Perspectives on Existing Genetic Variation Resources: A Researcher's Perspective

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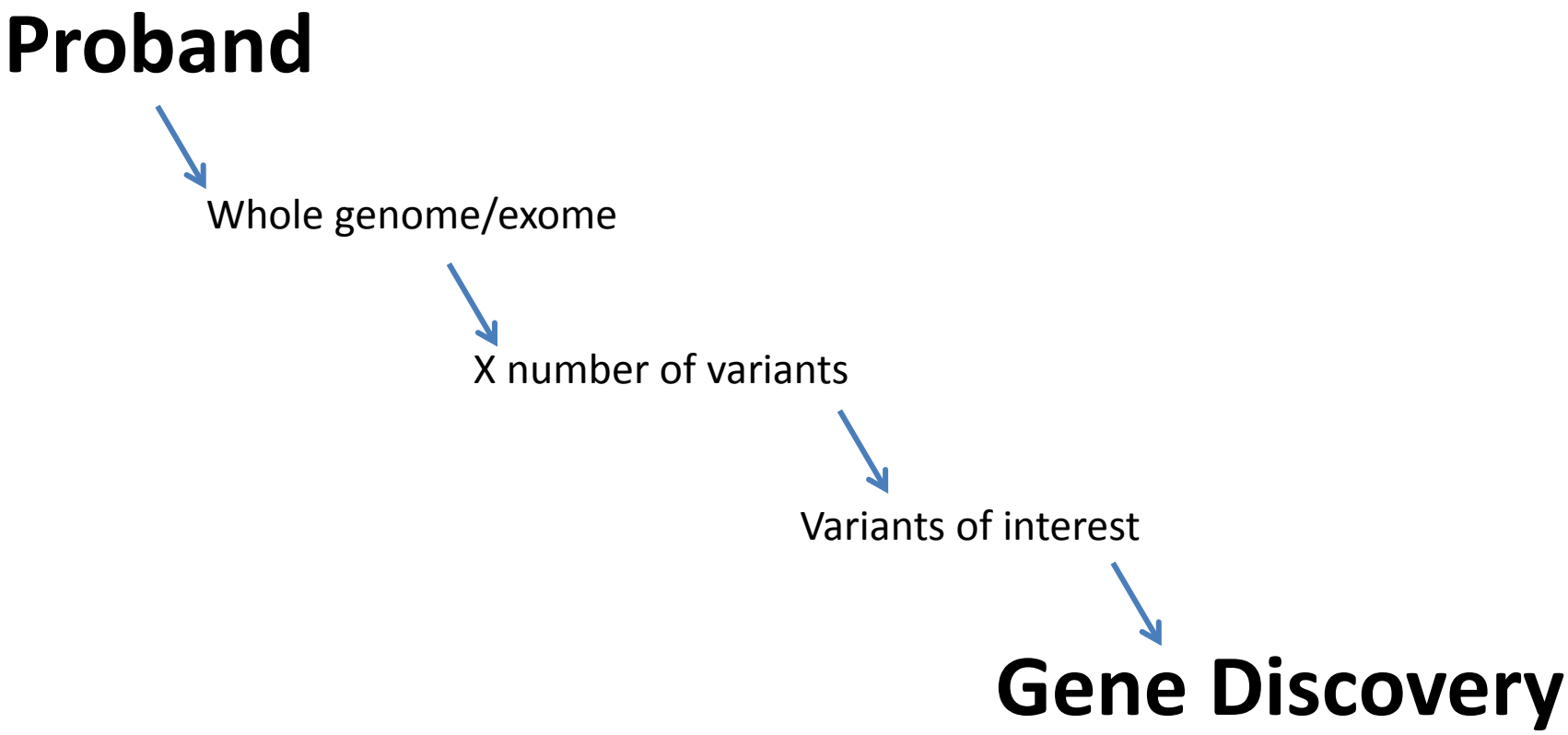
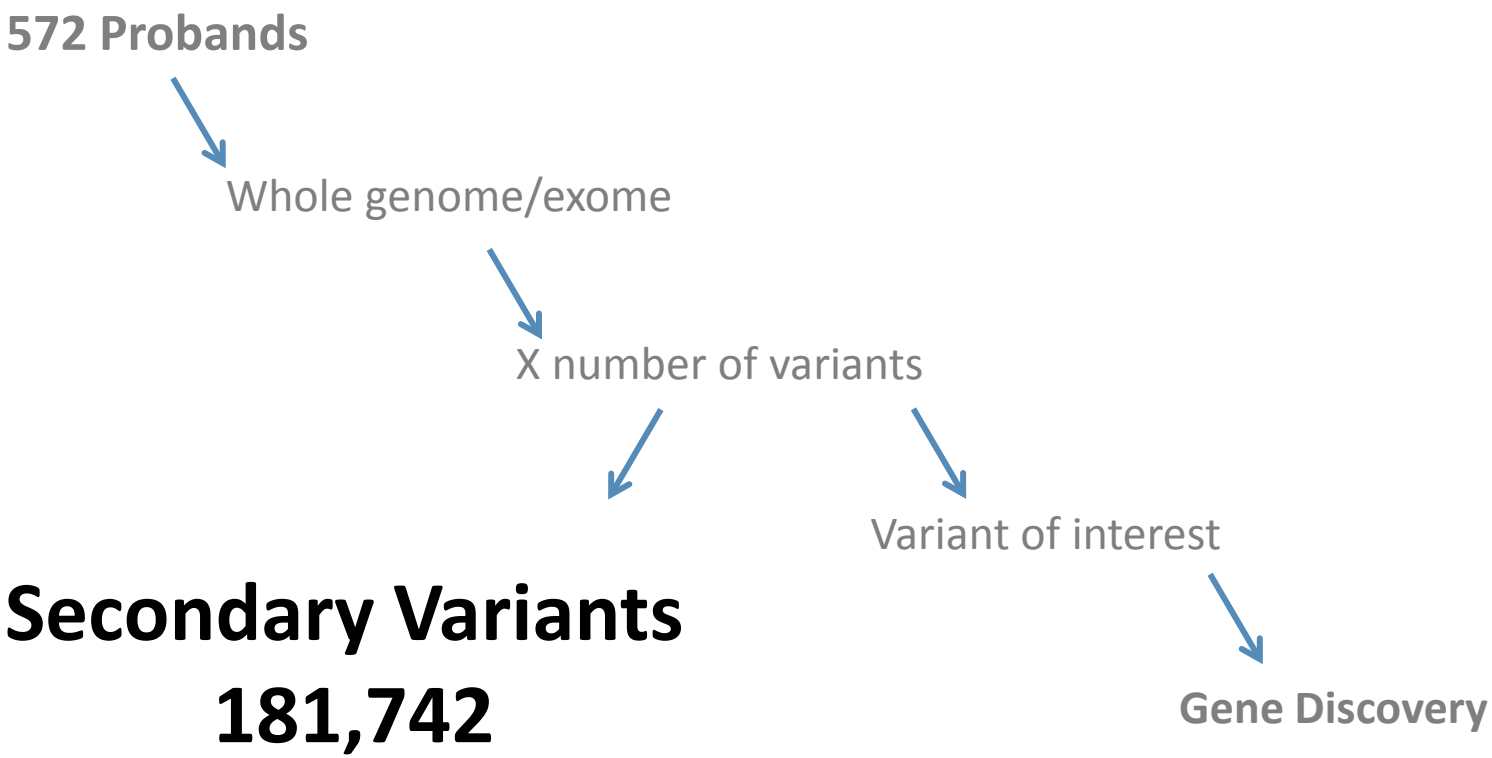
NHGRI

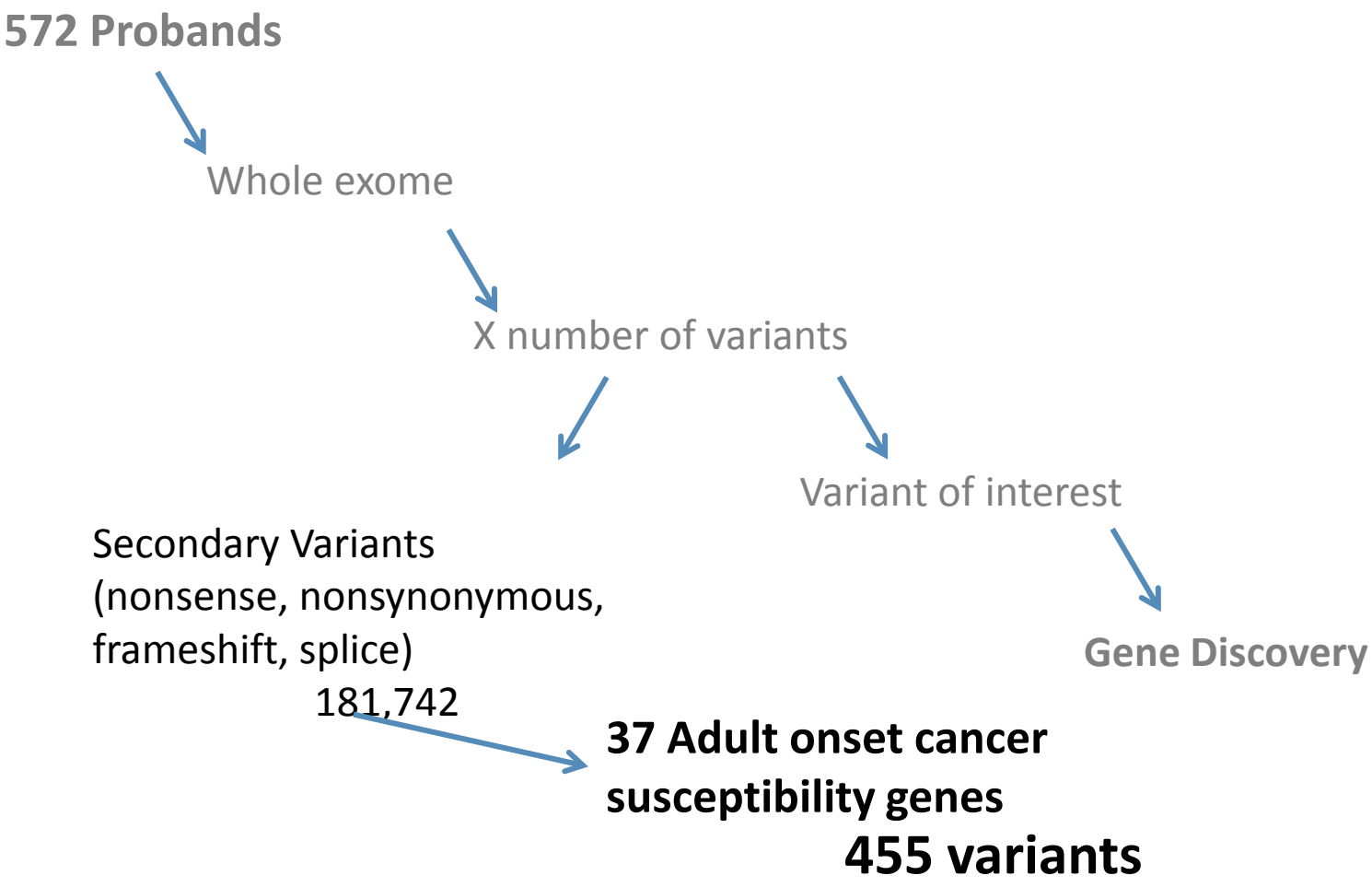
Primary Variant



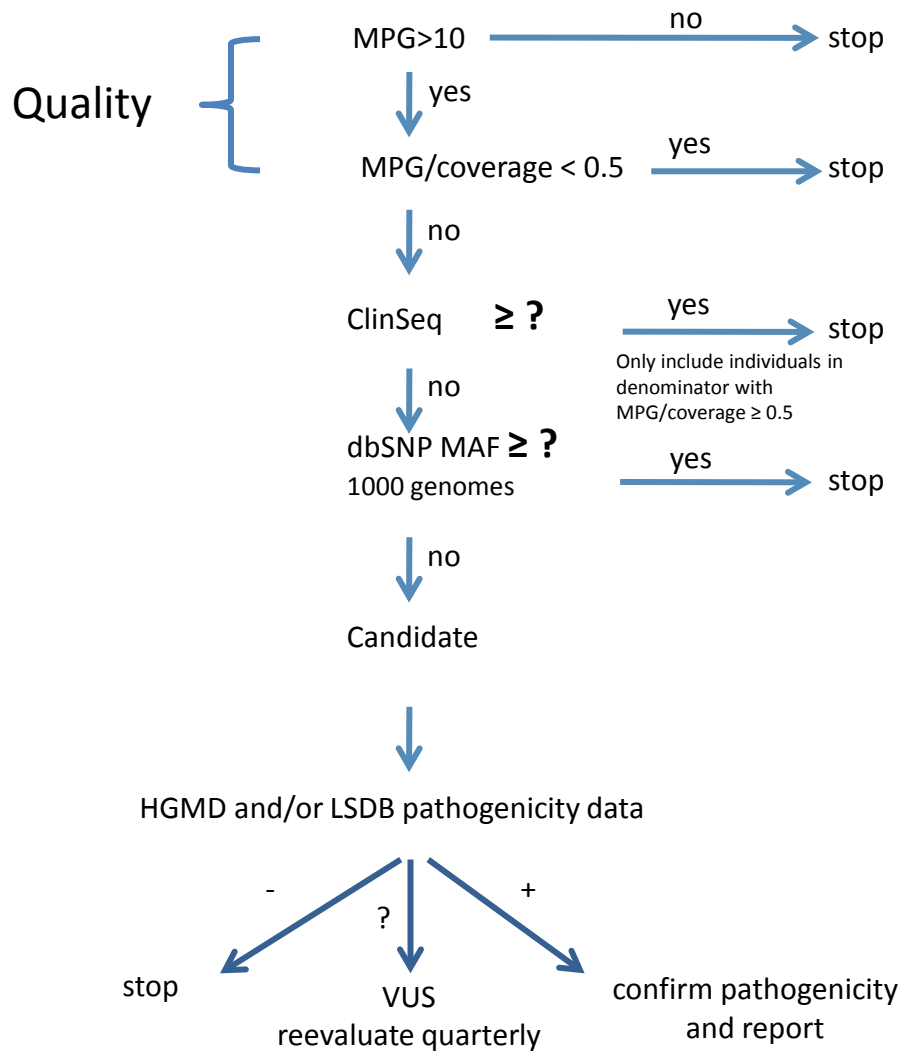
CS Secondary Variant



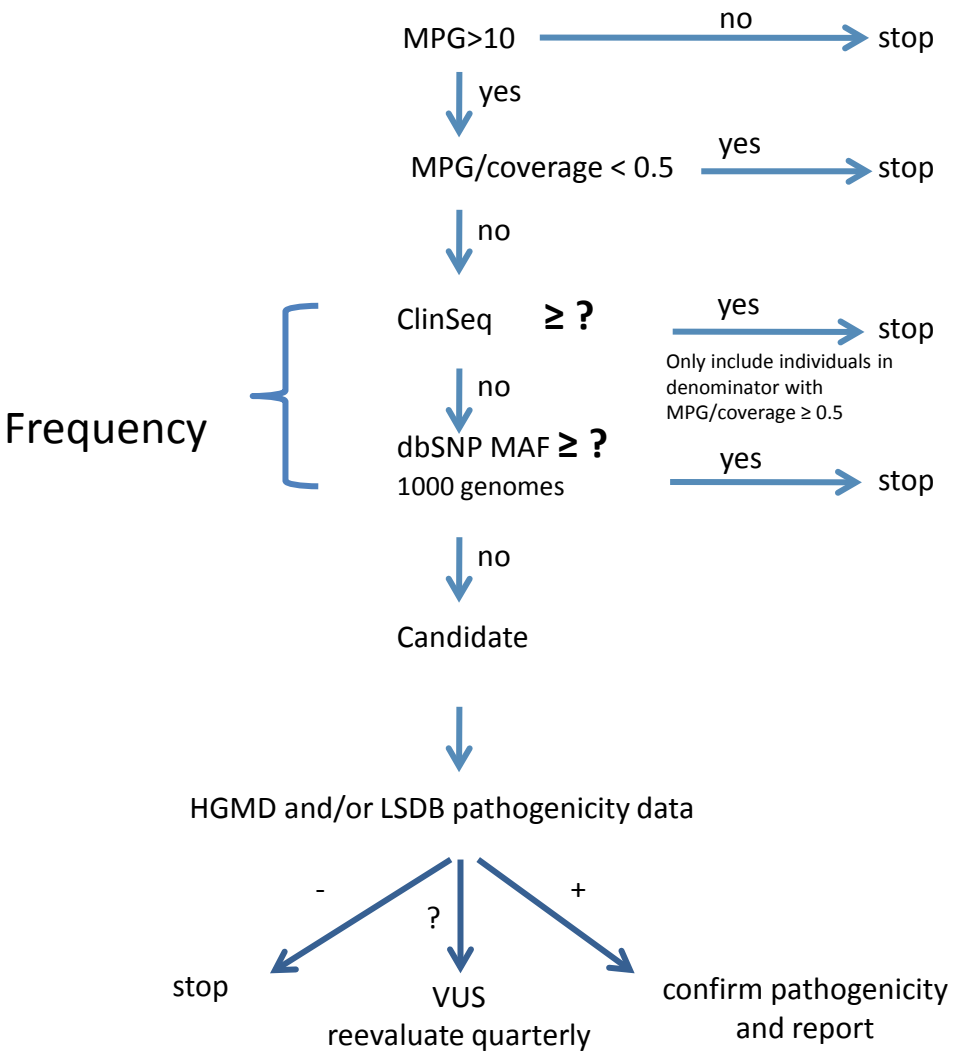
CS Secondary Variant



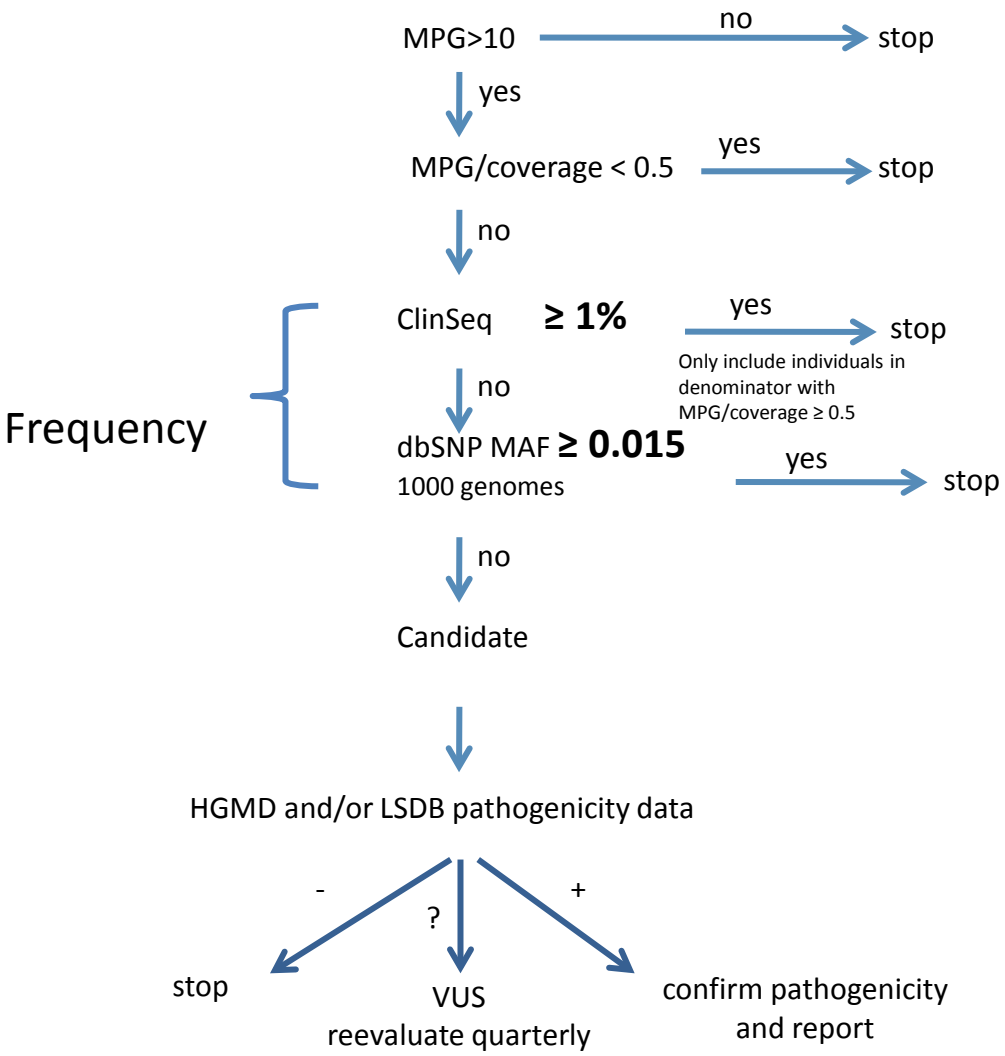
Framework for Variant Interpretation



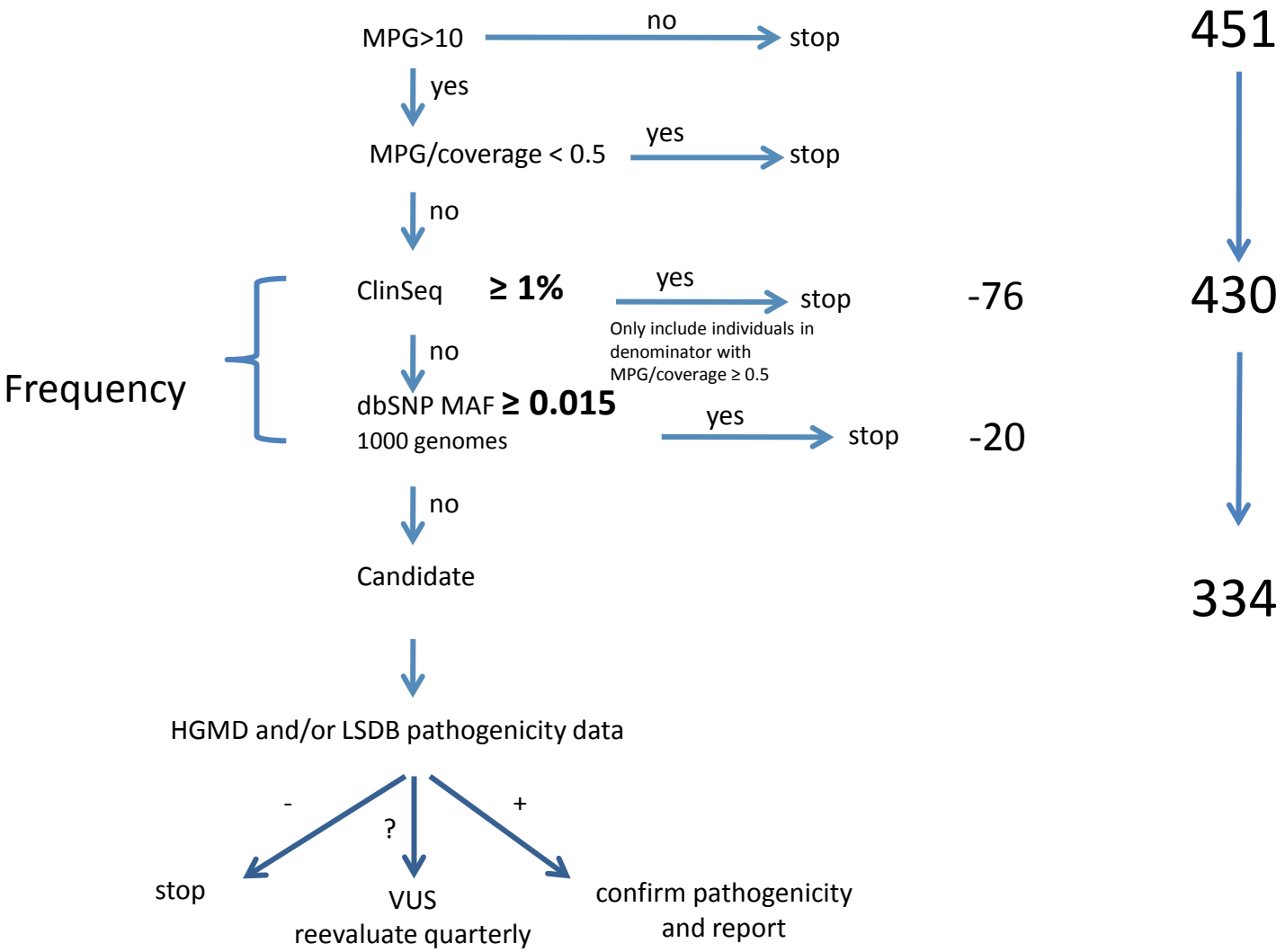
Framework for Variant Interpretation



ClinSeq™ Cancer Variant Filtering



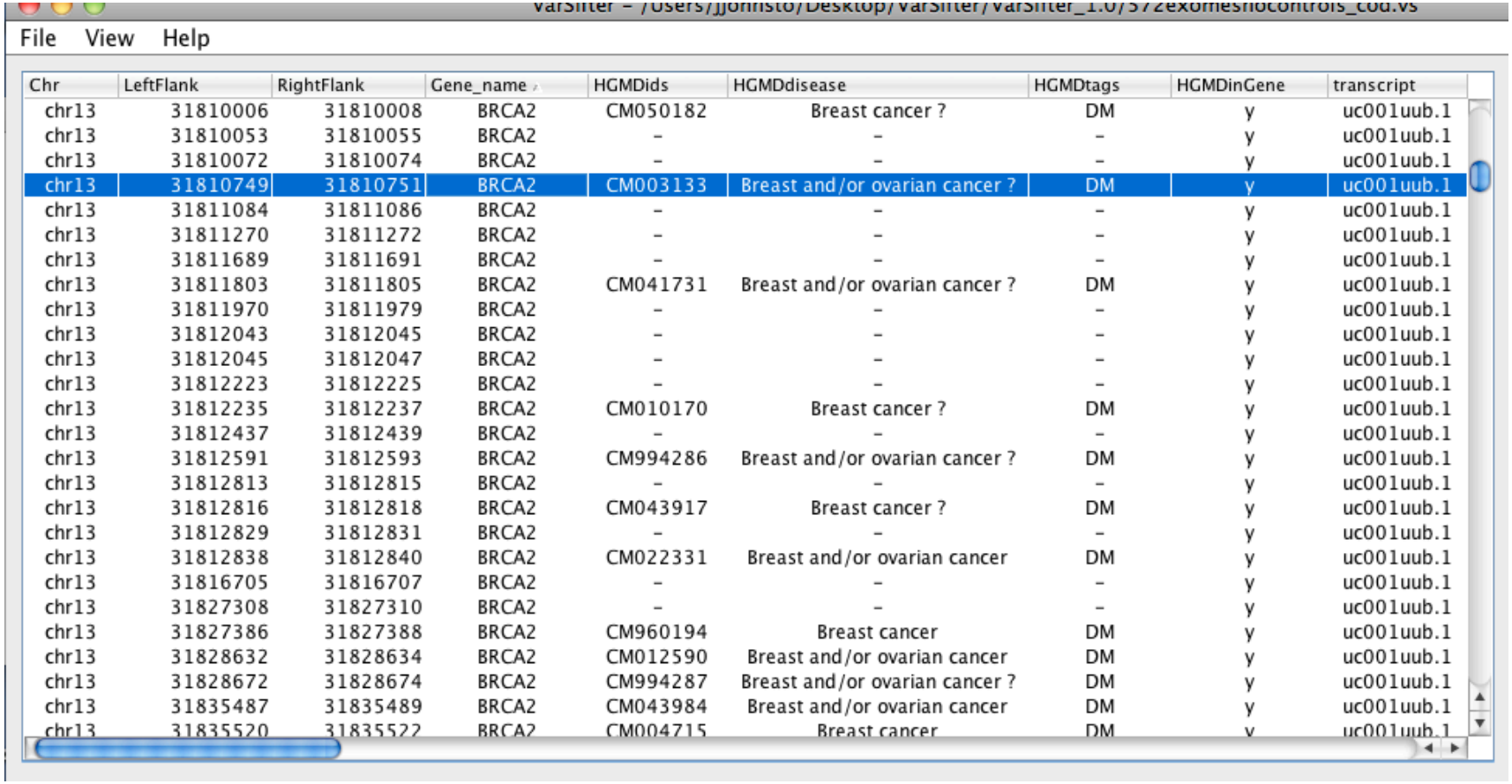
ClinSeq™ Cancer Variant Filtering



Evaluation of Candidates

- ❑Controls
- ❑Multiple reports
- ❑Functional data
- ❑Presence with other causative mutations
- ❑Segregation with disease (LD & linkage caveat)
- ❑*De novo* (assuming parentage)
- ❑Penetrance
- ❑Phenocopies

VarSifter - HGMD



Chr	LeftFlank	RightFlank	Gene_name	HGMDids	HGMDdisease	HGMDtags	HGMDinGene	transcript
chr13	31810006	31810008	BRCA2	CM050182	Breast cancer ?	DM	y	uc001uub.1
chr13	31810053	31810055	BRCA2	-	-	-	y	uc001uub.1
chr13	31810072	31810074	BRCA2	-	-	-	y	uc001uub.1
chr13	31810749	31810751	BRCA2	CM003133	Breast and/or ovarian cancer ?	DM	y	uc001uub.1
chr13	31811084	31811086	BRCA2	-	-	-	y	uc001uub.1
chr13	31811270	31811272	BRCA2	-	-	-	y	uc001uub.1
chr13	31811689	31811691	BRCA2	-	-	-	y	uc001uub.1
chr13	31811803	31811805	BRCA2	CM041731	Breast and/or ovarian cancer ?	DM	y	uc001uub.1
chr13	31811970	31811979	BRCA2	-	-	-	y	uc001uub.1
chr13	31812043	31812045	BRCA2	-	-	-	y	uc001uub.1
chr13	31812045	31812047	BRCA2	-	-	-	y	uc001uub.1
chr13	31812223	31812225	BRCA2	-	-	-	y	uc001uub.1
chr13	31812235	31812237	BRCA2	CM010170	Breast cancer ?	DM	y	uc001uub.1
chr13	31812437	31812439	BRCA2	-	-	-	y	uc001uub.1
chr13	31812591	31812593	BRCA2	CM994286	Breast and/or ovarian cancer ?	DM	y	uc001uub.1
chr13	31812813	31812815	BRCA2	-	-	-	y	uc001uub.1
chr13	31812816	31812818	BRCA2	CM043917	Breast cancer ?	DM	y	uc001uub.1
chr13	31812829	31812831	BRCA2	-	-	-	y	uc001uub.1
chr13	31812838	31812840	BRCA2	CM022331	Breast and/or ovarian cancer	DM	y	uc001uub.1
chr13	31816705	31816707	BRCA2	-	-	-	y	uc001uub.1
chr13	31827308	31827310	BRCA2	-	-	-	y	uc001uub.1
chr13	31827386	31827388	BRCA2	CM960194	Breast cancer	DM	y	uc001uub.1
chr13	31828632	31828634	BRCA2	CM012590	Breast and/or ovarian cancer	DM	y	uc001uub.1
chr13	31828672	31828674	BRCA2	CM994287	Breast and/or ovarian cancer ?	DM	y	uc001uub.1
chr13	31835487	31835489	BRCA2	CM043984	Breast and/or ovarian cancer	DM	y	uc001uub.1
chr13	31835520	31835522	BRCA2	CM004715	Breast cancer	DM	y	uc001uub.1

HGMD – Literature Links

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Breast Cancer Res. 2011 Feb 28;13(1):R20. [Epub ahead of print]

Screening for BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD50, and CDH1 mutations in high-risk Finnish BRCA1/2-founder mutation-negative breast and/or ovarian cancer individuals.

Kuusisto KM, Bebel A, Vihinen M, Schleutker J, Sallinen SL.

Department of Pediatrics, Genetics Outpatient Clinic, Tampere University Hospital, Biokatu 8, Tampere, 33520, Finland. Satu-Leena.Sallinen@pshp.fi.

Abstract

ABSTRACT:

INTRODUCTION: Two major high-penetrance breast cancer genes, BRCA1 and BRCA2, are responsible for approximately 20% of hereditary breast cancer (HBC) cases in Finland. Additionally, rare mutations in several other genes that interact with BRCA1 and BRCA2 increase the risk of HBC. Still, a majority of HBC cases remain unexplained which is challenging for genetic counseling. We aimed to analyze additional mutations in HBC-associated genes and to define the sensitivity of our current BRCA1/2 mutation analysis protocol used in genetic counseling.

METHODS: Eighty-two well-characterized, high-risk hereditary breast and/or ovarian cancer (HBOC) BRCA1/2-founder mutation-negative Finnish individuals, were screened for germline alterations in seven breast cancer susceptibility genes, BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD50, and CDH1. BRCA1/2 were analyzed by multiplex ligation-dependent probe amplification (MLPA) and direct sequencing. CHEK2 was analyzed by the high resolution melt (HRM) method and PALB2, RAD50, BRIP1 and CDH1 were analyzed by direct sequencing. Carrier frequencies between 82 (HBOC) BRCA1/2-founder mutation-negative Finnish individuals and 384 healthy Finnish population controls were compared by using Fisher's exact test. In silico prediction for novel missense variants effects was carried out by using Pathogenic-Or-Not -Pipeline (PON-P).

RESULTS: Three previously reported breast cancer-associated variants, BRCA1 c.5095C > T, CHEK2 c.470T > C, and CHEK2 c.1100delC, were observed in eleven (13.4%) individuals. Ten of these individuals (12.2%) had CHEK2 variants, c.470T > C and/or c.1100delC. Fourteen novel sequence alterations and nine individuals with more than one non-synonymous variant were identified. One of the novel variants, BRCA2 c.72A > T (Leu24Phe) was predicted to be likely pathogenic in silico. No large genomic rearrangements were detected in BRCA1/2 by multiplex ligation-dependent probe amplification (MLPA).

CONCLUSIONS: In this study, mutations in previously known breast cancer susceptibility genes can explain 13.4% of the analyzed high-risk BRCA1/2-negative HBOC individuals. CHEK2 mutations, c.470T > C and c.1100delC, make a considerable contribution (12.2%) to these high-risk individuals but further segregation analysis is needed to evaluate the clinical significance of these mutations before applying them in clinical use. Additionally, we identified novel variants that warrant additional studies. Our current genetic testing protocol for 28 Finnish BRCA1/2-founder mutations and protein truncation test (PTT) of the largest exons is sensitive enough for clinical use as a primary screening tool.

PMID: 21356067 [PubMed - as supplied by publisher] PMCID: PMC3109589 **Free PMC Article**

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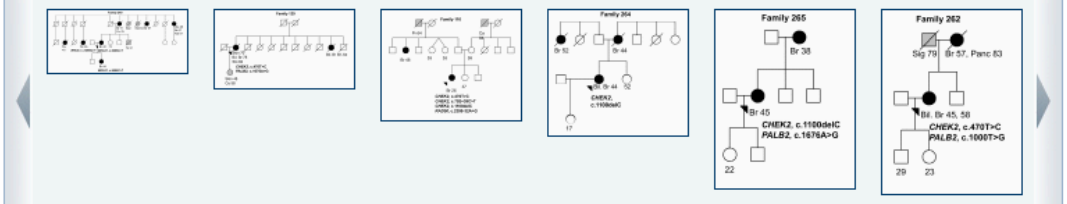

Related citations

Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of br [JAMA. 2006]

Selected Aspects of Molecular Diagnostics of Constitutional Alte [Hered Cancer Clin Pract. 2006]

BRCA1/BRCA2 rearrangements and CHEK2 common mutation [Breast Cancer Res Treat. 2008]

Review Pitfalls and caveats in BRCA sequencing. [Ultrastruct Pathol. 2006]

Review Breast cancer genetics in African Americans. [Cancer. 2003]

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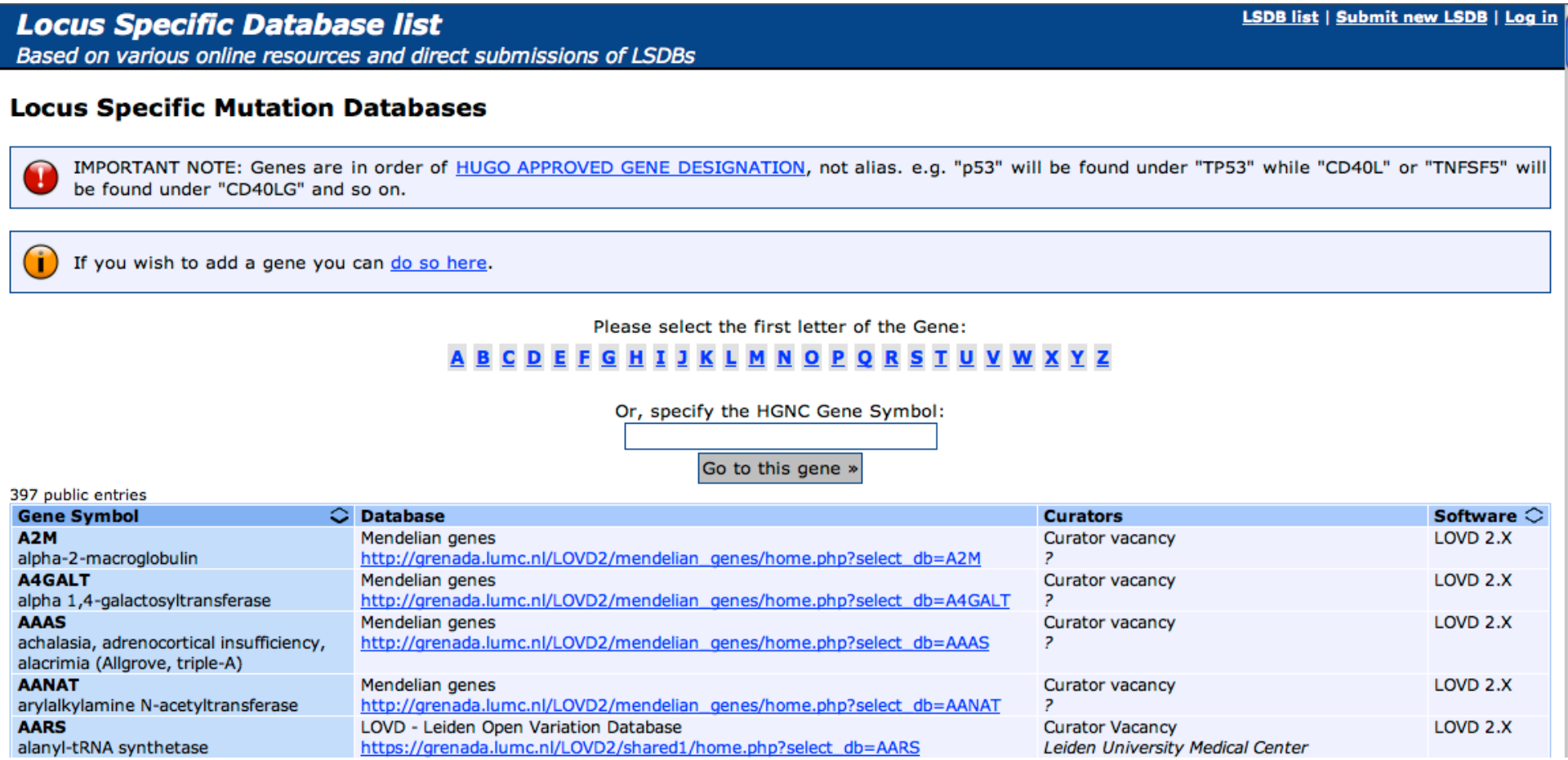

Locus Specific Database list

Based on various online resources and direct submissions of LSDBs

LSDB list | Submit new LSDB | Log in

Locus Specific Mutation Databases

IMPORTANT NOTE: Genes are in order of HUGO APPROVED GENE DESIGNATION, not alias. e.g. "p53" will be found under "TP53" while "CD40L" or "TNFSF5" will be found under "CD40LG" and so on.

If you wish to add a gene you can do so here.

Please select the first letter of the Gene:

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Or, specify the HGNC Gene Symbol:

Go to this gene »

397 public entries

Gene Symbol	Database	Curators	Software
A2M alpha-2-macroglobulin	Mendelian genes http://grenada.lumc.nl/LOVD2/mendelian_genes/home.php?select_db=A2M	Curator vacancy ?	LOVD 2.X
A4GALT alpha 1,4-galactosyltransferase	Mendelian genes http://grenada.lumc.nl/LOVD2/mendelian_genes/home.php?select_db=A4GALT	Curator vacancy ?	LOVD 2.X
AAAS achalasia, adrenocortical insufficiency, alacrimia (Allgrove, triple-A)	Mendelian genes http://grenada.lumc.nl/LOVD2/mendelian_genes/home.php?select_db=AAAS	Curator vacancy ?	LOVD 2.X
AANAT arylalkylamine N-acetyltransferase	Mendelian genes http://grenada.lumc.nl/LOVD2/mendelian_genes/home.php?select_db=AANAT	Curator vacancy ?	LOVD 2.X
AARS alanyl-tRNA synthetase	LOVD - Leiden Open Variation Database https://grenada.lumc.nl/LOVD2/shared1/home.php?select_db=AARS	Curator Vacancy *Leiden University Medical Center*	LOVD 2.X

http://www.hgvs.org/dblist/glsdb.html

http://grenada.lumc.nl/LSDB_list/lsdb.phpaction=view_all&symbol_start=M

LSDB

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LOVD - Variant listings

Unhide all columns | **Hide Specific Columns** | **Hide all columns**

About this overview [Show]

3783 public entries

100 entries per page

Path.	Exon	Codon_nr	DNA change	DNA_reported	RNA change	Protein	Type	Cons_predicted	DB-ID	Variant remarks	Origin	Variant reference
-/?	00	-	c.-?C>G	-47306C>G (5' of ATG)	-	-	-	-	APC_00415	numbering 5' of ATG	-	-
-/?	00	-	c.?C>T	-47287C>T	-	-	-	-	APC_00416	numbering 5' of ATG	-	-
-/?	00	-	c.?insG	-47307insG	-	-	-	-	APC_00417	numbering 5' of ATG	-	-
-/?	00	-	c.?T>G	-47408T>G	-	-	-	-	APC_00418	numbering 5' of ATG	-	-
+/?	01_15+promoter	del	cytogeneticdeletion	-	-	-	deletion, large	deletion, large	APC_00200	cytogenetic deletion	unknown	Raedle et al. 2001
+/?	01_15+promoter	del	cytogeneticdeletion	-	-	-	deletion, large	deletion, large	APC_00200	cytogenetic deletion	de novo	Aretz et al. 2005
+/?	01_15+promoter	del	cytogeneticdeletion	-	-	-	deletion, large	deletion, large	APC_00200	cytogenetic deletion	de novo	Aretz et al. 2005
+/?	01_15+promoter	del	cytogeneticdeletion	-	-	-	deletion, large	deletion, large	APC_00200	cytogenetic deletion	unknown	Aretz and Friedl (unpublished)
+/?	01	24	c.70C>T	-	-	p.Arg24X	substitution, base pair	nonsense	APC_00551	-	-	Kanter-Smoler et al. 2008
+/?	01_15	del	g.26940-?_133343+?del	-	-	-	deletion, large	deletion, large	APC_00587	-	familial	Kanter-Smoler et al. 2008
+/?	01+promoter	del	g.35041-?_52505+?del	-	-	-	deletion, large	deletion, large	APC_00526	-	familial	Aretz et al. 2005
+/?	01+promoter	del	g.35041-?_52505+?del	-	-	-	deletion, large	deletion, large	APC_00526	-	familial	Aretz et al. 2005
+/?	01+promoter	del	g.35041-?_52505+?del	-	-	-	deletion, large	deletion, large	APC_00526	-	familial	Aretz et al. 2005
+/?	01_05+promoter	del	g.35041-?_78383+?del	-	-	-	deletion, large	deletion, large	APC_00527	-	familial	Aretz et al. 2005

LSDB

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LOVD - Variant listings

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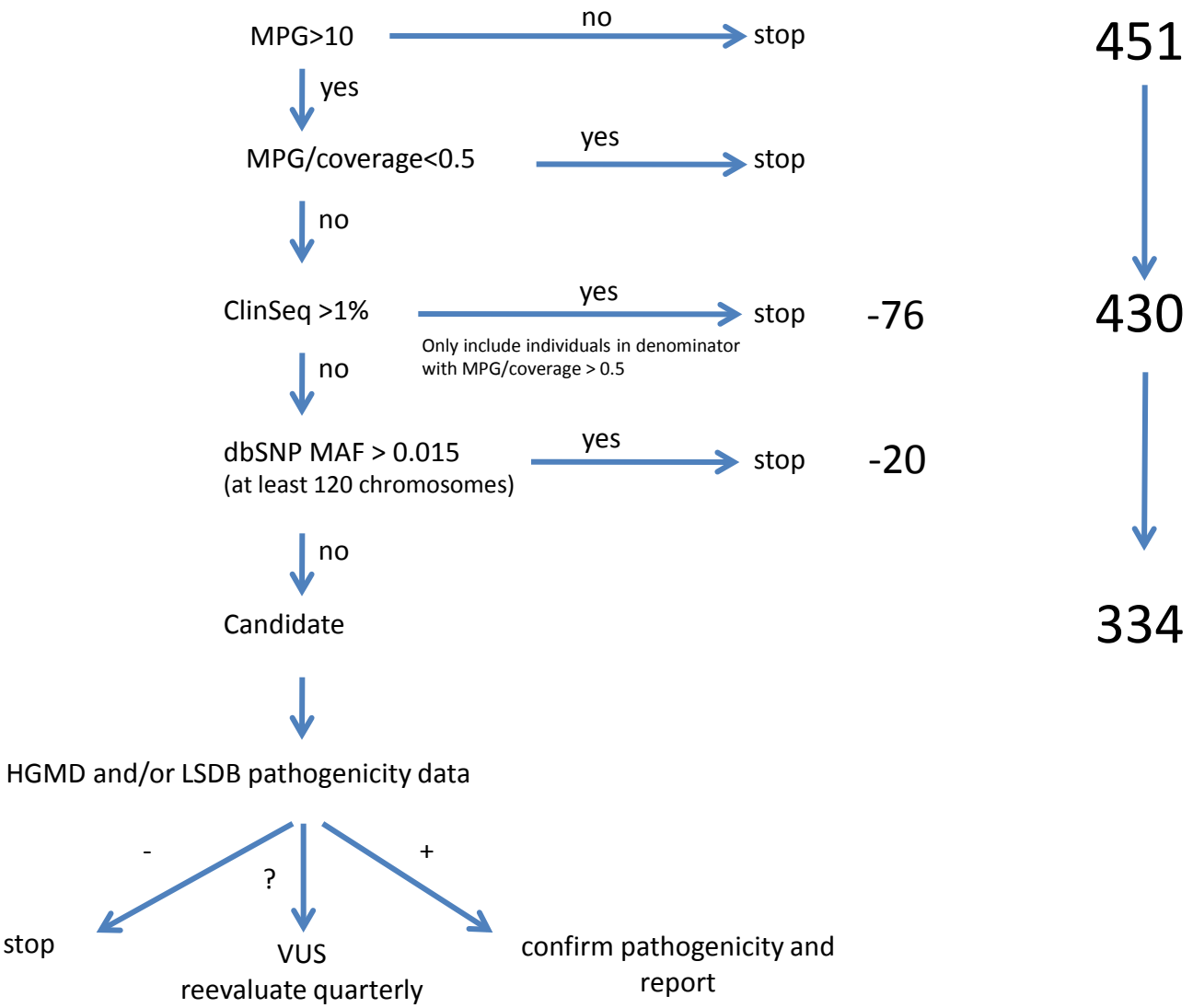
-/?	00	-	c.-?C>G	-47306C>G (5' of ATG)	-	-	-	-	APC_00415	numbering 5' of ATG	-	-
-/?	00	-	c.?C>T	-47287C>T	-	-	-	-	APC_00416	numbering 5' of ATG	-	-
-/?	00	-	c.?insG	-47307insG	-	-	-	-	APC_00417	numbering 5' of ATG	-	-
-/?	00	-	c.?T>G	-47408T>G	-	-	-	-	APC_00418	numbering 5' of ATG	-	-
+/?	01_15+promoter	del	cytogeneticdeletion	-	-	-	deletion, large	deletion, large	APC_00200	cytogenetic deletion	unknown	Raedle et al. 2001
+/?	01_15+promoter	del	cytogeneticdeletion	-	-	-	deletion, large	deletion, large	APC_00200	cytogenetic deletion	de novo	Aretz et al. 2005
+/?	01_15+promoter	del	cytogeneticdeletion	-	-	-	deletion, large	deletion, large	APC_00200	cytogenetic deletion	de novo	Aretz et al. 2005
+/?	01_15+promoter	del	cytogeneticdeletion	-	-	-	deletion, large	deletion, large	APC_00200	cytogenetic deletion	unknown	Aretz and Friedl (unpublished)
+/?	01	24	c.70C>T	-	-	p.Arg24X	substitution, base pair	nonsense	APC_00551	-	-	Kanter-Smoler et al. 2008
+/?	01_15	del	g.26940-?_133343+?del	-	-	-	deletion, large	deletion, large	APC_00587	-	familial	Kanter-Smoler et al. 2008
+/?	01+promoter	del	g.35041-?_52505+?del	-	-	-	deletion, large	deletion, large	APC_00526	-	familial	Aretz et al. 2005
+/?	01+promoter	del	g.35041-?_52505+?del	-	-	-	deletion, large	deletion, large	APC_00526	-	familial	Aretz et al. 2005
+/?	01+promoter	del	g.35041-?_52505+?del	-	-	-	deletion, large	deletion, large	APC_00526	-	familial	Aretz et al. 2005
+/?	01_05+promoter	del	g.35041-?_78383+?del	-	-	-	deletion, large	deletion, large	APC_00527	-	familial	Aretz et al. 2005

CS Cancer Filtering



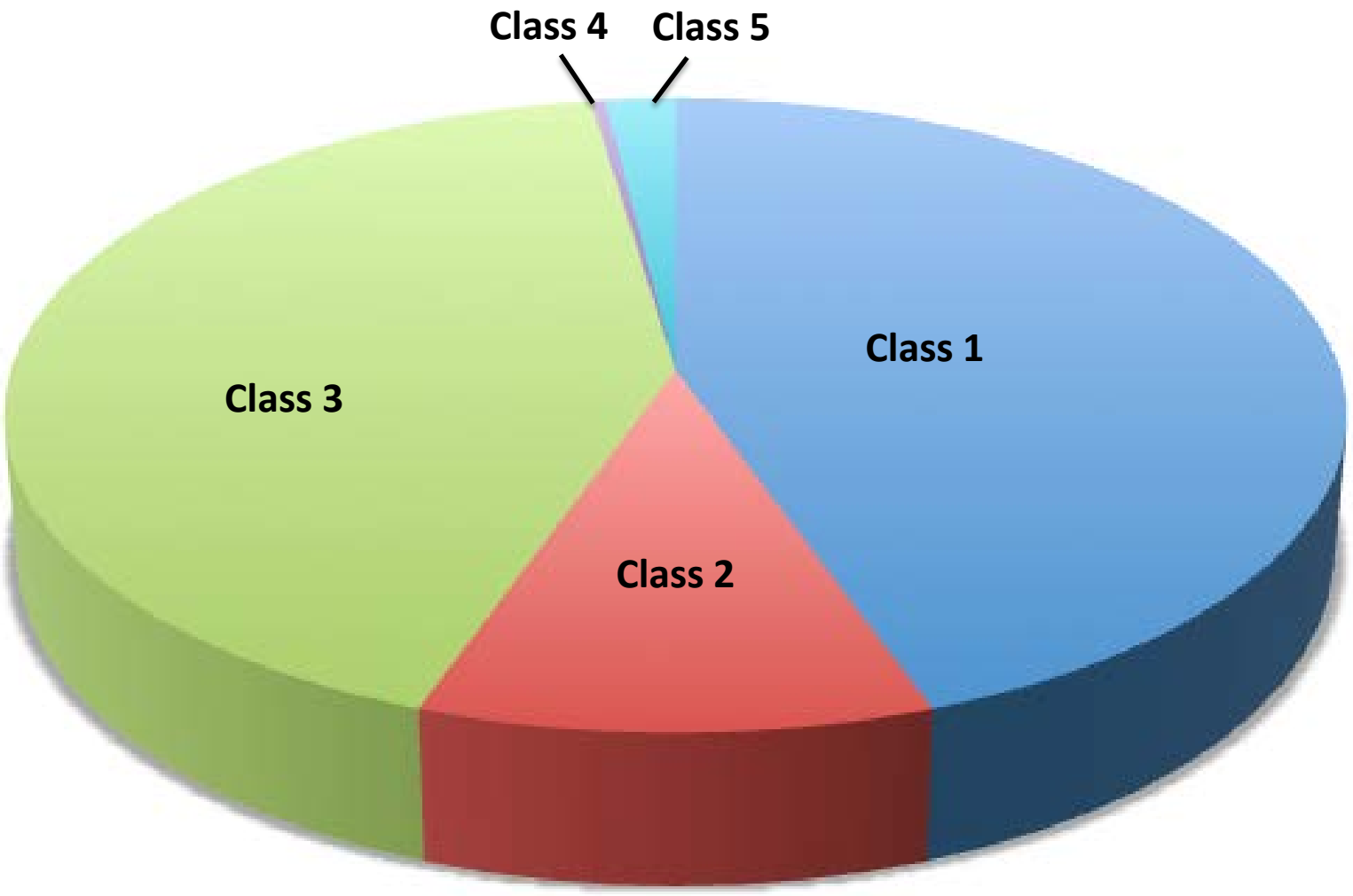
International Association for Research on Cancer (IARC) Pathogenicity Scale

Proposed Classification System for Sequence Variants Identified by Genetic Testing

Class	Description	Probability of being pathogenic
5	Definitely pathogenic	>0.99
4	Likely pathogenic	0.95-0.99
3	Uncertain	0.05-0.949
2	Likely not pathogenic or of little clinical significance	0.001-0.049
1	Not pathogenic or of no clinical significance	<0.001
0	Insufficient information i.e., did not pass quality filter	

Plon et al. Human Mut. (2008)

Summary of Variant Scores



Lessons Learned

- Most variants don't need neurons
  - Filter away variants that are highly likely benign
  - Set thresholds that reflect best judgment of:
    - Disease biology, medical reality, genetics, & patient attributes
- Focus on those few that do
  - Acquire and display most useful and robust data that can be mustered *and think*
- Capture and store judgments
- Continually reassess interpretations

What is at Stake

- Among 572 participants *preliminary analysis showed likely pathologic variants for:*
  - *9 with familial hypercholesterolemia*
  - *7 with high penetrance Br/Ov Cancer*
  - *6 with malignant hyperthermia*
  - *3 with HNPP*
  - *2 with cardiac dysrythmia*