70TH ESCVS CONGRESS & 7TH IMAD MEETING

Variant curation:
tips and tricks

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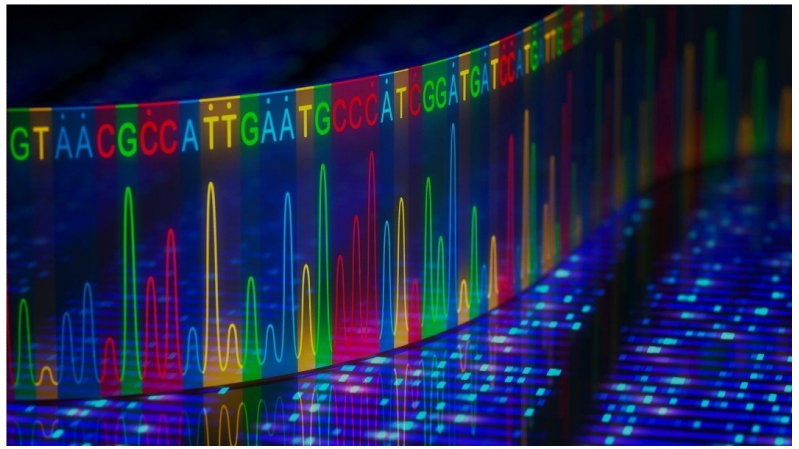
ANEURYSMAL PATHOLOGY Foundation 2009

Challenges of next generation sequencing



Loads of data

Challenge:
Distinguish which variants cause disease and which are normal genetic variations

Albinism:
OCA2

Variant classification guidelines

2015

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards [1], Nazneen Aziz [2], Sherri Bale [3], David Bick [4], Soma Das [5], Julie Gastier-Foster [6], Wayne W Grody [7], Madhuri Hegde [8], Elaine Lyon [9], Elaine Spector [10], Karl Voelkerding [9], Heidi L Rehm [11], ACMG Laboratory Quality Assurance Committee

2022

Stepwise ABC system for classification of any type of genetic variant

Gunnar Houge [1] · Andreas Laner [2] · Sebahattin Cirak [3] · Nicole de Leeuw [4] · Hans Scheffer [4] · Johan T. den Dunnen [5]

2017

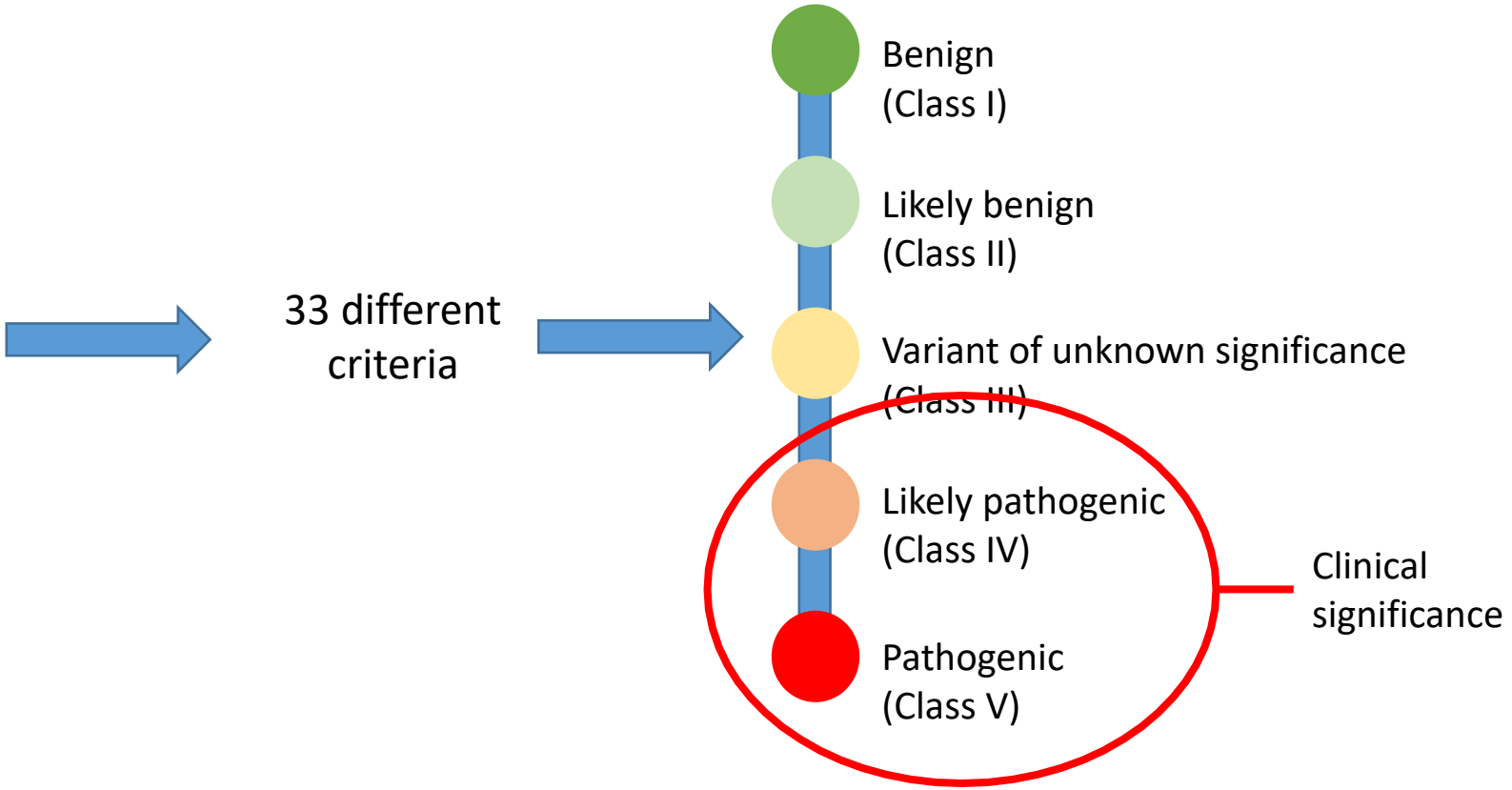
Sherloc: a comprehensive refinement of the ACMG–AMP variant classification criteria

Keith Nykamp, PhD[1], Michael Anderson, PhD[1], Martin Powers, MD[1], John Garcia, PhD[1], Blanca Herrera, PhD[1], Yuan-Yuan Ho, PhD[1], Yuya Kobayashi, PhD[1], Nila Patil, PhD[1], Janita Thusberg, PhD[1], Marjorie Westbrook, PhD[1], The Invitae Clinical Genomics Group[2] and Scott Topper, PhD, FACMG[1]

ACMG guidelines

5 categories

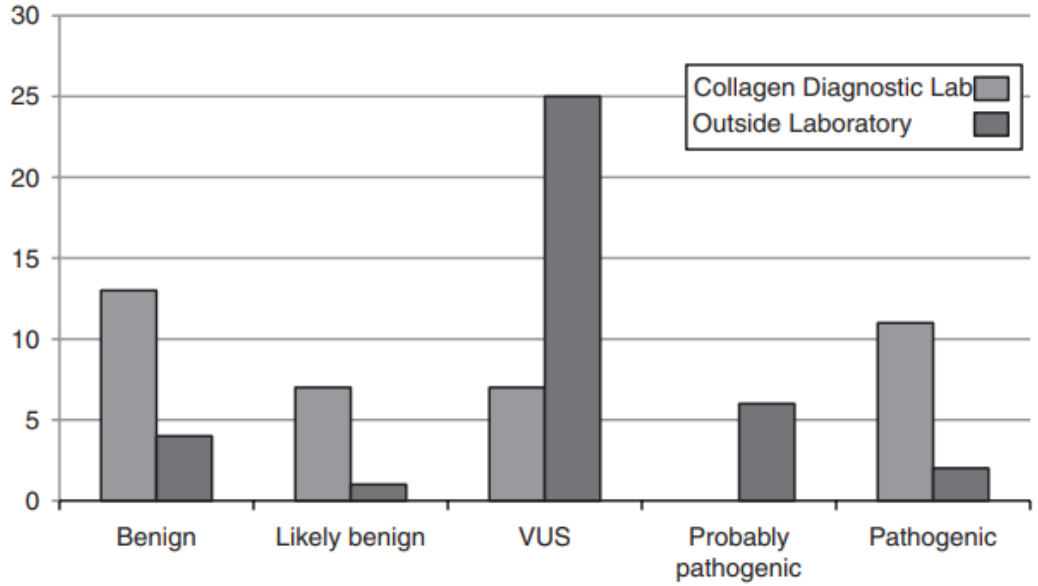
- Frequency in the general population
- Phenotypic features
- Computational predictions
- Functional data
- Segregation data



Richards et al., *Genet Med* 2015

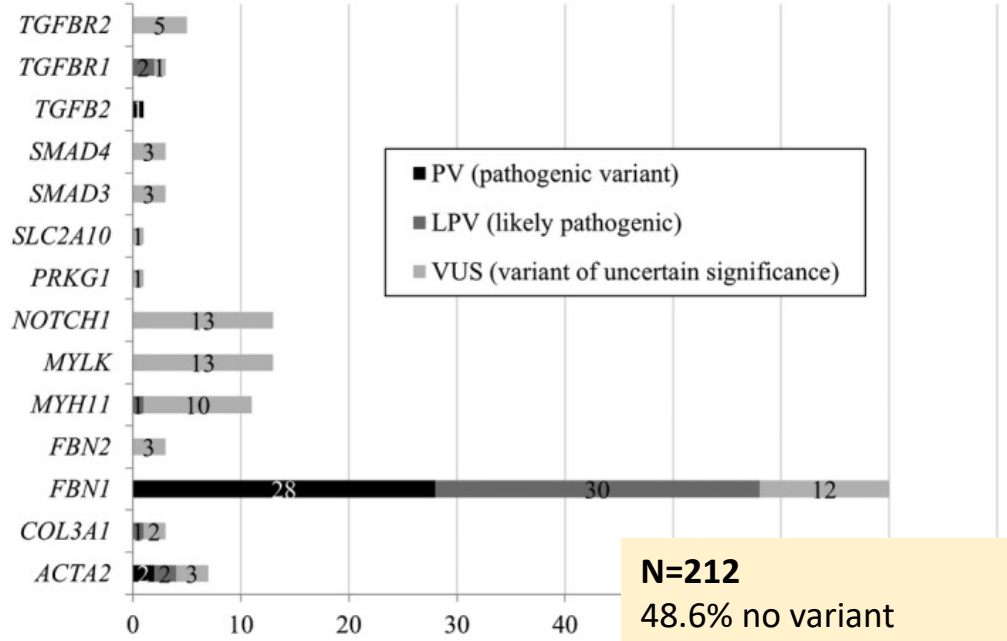
Major challenges

(1) Classification differs between labs



Pepin et al., *Genet Med* 2016

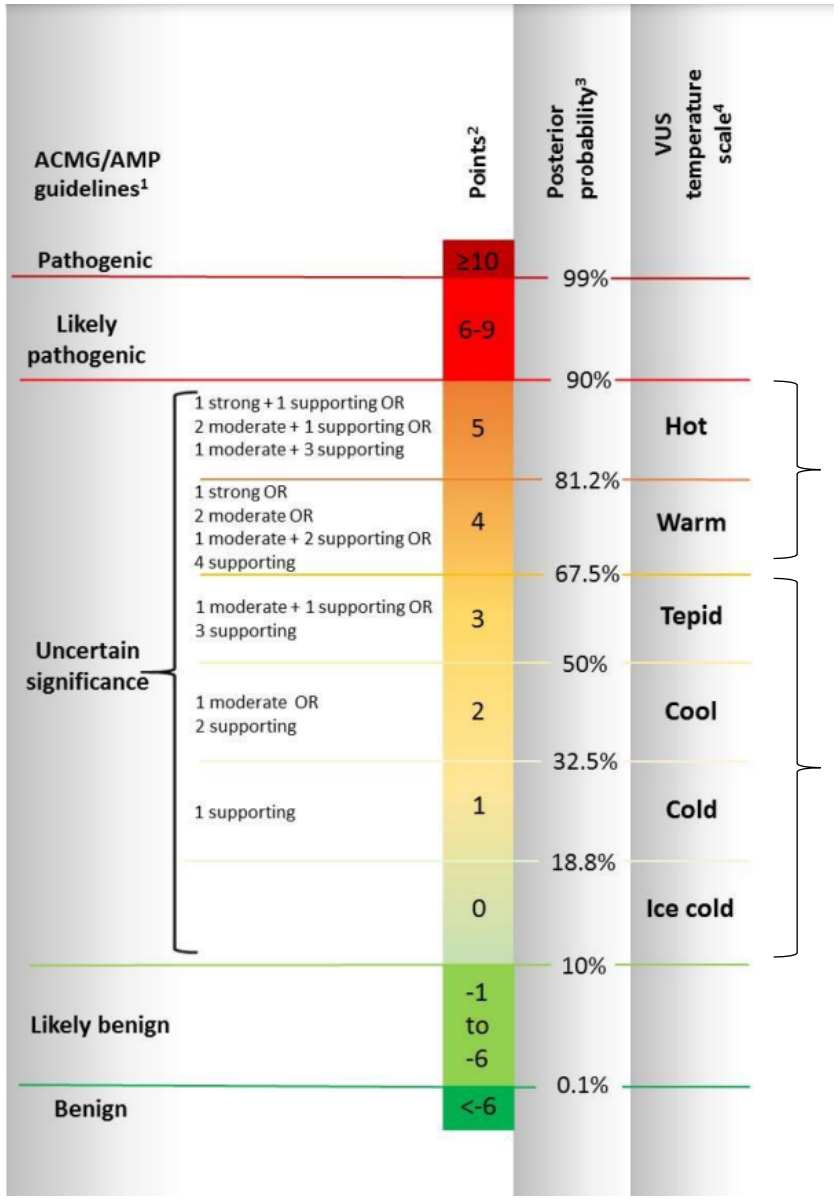
(2) High amount of variants of unknown significance



Lit et al; Mol Gent Genomic Med 2021

N=212
48.6% no variant
31,6% LP/P
19,8% VUS

Not all VUS are the same!

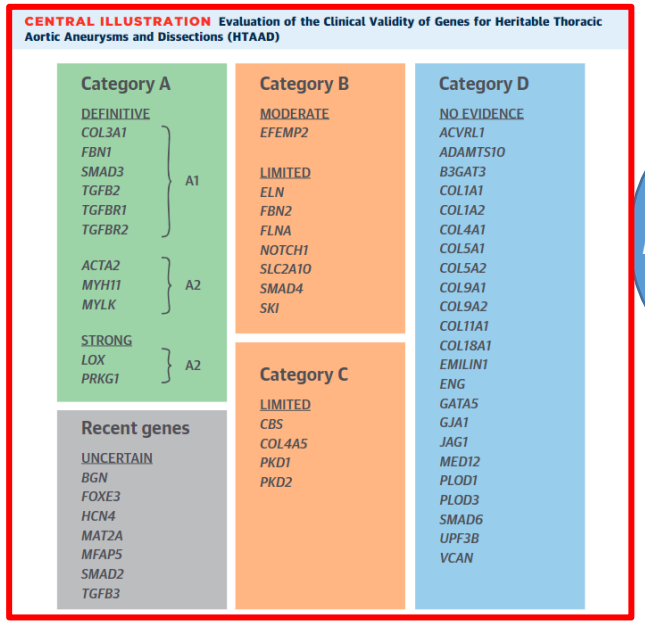


To be communicated to patients
Further work-out if necessary and possible
Future reclassification

Not to be communicated to patients

Ellard et al., *ACGS*, 2020

TIPS AND TRICKS TO INCREASE CONSISTENCY AND DECREASE VUS



Renard et al., *JACC* 2018

Gene curation
Is a gene associated with the disease?

↑ clinical validity of genes
↑ gene-specific knowledge

Gene specific-guidelines

ClinGen
Clinical Genome Resource

ClinGen FBN1 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1
This version specified for the following genes: *FBN1*
Expert Panel Page: https://www.clinicalgenome.org/affiliation/50046

ACMG Classification Rules Specified for Fibrillin-1 (FBN1) Variants

Gene	Disease (MONDO ID)	Transcript
FBN1	MONDO: 0007947	NM_000138

Gene specific-knowledge
Specific features

Ectopia lentis + TAD = FBN1
Periventricular nodular heterotopia + TAD = FLNA

ACMG general guidelines:
PM1: Located in a mutational hot spot and/or critical and well-established functional domain

ACMG specified rules for *FBN1*:
PM1_strong: Affecting Cys residues in cb-EGF domain
PM1: Cys in EGF-like domain, Cys in TB domain, Cys in hybrid domain, **(D/N)**-X-**(D/N)**-**(E/Q)**-Xm-**(D/N)**-Xn-**(Y/F)** substitution in cbEGF-like domain, invariant calcium-binding or hydroxylation residue in cbEGF-like domain, critical Gly between Cys2-Cys3 in cbEGF-like domain, Gly between Cys3-Cys4 if there is an upstream cbEGF domain, Cys-creating variants

https://www.clinicalgenome.org/site/assets/files/7445/clingen_fbn1_acmg_specifications_v1.pdf

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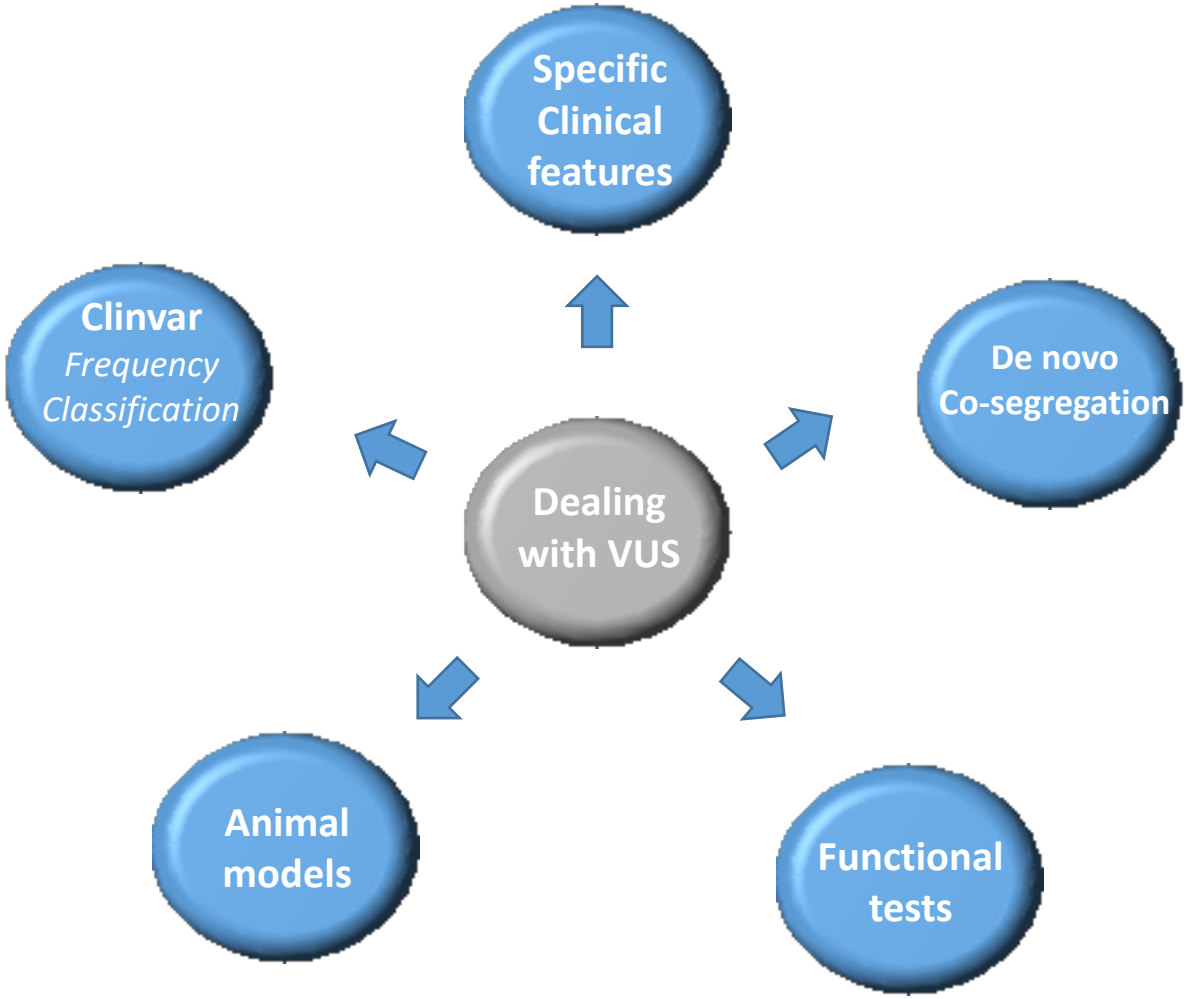
TIPS AND TRICKS TO INCREASE CONSISTENCY AND DECREASE VUS



CONCLUSION

1. The advent of NGS has been a great step forward in genetic diagnosis but has brought alone the difficult task of variant classification.

2. There are still too many variants of unknown significance and seeking the way to decrease these numbers is very important for clinical decision making.

3. Gene curation, gene specific guidelines and gene specific knowledge can aid in reducing the amount of VUS

4. Further investigations might be necessary to learn the significance of a certain variant

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Thank you!

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