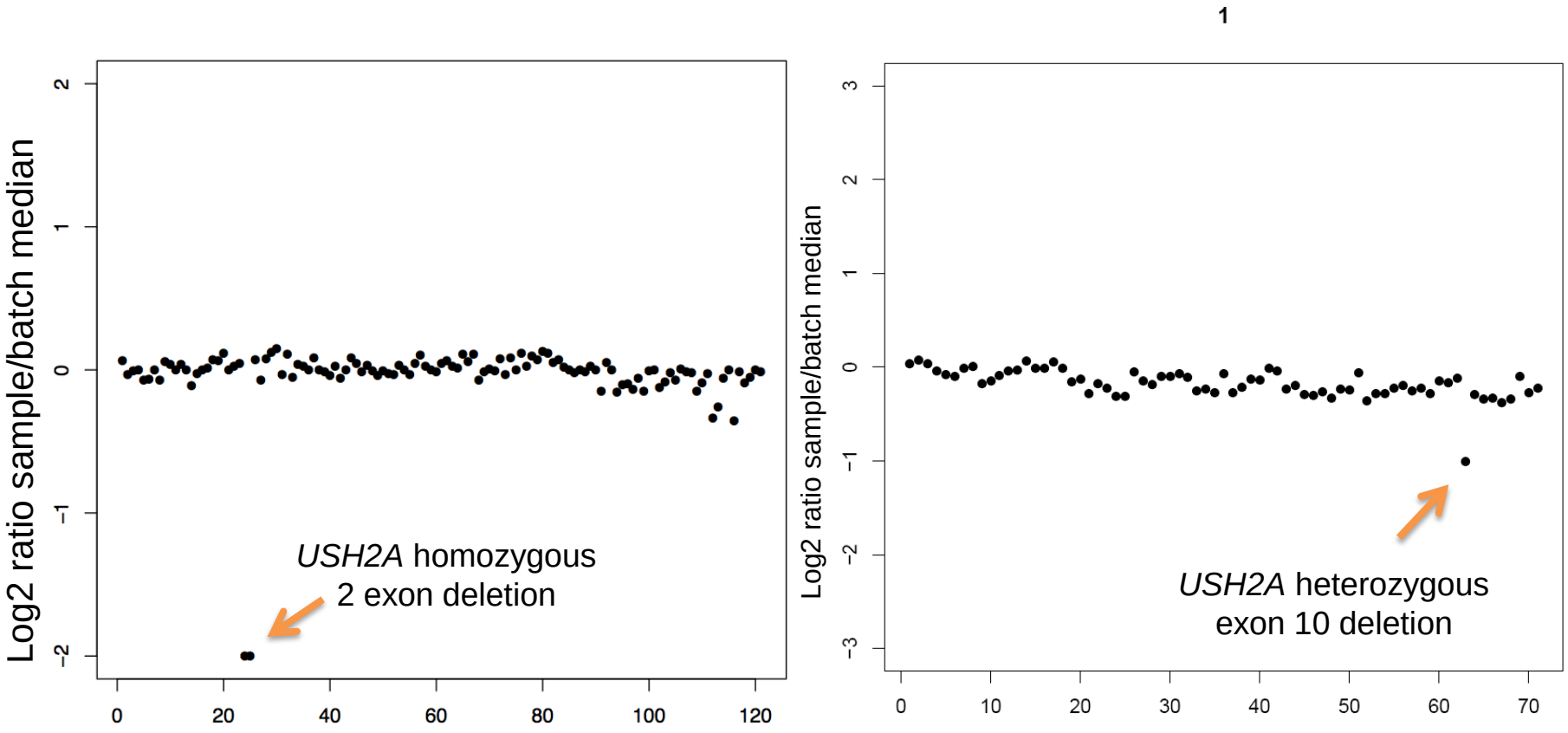
Mutations in Usher Type 1 genes may not cause an Usher Type 1 phenotype

Gene and variant spectrum in positive OtoGenome cases



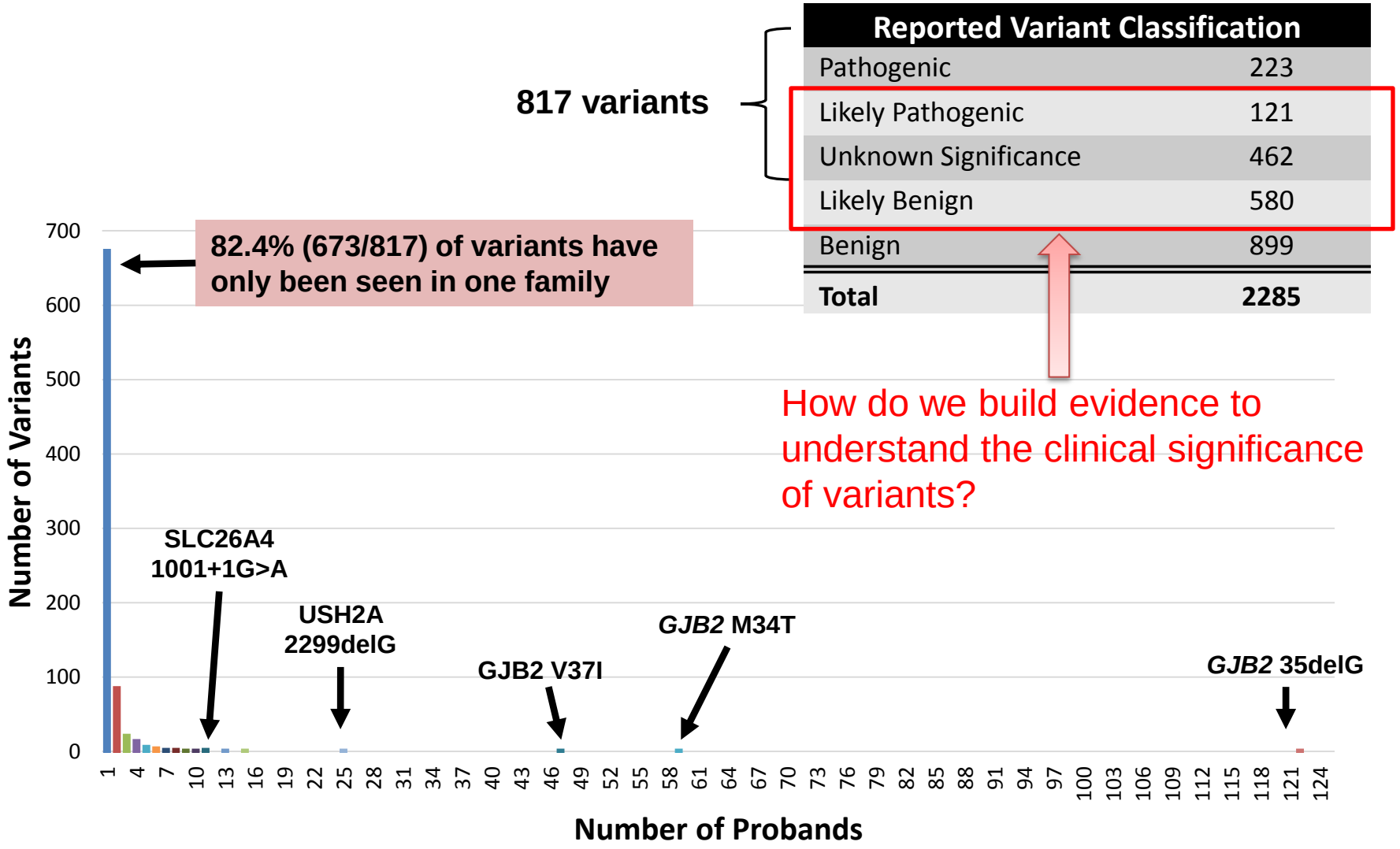
Courtesy of Sami Amr

Deletions detected by NGS



Copy number variants confirmed by digital droplet PCR

Hearing loss variants in over 3000 cases



Courtesy of Sami Amr

ClinGen

The Clinical Genome Resource

Launched Sept 2013

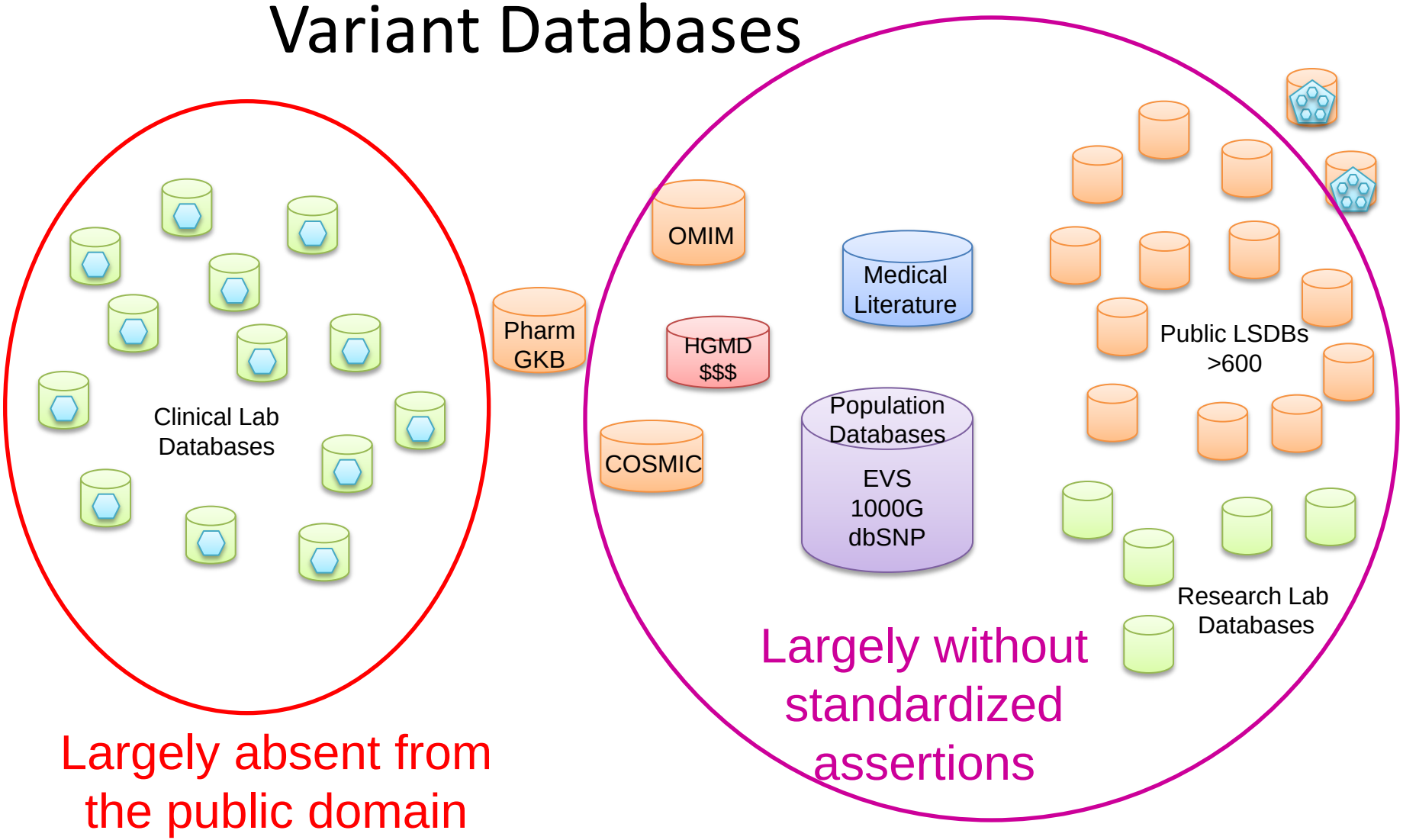
NCBI ClinVar Leads Melissa Landrum Donna Maglott Steve Sherry	**U41 Grant PIs** David Ledbetter Christa Martin Bob Nussbaum Heidi Rehm	**U01 PIs** Jonathan Berg Jim Evans David Ledbetter Mike Watson	**U01 PIs** Carlos Bustamante Sharon Plon	**NHGRI Program Directors** Lisa Brooks Erin Ramos
ClinGen Working Groups (WG)				
Sequence Variant WG **Chairs**: Sherri Bale & Madhuri Hegde	**ClinVar IT Standards and Data Submission WG** **Chairs**: Sandy Aronson & Karen Eilbeck	**Clinical Domain WGs** **Chairs**: Jonathan Berg & Sharon Plon **Cancer co-chairs**: Matthew Ferber, Ken Offit, Sharon Plon **Cardiovascular co-chairs**: Euan Ashley, Birgit Funke, Ray Hershberger **Metabolic co-chairs**: Rong Mao, Robert Steiner, David Valle **Pharmacogenomic co-chairs**: Teri Klein, Howard McLeod	**Education, Engagement, Access WG** **Chair**: Andy Faucett	**Gene Curation WG** **Chairs**: Jonathan Berg & Christa Martin
Structural Variant WG **Chairs**: Swaroop Arahdya & Erik Thorland	**Data Model WG** **Chairs**: Jonathan Berg & Heidi Rehm			**Actionability WG** **Chair**: Jim Evans
Phenotyping WG **Chair**: David Miller	**Informatics WG** **Chair**: Carlos Bustamante		**ELSI and Genetic Counseling WG** **Chair**: Andy Faucett & Kelly Ormond	**EHR WG** **Chair**: Marc Williams

Goals of ClinGen

To raise the quality of patient care by:

- ***Standardizing*** **the annotation and interpretation of genomic variants**
- **Sharing variant and case level data through a *centralized database* for clinical and research use**
- **Developing *machine-learning algorithms* to improve the throughput of variant interpretation**
- **Implementing an *evidence-based expert consensus* process for curating genes and variants**
- **Assessing the *actionability* of genes and variants and supporting their use in *clinical care systems***

Variant Databases



ClinVar

>100,000 variants
from 139 submitters

NCBI Resources How To

ClinVar ClinVar Search

Advanced

ClinVar

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

Using ClinVar

- About ClinVar
- Data Dictionary
- Downloads/FTP site
- FAQ
- Contact Us
- ClinVar News and Announcements

Tools

Related Sites

You are here: NCBI > ClinVar

GETTING STARTED

NCBI Education

D980–D985 *Nucleic Acids Research, 2014, Vol. 42, Database issue* *Published online 14 November 2013*
doi:10.1093/nar/gkt1113

ClinVar: public archive of relationships among sequence variation and human phenotype

Melissa J. Landrum, Jennifer M. Lee, George R. Riley, Wonhee Jang, Wendy S. Rubinstein, Deanna M. Church and Donna R. Maglott*

National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, 8600 Rockville Pike, Bethesda, MD 20894, USA

Received September 13, 2013; Revised October 21, 2013; Accepted October 22, 2013

ClinVar

120,830 submissions
107,098 unique variants

62,425 variants with assertions from >3360 genes

50,063 variants without assertions from 111 submitters

Submitter	Variants	Genes
Clinical Labs		
Harvard Medical School and Partners Healthcare	6996	155
Emory Genetics Laboratory	5252	507
Ambry Genetics	4167	?
International Standards For Cytogenomic Arrays	4134	17711
GeneDx	3700	250
University of Chicago	3687	462
Sharing Clinical Reports Project	2045	2
ARUP Laboratories	1417	7
LabCorp	1391	140
InVitae	436	
Counsyl	112	20
University Pennsylvania Genetic Diagnostic Lab	68	1
American College of Med Genetics and Genomics	23	1
	26459	
General Databases		
OMIM	24443	3360
GeneReviews	3738	406
	28181	
LSDB/Researcher – Assertions Submitted		
Breast Cancer Information Core (BIC)	3793	2
InSiGHT	2360	4
Juha Muilu Group; FIMM, Finland (FIMM)	840	39
ClinSeq Project	425	35
Martin Pollak (Nephrology, BIDMC, Harvard)	234	39
CFTR2	133	1
	7785	
LSDB/Researcher – No Assertions		
111 Submitters	**50063**	>6957

ClinGen
Clinical Genome Resource

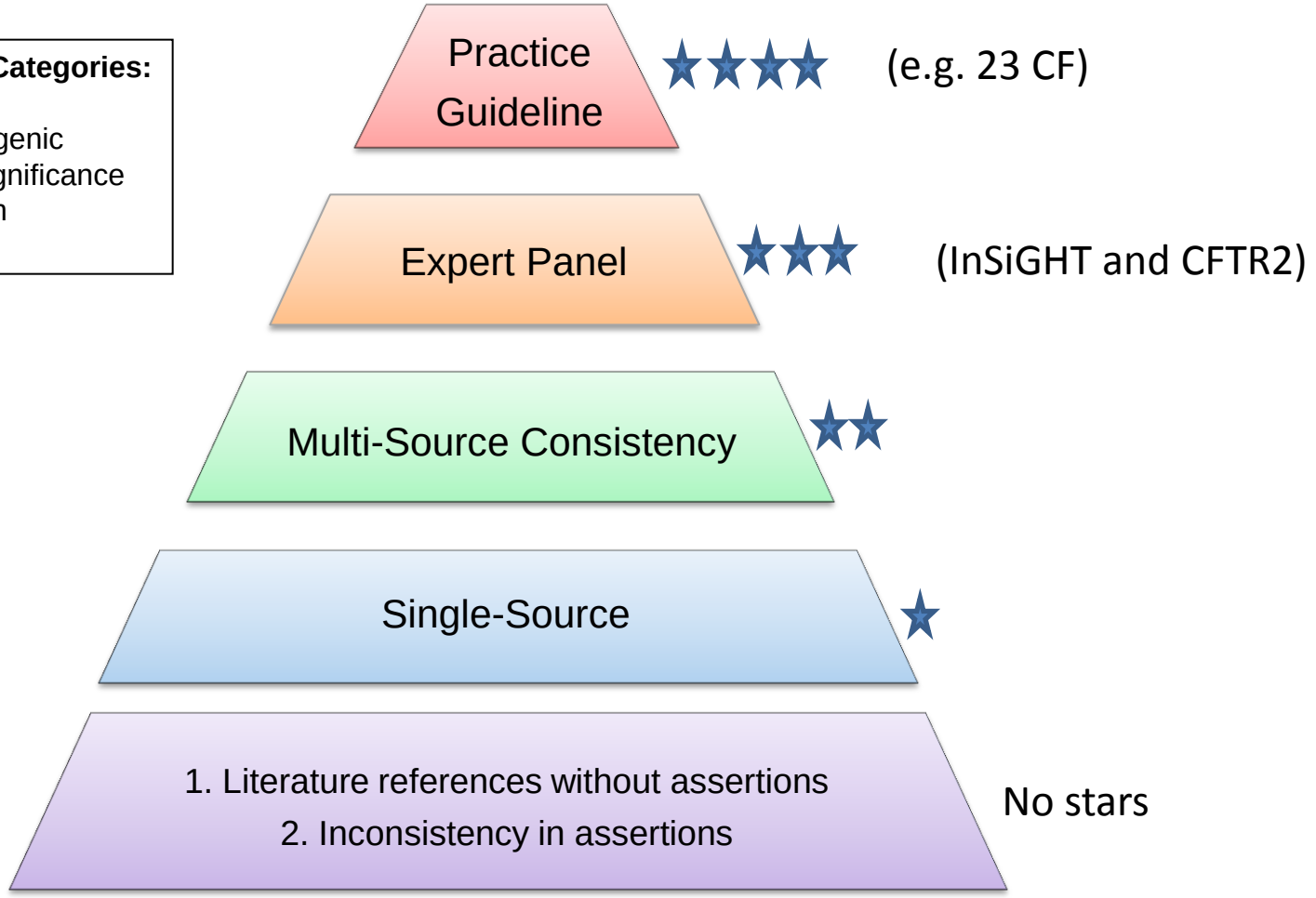
LMM's Submissions to ClinVar

6996 Interpreted Variants

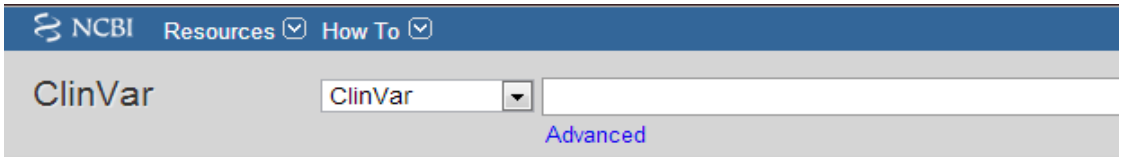
Phenotypes	Probands	Genes	Unique Variants
Cardiomyopathy	5485	51	3929
Somatic Cancer	3421	21	178
RASopathies	2781	12	376
Hearing Loss and Related Syndromes	2048	65	2218
Connective Tissue Disorders	915	3	227
Hereditary Cancer	665	9	81
Congenital Heart Defects	91	4	43
Ectodermal Dysplasia	81	1	36
Other			867

ClinVar Review Levels

Mendelian Categories:
Pathogenic
Likely pathogenic
Uncertain significance
Likely benign
Benign



Summary Interpretations in ClinVar



Clinical significance

MYO7A:c.635G>A (p.Arg212His)

Clinical significance:	Pathogenic/Likely pathogenic
Review status:	★★☆☆
Number of submission(s):	2

Condition(s)

Retinitis pigmentosa-deafness syndrome [MedGen OMIM]

Usher syndrome, type 1B [MedGen]

Clinical significance

MYO7A:c.905G>A (p.Arg302His)

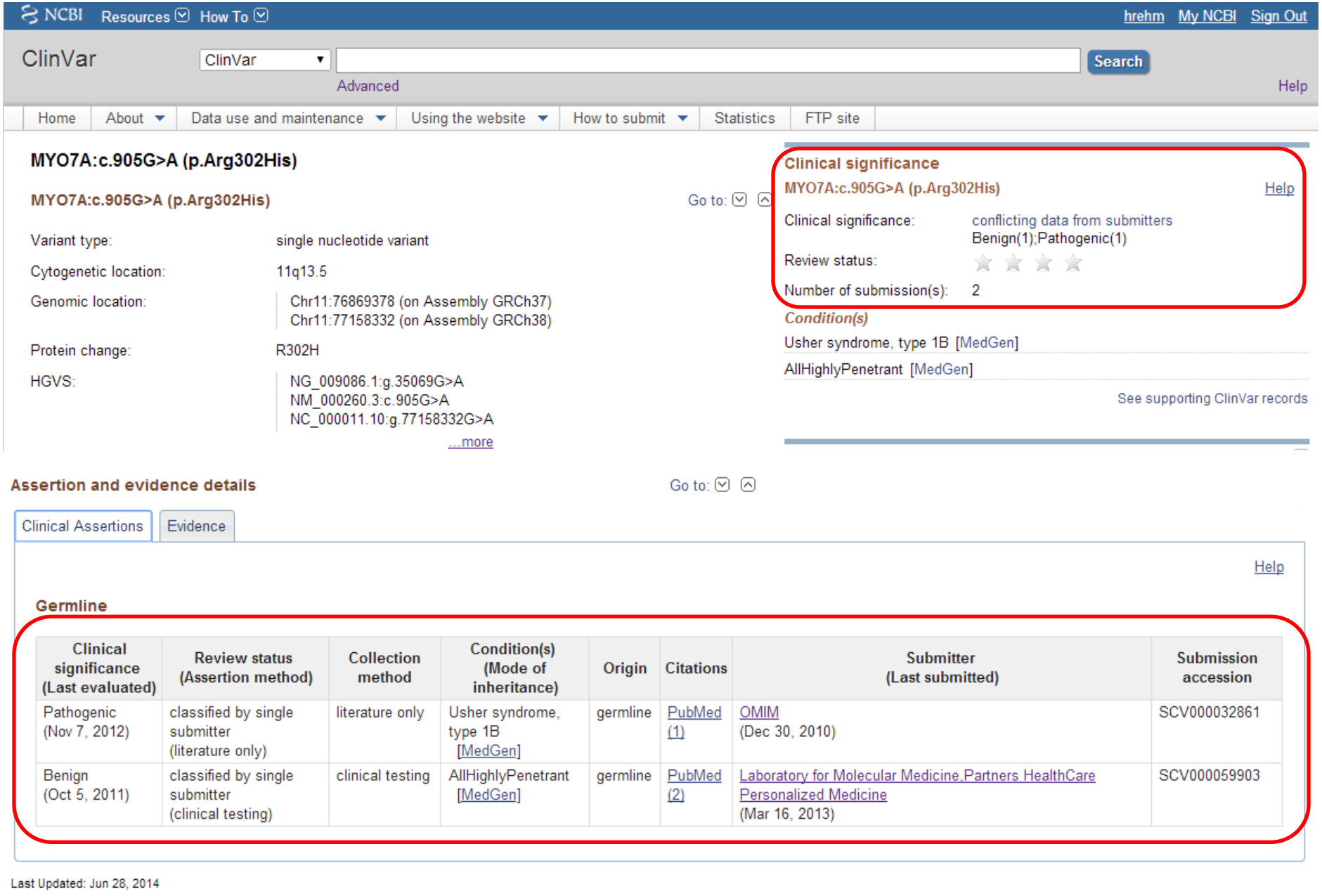
Clinical significance:	conflicting data from submitters Benign(1);Pathogenic(1)
Review status:	☆☆☆☆
Number of submission(s):	2

Condition(s)

Usher syndrome, type 1B [MedGen]

AllHighlyPenetrant [MedGen]

Clinical Assertions



ClinVar Evidence Tab

Assertion and evidence details Go to:

Clinical Assertions | Evidence

Help

Summary

Families	Individuals	Segregation	Allele origin	Ethnicity	Geographic origin
4	not provided	not provided	germline	not provided	not provided

Laboratory for Molecular Medicine

Observations

Families	Individuals	Segregation	Allele origin	Observed phenotypes	Ethnicity	Geographic origin	Collection method	Description
4	not provided	not provided	germline	not provided	not provided	not provided	clinical testing	See description

This variant has been identified in 4.2% of controls(rs41298135) and functional studies do not show an impact to protein function (Watanabe 2008).

OMIM

Data published from literature

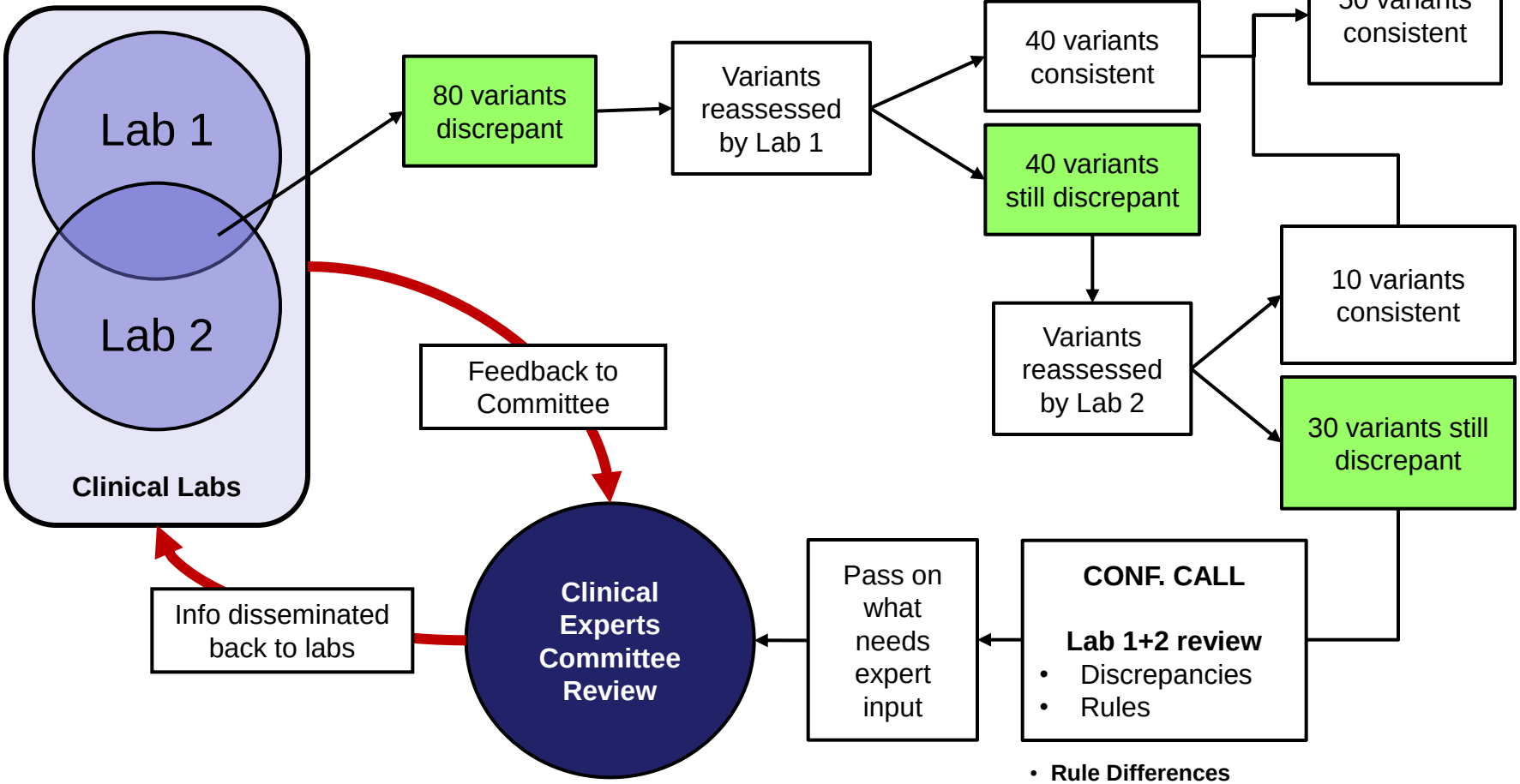
Families	Individuals	Segregations	Allele origin	Citations
not provided	not provided	not provided	germline	PubMed [See all records that cite this PMID]

Description

Weston et al. (1996) found that 8 of 23 mutant alleles detected in their study of Usher syndrome type IB were either R212H or R212C. In some instances, the R212H mutation was in cis with an R302H (276903.0006) mutation in exon 9. Affected sibs in a Dutch family were homozygous for the double mutation at both codons, while the affected sibs in a Finnish family showed only paternal inheritance of both mutations. Both R302H and R212H have been observed singly in affected persons; neither has been observed in controls, either singly or as double mutations. Although these 3 mutations were the most common ones observed, comprising approximately 50% of all mutations found, they still represented less than 3% of the total USH1B chromosomes studied. Furthermore, no linkage disequilibrium between USH1B and several adjacent polymorphic markers was found, suggesting that there are several independently occurring mutations rather than a common USH1B allele.

Last Updated: Jun 28, 2014

VARIANT HARMONIZATION (LMM – EMORY GENETICS LAB)



Expert Committee Review

- Discuss classification rules
- Review discrepant variants with input from experts in that disease and assign classification

- **Rule Differences**
  - Silent (VUS vs LB)
  - Differences in frequency cut-offs
- **Reporting differences influence stringency!**
  - *Lab 1 excludes Lik Ben, Lab 2 includes*
  - *Greater willingness of Lab 1 to classify as Lik Ben!*
- **Other (use of computational data)**
  - *1/80 variants* needs expert input
  - *atypical GLA/Fabry variant*

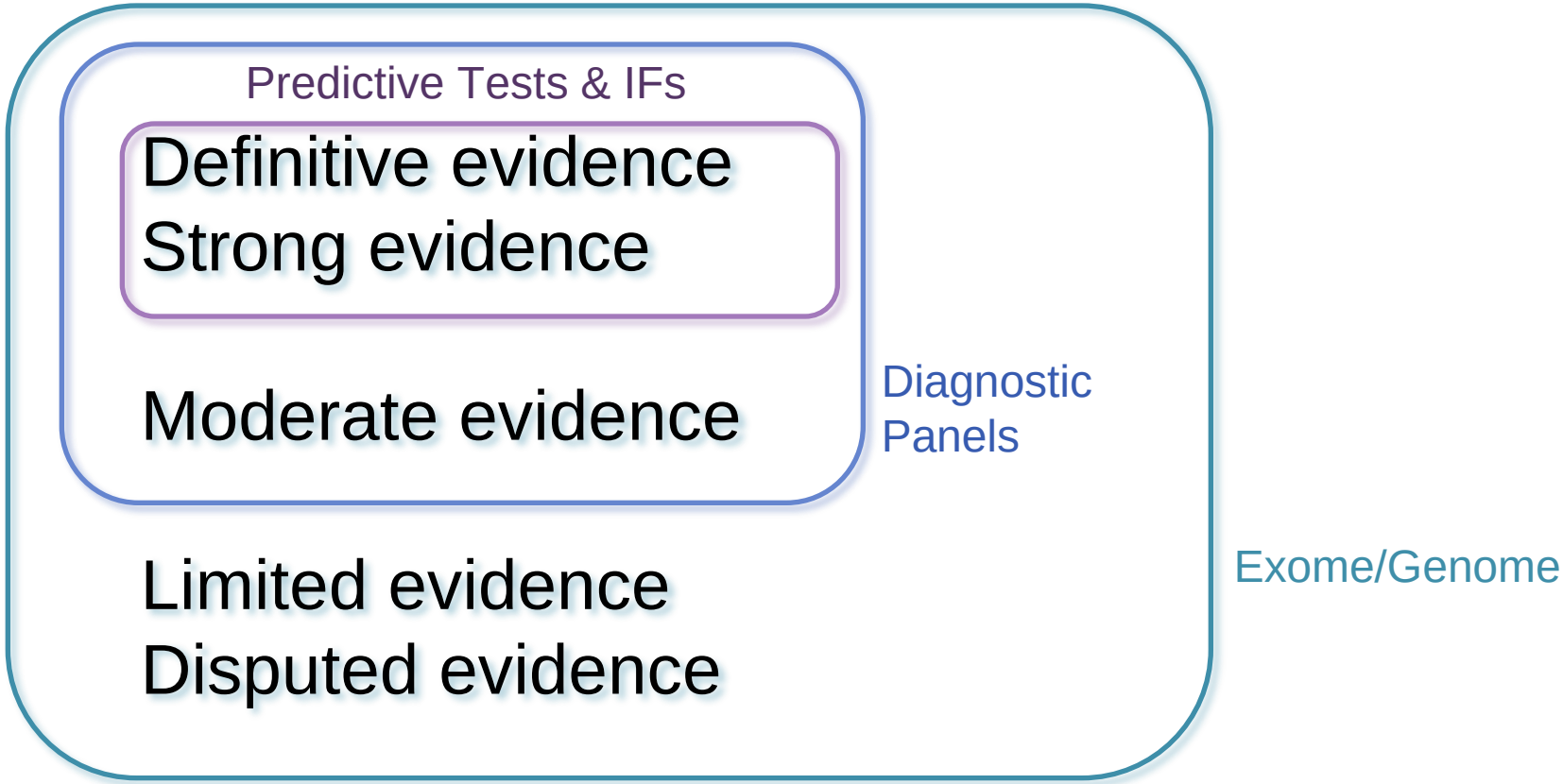
Courtesy of Birgit Funke

Evaluating Evidence for Gene-Disease Associations

Definitive evidence
Strong evidence
Moderate evidence
Limited evidence
No evidence
Disputed evidence
Evidence against

Evidence Level	Evidence Description
DEFINITIVE	The role of this gene in this particular disease has been repeatedly demonstrated in both the research and clinical diagnostic settings, and has been upheld over time (in general, at least 3 years). No valid evidence has emerged that contradicts the role of the gene in the specified disease.
STRONG	There is **strong** evidence by at least two independent studies to support a causal role for this gene in this disease, such as: •Strong statistical evidence demonstrating an excess of pathogenic variants[1] in affected individuals as compared to appropriately matched controls •Multiple pathogenic variants[1] within the gene in unrelated probands with several different types of supporting experimental data[2]. The number and type of evidence might vary (eg. fewer variants with stronger supporting data, or more variants with less supporting data) In addition, no valid evidence has emerged that contradicts the role of the gene in the noted disease.
MODERATE	There is **moderate** evidence to support a causal role for this gene in this disease, such as: •At least 3 unrelated probands with pathogenic variants[1] within the gene with some supporting experimental data[2]. The role of this gene in this particular disease may not have been independently reported, but no valid evidence has emerged that contradicts the role of the gene in the noted disease.
LIMITED	There is **limited** evidence to support a causal role for this gene in this disease, such as: •Fewer than three observations of a pathogenic variant[1] within the gene •Multiple variants reported in unrelated probands but *without* sufficient evidence for pathogenicity per 2014 ACMG criteria
NO EVIDENCE	No evidence reported for a causal role in disease.
DISPUTED	Valid evidence of approximate equivalent weight exists both supporting and refuting a role for this gene in this disease.
EVIDENCE AGAINST	Evidence refuting the role of the gene in the specified disease has been reported and significantly outweighs any evidence supporting the role.

Proposed Evidence Required to Include a Gene In a Clinical Test?



Hearing Loss and Related Disorders (Genes)							
Gene	Evid.	Inher.	Mutation Spect.	NonSynd.	Synd.	Phenotype	
						HL	Other
ACTG1	3	AD	M	X[3]	X[2]	Postlingual, progressive sloping SNHL	Baraitser-Winter syndrome
ATP6V1B1	3	AR	M, LOF		X	Childhood onset, progressive sloping SNHL	Distal renal tubular acidosis
BSND	3	AR	M, LOF	X[1]	X[3]	Prelingual, severe to profound, flat SNHL	Bartter Syndrome
CABP2	2	AR	LOF	X		Prelingual, moderate to sever, cookie-bite SNHL	
CACNA1D	2	AR	LOF		X	Congenital, severe to profound, flat SNHL	Bradycardia and deafness
CCDC50	2	AD	LOF	X		Postlingual, progressive, moderate to profound SNHL	
CDH23	3	AR	M, LOF	X[3]	X[3]	Congenital, moderate to profound SNHL	Usher type 1
CEACAM16	2	AD	M	X		Postlingual, progressive, moderate SNHL	
CIB2	3	AR	M	X[3]	X[1]	Prelingual, severe to profound, flat SNHL	Usher type 1J
CISD2	3	AR	M/LOF		X	Variable onset, progerssive SNHL	WFS2
CLDN14	3	AR	M, LOF	X		Prelingual, flat SNHL (variable progression)	
CLPP	3	AR	M, LOF		X	Congenital, severe to profound, flat SNHL	Perrault Syndrome
CLRN1	3	AR	M, LOF		X	Variable onset, progerssive, moderate to severe SNHL	Usher type 3A
COCH	3	AD	M	X		Postlingual, progressive, profound SNHL	Vestibular impairment
COL11A2	3	AD[3]	M, In-frame del	X[3]		Congenital, mild to moderately severe cookie-bite SNHL	
					X[3]	Childhood/adulthood onset, mild to moderate SNHL	Non-ocular stickler (STL3)
		AR[3]	M, LOF	X[1-2]		Prelingual, profound, flat/cookiee-bite SNHL	
					X[3]	Childhood, moderate to profound. Flat SNHL	OSMED
DIABLO	3	AD	M	X		Adulthood onset, progressive, mild to moderate, flat SNHL	
DFNA5	2	AD	Exon 8 skipping	X		Postlingual, progressive SNHL	
DFNB59	3	AR	M, LOF	X		Prelingual, severe to profound, flat SNHL	Auditory neuropathy
DIAPH1	3	AD	M, LOF	X		Postlingual, low frequency progressive SNHL	
EDN3	3	AD/AR	M, LOF		X	Variable HL	Waardenburg type 4B
EDNRB	3	AD/AR	M, LOF		X	Variable HL	Waardenburg type 4B
ESPN	3	AD[3], AR[3]	LOF	X		Prelingual, severe to profound, flat SNHL	Vestibular areflexia, in some
ESRRB	3	AR	M*, LOF	X		Early onset, severe to profound, flat/slightly sloping SNHL	
EYA1	3	AD	M, LOF		X	Variable onset, mild to profound SNHL	BOR
EYA4	3	AD	LOF	X		Postlingual, progressive, moderate to profound, flat SNHL	
GIPC3	3	AR	M, LOF	X		Prelingual, mild to profound, flat SNHL	
GJB2	3	AD[3]	M	X[2-3]		Congenital/late onset, mild to profound SNHL	
					X[2-3]	Childhood onset, moderate to severe, high frequency SNHL	Dermatologic manifestations
		AR[3]	M, LOF	X		Congenital/childhood onset, mild to profound SNHL	
GJB6	3	AR	del	X[4]		Congenital/childhood onset, mild to profound SNHL	GJB2 dowregulation
		AD	M		X[2]	_	Hidrotic Ectodermal dysplasia
			M, LOF	X[1]		Variable SNHL	
GPR98	3	AR	M, LOF		X	Prelingual, moderate to profound, sloping SNHL	Usher type 2
GPSM2	3	AR	LOF			Prelingual, severe to profound, slightly sloping SNHL	McCullough syndrome
GRHL2	3	AD	LOF	X		Postlingual, progressive, mild to severe SNHL	
GRXCR1	2	AR	M, LOF	X		Congenital, moderate to profound, flat/slightly sloping SNHL	
HARS#	1-2	AR	M		X	Childhood onset, progressive SNHL	Usher type 3B
HARS2	2	AR	M		X	Childhood/teenage onset, progressive, mild to severe, flat SNHL	Perrault Syndrome
HGF	2	AR	Intronic del, splic	X		Prelingual, severe to profound, sloping SNHL	
HSD17B4	2	AR	M, LOF		X	Childhood onset, moderate to severe SNHL	Perrault Syndrome
ILDR1	3	AR	M, LOF*	X		Prelingual, moderate to profound, sloping SNHL	
KARS	3	AR	M	X[2]	X[2]	Prelingual, moderate to severe, flat SNHL	Peripheral neuropathy
KCNE1	3	AR	M		X	Congenital, severe to profound, flat SNHL	JLNS/Prolonged QT
KCNQ1	3	AR	M, LOF		X	Congenital, severe to profound, flat SNHL	JLNS/Prolonged QT
KCNQ4	3	AD	M, LOF	X		Postlingual, progressive, sloping SNHL	
LARS2	2	AR	M, LOF		X	Childhood onset, progressive, mild to severe, slightly rising SNHL	Perrault Syndrome
LHFPL5	3	AR	M, LOF	X		Prelingual, severe to profound SNHL	
LOXHD1	3	AR	M, LOF*	X[3]	X[1]	Variable onset, variable SNHL	Fuchs corneal dystrophy
LRTOMT	3	AR	M, LOF	X		Congenital, moderate to profound, flat SNHL	
MARVELD2	3	AR	LOF	X		Prelingual, moderate to profound, flat/sloping SNHL	
MIR96	3	AD	Seed region	X[3]	X[1]	Postlingual, progressive, flat/sloping SNHL	Vertigo in some
MITF	3	AD	M, LOF		X	Variable HL	Waardenburg type 2
MSRB3	2	AR	M, LOF	X		Prelingual, severe to profound, flat SNHL	
MTRNR1	3	Mito.	Point mutat.	X		Variable, progressive SNHL	Aminoglycoside exposure
MTTS1	3	Mito.	Point mutat.	X		Variable, progressive SNHL	
MYH14	3	AD	M*, LOF	X[3]	X[1]	Postlingual, moderate to profound, flat SNHL	Peripheral neuropathy
MYH9	3	AD	M*, LOF	X[2]	X[3]	Variable onset, progressive SNHL	Macrothrombocytopenia
MYO15A	3	AR	M, LOF	X		Congenital, severe to profound, flat SNHL	
MYO3A	3	AR	LOF	X		Postlingual, progressive, moderate to severe, sloping SNHL	
MYO6	3	AD[3]	M, LOF	X		Postlingual, progressive, moderate to profound sloping SNHL	
		AR[3]	LOF	X		Congenital, profound SNHL	Vestibular impairment in some
MYO7A	3	AR	M, LOF		X[3]	Congenital, severe to profound, flat SNHL	Usher type 1
			M, LOF	X[3]		Congenital, severe to profound, flat SNHL	Vestibular impairment
		AD	M, In-frame del	X[2]		Postlingual, mild to severe SNHL	Vestibular impairment
OTOA	3	AR	M, LOF	X		Prelingual, severe to profound, flat SNHL	
OTOF	3	AR	M, LOF	X		Congenital, severe to profound, flat SNHL	Auditory neuropathy
OTOG	2	AR	M, LOF	X		Prelingual/childhood onset, moderate, flat/slightly sloping SNHL	Vestibular impairment in some
OTOGL	3	AR	LOF	X		Congenital, moderate to modertaley severe, sloping SNHL	
P2RX2	3	AD	M	X		Teenage onset, progressive, moderately severe, flat SNHL	High frequency tinnitus
PAX3	3	AD	M, LOF		X	Variable HL	Waardenburg type 1 and 3
PCDH15	3	AR	M, LOF	X[3]	X[3]	Congenital, profound, flat SNHL	Usher type 1
POU3F4	3	X-linked	M, LOF	X		Cogenital, moderate to profound, flat mixed HL	IAC dilation/Perilymph. Gusher
POU4F3	3	AD	M, LOF	X		Adult onset, progressive, moderate to severe, sloping SNHL	
PRPS1	3	X-linked	M	X[3]	X[3]	Postlingual, progressive, severe to profound, flat SNHL	PRS-I/Arts/CMT
PTPRQ	3	AR	M, LOF	X		Congenital, moderate to profound, flat SNHL	
RDX	3	AR	M, LOF	X		Prelingual, severe to profound, flat SNHL	
SERPINB6	2	AR	LOF	X		Postlingual, moderate to severe, sloping SNHL	
SIX1	3	AD	M, LOF		X	Variable (3wk-22y) onset, mild to severe, mixed HL	BOR
SLC26A4	3	AR	M, LOF	X[3]	X[3]	Congenital, progressive, severe to profound, SNHL	Pendred/EVA
SMPX	3	X-linked	LOF	X		Postlingual, progressive, moderate to profound, flat/sloping SNHL	
SNAI2	1-2	AR	del		X	Severe/profound HL	Waardenburg type 2D
SOX10	3	AD	M, LOF		X	Variable HL	Waardenburg types 2E and 4C
STRC	3	AR	M, LOF, del	X[3]	X[3]	Childhood onset, mild to moderate, sloping SNHL	Deafness Infertility Syndrome
SYNE4	2	AR	LOF	X		pre/postlingual progressive, mild to profound, sloping SNHL	
TBC1D24	3	AR	M	X[3]	X[3]	Prelingual, profound, flat SNHL	Epilepsy
TECTA	3	AD[3]	M	X		Pre/postlingual, progressive (in some), mild to severe SNHL	
		AR[2]	LOF	X		Prelingual, moderate to profound, high/mid frequency SNHL	
TIMM8A	3	X-linked	M, LOF*		X	Congenital/early childhood onset, progressive, profound flat SNHL	Mohr-Tranebjaerg syndrome
TMC1	3	AD[3]	M	X		Postlingual, progressive SNHL	
		AR[3]	LOF	X		Congenital, profound, flat /slightly slopingSNHL	
TMIE	3	AR	M, LOF	X		Congenital, severe to profound, flat SNHL	
TMPRSS3	3	AR	M, LOF	X		Congenital/childhood onset, severe to profound, flat SNHL	
TPRN	3	AR	LOF	X		Prelingual, severe to prfound, flat/slighty sloping SNHL	
TRIOBP	3	AR	LOF	X		Prelingual, severe to profound, flat SNHL	
TSPEAR	2	AR	LOF	X		Congenital, profound, flat SNHL	
USH1C	3	AR	M, LOF	X[3]	X[3]	Prelingual, severe to profound, flat SNHL	Usher type 1
USH1G	3	AR	M, LOF*		X	Congenital, profound, flat SNHL	Usher type 1
USH2A	3	AR	M, LOF		X	Prelingual, moderate to profound, sloping SNHL	Usher type 2
WFS1	3	AD[3]	M	X[3]		Congenital, slowly progressive, low frequency SNHL	
					X[2]	Childhood onset, progressive, mild to moderate, low-mid freq. SNHL	WFS-like disorder
		AR[3]	M, LOF		X[3]	Early onset, progressive, high freq. SNHL	Wolfram syndrome
VHRN/DFNB31	3	AR	M, LOF*	X[3]	X[3]	Prelingual, moderate to profound, sloping SNHL	Usher type 2

Key:

1 - Weak Association
2 - Moderate Association
3 - Definitive Association
* - Most common
# - included on subpanel only

Gene included on Subpanel:

Usher syndrome panel

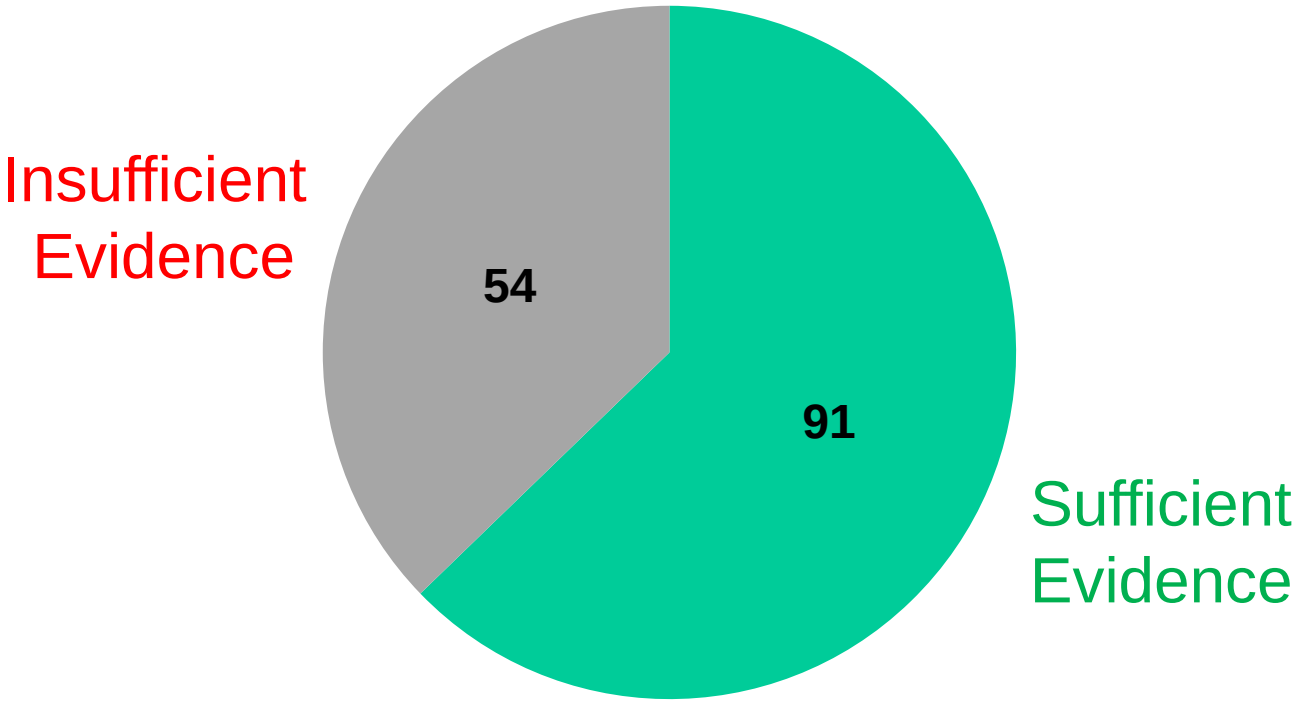
Ahmad
Abou Tayoun

Sami Amr

GJB6	3	AR	del	X		Congenital/childhood onset, mild to profound SNHL	GJB2 dowregulation
		AD	M		X[2]	_	Hidrotic Ectodermal dysplasia
			M, LOF	X[1]		Variable SNHL	
GPR98	3	AR	M, LOF		X	Prelingual, moderate to profound, sloping SNHL	Usher type 2
GPSM2	3	AR	LOF			Prelingual, severe to profound, slightly sloping SNHL	McCullough syndrome
GRHL2	3	AD	LOF	X		Postlingual, progressive, mild to severe SNHL	
GRXCR1	2	AR	M, LOF	X		Congenital, moderate to profound, flat/slightly sloping SNHL	
HARS[#]	1-2	AR	M		X	Childhood onset, progressive SNHL	Usher type 3B
HARS2	2	AR	M		X	Childhood/teenage onset, progressive, mild to severe, flat SNHL	Perrault Syndrome
HGF	2	AR	Intronic del, splic	X		Prelingual, severe to profound, sloping SNHL	
HSD17B4	2	AR	M, LOF		X	Childhood onset, moderate to severe SNHL	Perrault Syndrome
ILDR1	3	AR	M, LOF*	X		Prelingual, moderate to profound, sloping SNHL	
KARS	3	AR	M	X[2]	X[2]	Prelingual, moderate to severe, flat SNHL	Peripheral neuropathy
KCNE1	3	AR	M		X	Congenital, severe to profound, flat SNHL	JLNS/Prolonged QT
KCNQ1	3	AR	M, LOF		X	Congenital, severe to profound, flat SNHL	JLNS/Prolonged QT
KCNQ4	3	AD	M, LOF	X		Postlingual, progressive, sloping SNHL	
LARS2	2	AR	M, LOF		X	Childhood onset, progressive, mild to severe, slightly rising SNHL	Perrault Syndrome
LHFPL5	3	AR	M, LOF	X		Prelingual, severe to profound SNHL	
LOXHD1	3	AR	M, LOF*	X[3]	X[1]	Variable onset, variable SNHL	Fuchs corneal dystrophy
LRTOMT	3	AR	M, LOF	X		Congenital, moderate to profound, flat SNHL	
MARVELD2	3	AR	LOF	X		Prelingual, moderate to profound, flat/sloping SNHL	
MIR96	3	AD	Seed region	X[3]	X[1]	Postlingual, progressive, flat/sloping SNHL	Vertigo in some
MITF	3	AD	M, LOF		X	Variable HL	Waardenburg type 2
MSRB3	2	AR	M, LOF	X		Prelingual, severe to profound, flat SNHL	
MTRNR1	3	Mito.	Point mutat.	X		Variable, progressive SNHL	Aminoglycoside exposure
MTTS1	3	Mito.	Point mutat.	X		Variable, progressive SNHL	
MYH14	3	AD	M*, LOF	X[3]	X[1]	Postlingual, moderate to profound, flat SNHL	Peripheral neuropathy
MYH9	3	AD	M*, LOF	X[2]	X[3]	Variable onset, progressive SNHL	Macrothrombocytopenia
MYO15A	3	AR	M, LOF	X		Congenital, severe to profound, flat SNHL	
MYO3A	3	AR	LOF	X		Postlingual, progressive, moderate to severe, sloping SNHL	
MYO6	3	AD[3]	M, LOF	X		Postlingual, progressive, moderate to profound sloping SNHL	
		AR[3]	LOF	X		Congenital, profound SNHL	Vestibular impairment in some
MYO7A	3	AR	M, LOF		X[3]	Congenital, severe to profound, flat SNHL	Usher type 1
			M, LOF	X[3]		Congenital, severe to profound, flat SNHL	Vestibular impairment
		AD	M, In-frame del	X[2]		Postlingual, mild to severe SNHL	Vestibular impairment
OTOA	3	AR	M, LOF	X		Prelingual, severe to profound, flat SNHL	
OTOF	3	AR	M, LOF	X		Congenital, severe to profound, flat SNHL	Auditory neuropathy
OTOG	2	AR	M, LOF	X		Prelingual/childhood onset, moderate, flat/slightly sloping SNHL	Vestibular impairment in some
OTOGL	3	AR	LOF	X		Congenital, moderate to modertaley severe, sloping SNHL	
P2RX2	3	AD	M	X		Teenage onset, progressive, moderately severe, flat SNHL	High frequency tinnitus
PAX3	3	AD	M, LOF		X	Variable HL	Waardenburg type 1 and 3
PCDH15	3	AR	M, LOF	X[3]	X[3]	Congenital, profound, flat SNHL	Usher type 1
POU3F4	3	X-linked	M, LOF	X		Cogenital, moderate to profound, flat mixed HL	IAC dilation/Perilymph. Gusher
POU4F3	3	AD	M, LOF	X		Adult onset, progressive, moderate to severe, sloping SNHL	
PRPS1	3	X-linked	M	X[3]	X[3]	Postlingual, progressive, severe to profound, flat SNHL	PRS-I/Arts/CMT
PTPRQ	3	AR	M, LOF	X		Congenital, moderate to profound, flat SNHL	

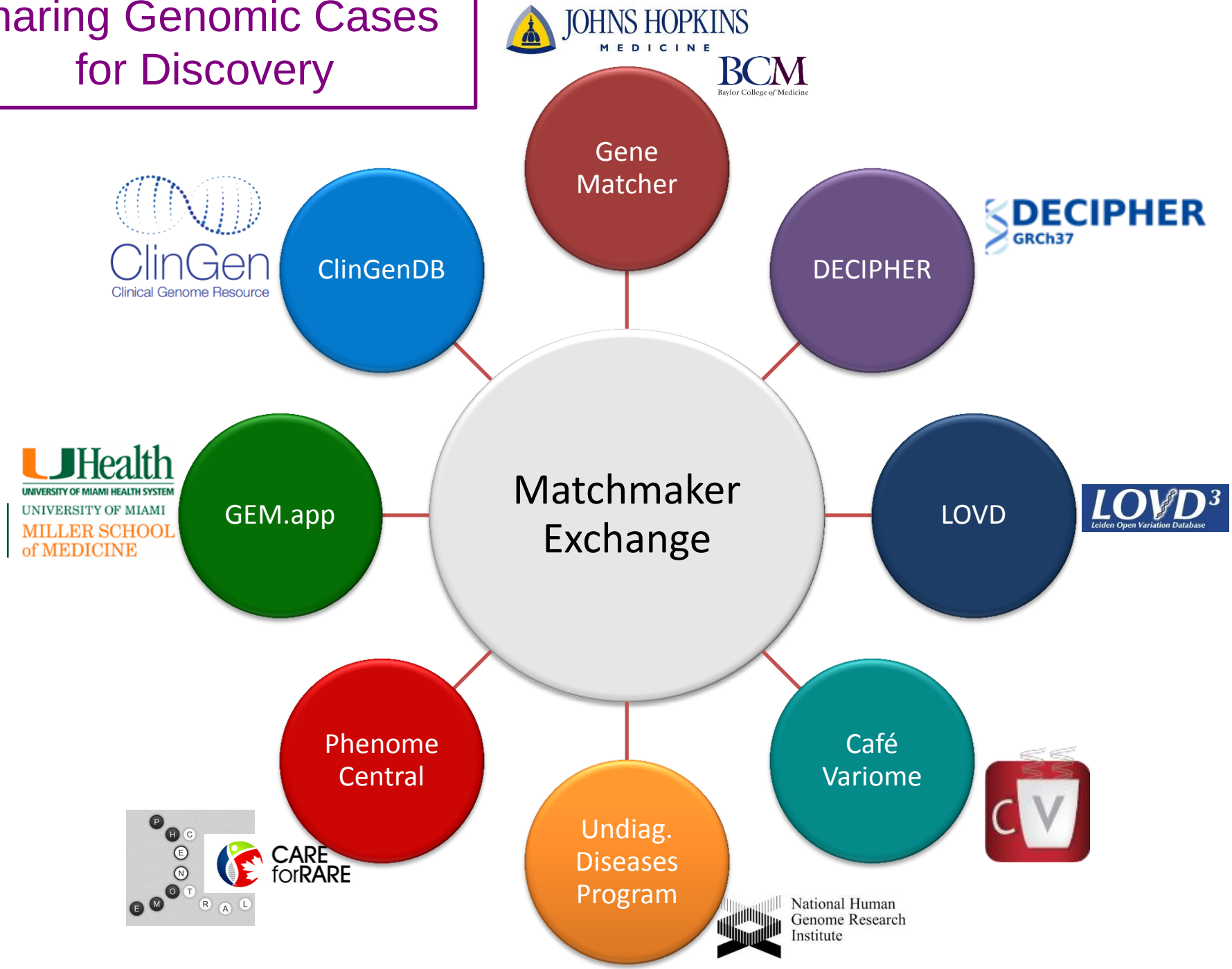
Hearing Loss Gene Assessment

of 145 genes with published hearing loss associations



Courtesy of Ahmad Abou Tayoun

Sharing Genomic Cases for Discovery



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