

An automated guidelines-based approach for variants pathogenicity assessment in the diagnosis of genetic cardiovascular diseases

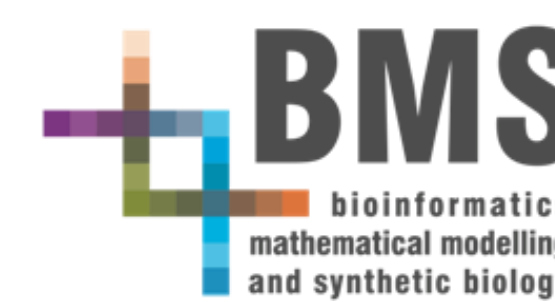
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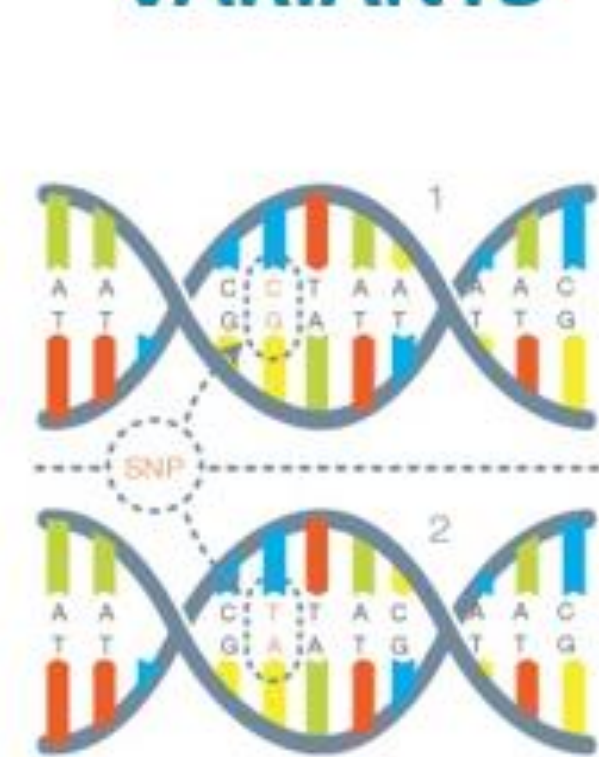
BACKGROUND

ACMG/AMP guidelines establish a set of rules to reduce the number of uncertain genomic variants (VUS) in clinical routine (PMID 25741868). However, these criteria need to be interpreted or adjusted accordingly to specific diseases of interest, such as cardiovascular diseases (CVDs). An assessment of these guidelines has not yet been conducted for CVDs and neither exists a specialized tool that can easily support their fast implementation.

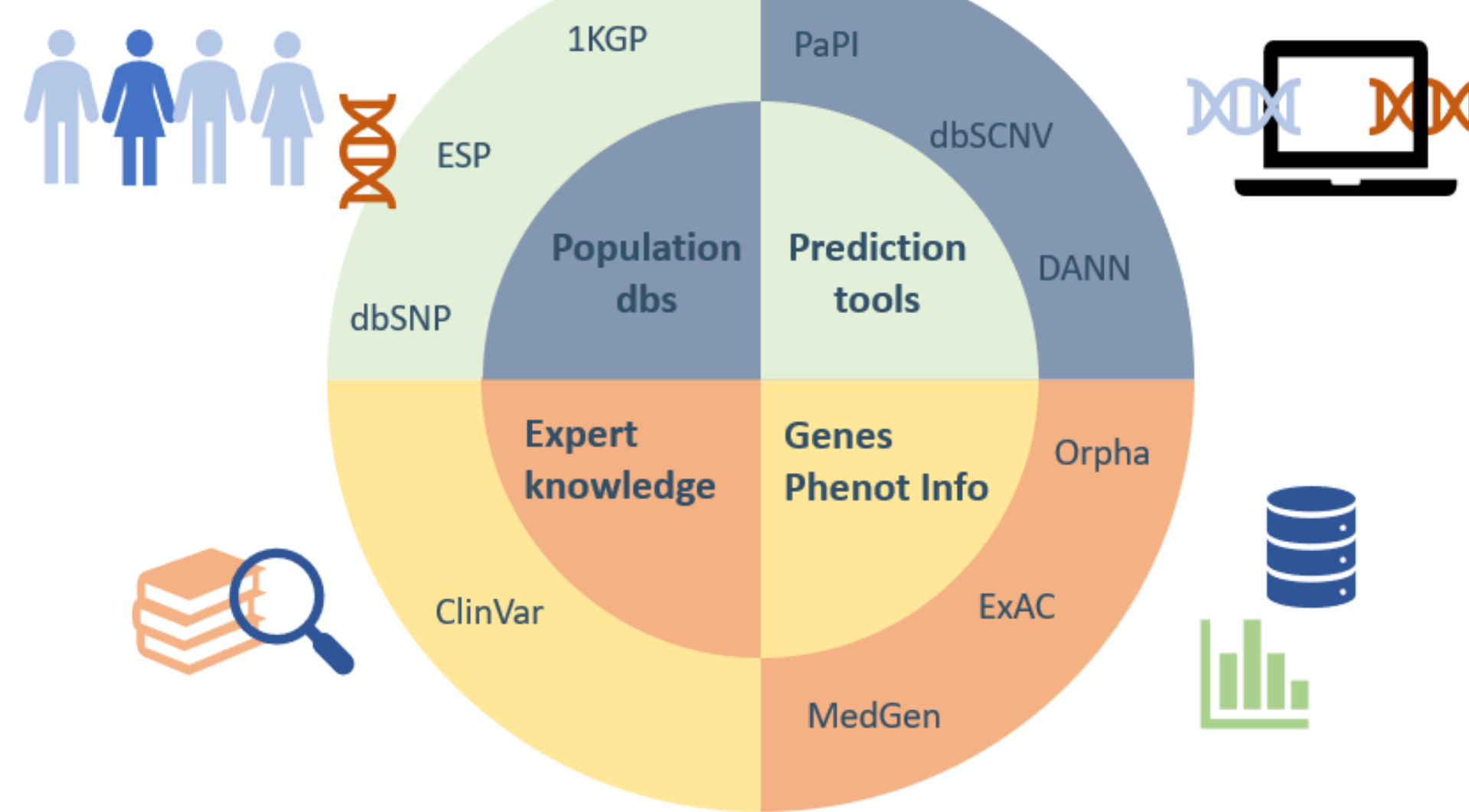
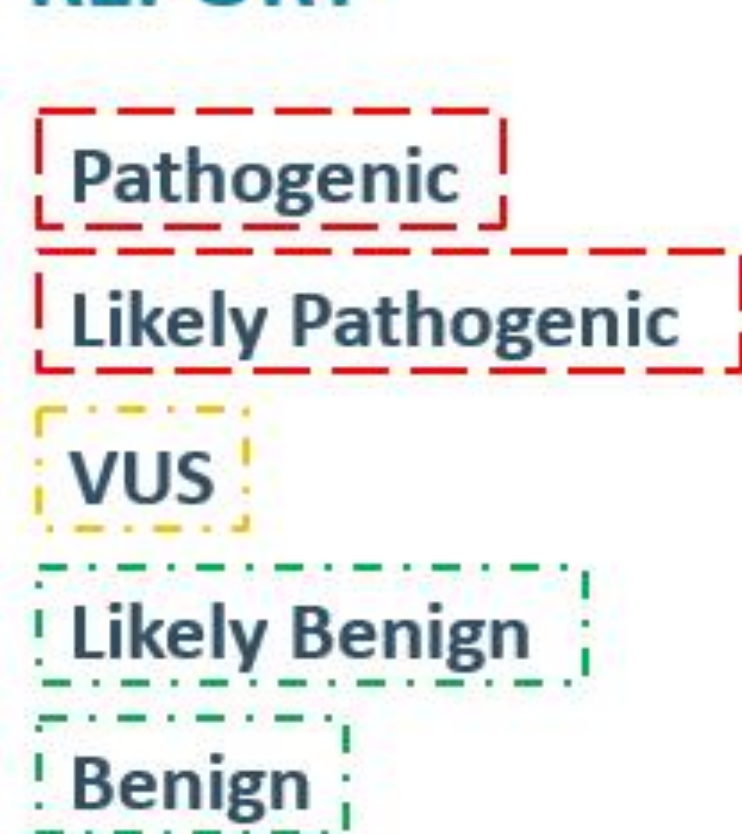
MATERIALS AND METHODS

We designed a systematic approach to classify variants according to ACMG/AMP guidelines, developing the Variant Interpreter software (eVAI). ACMG/AMP criteria were implemented based on data integration of different omics-resources. Other criteria were tailored to CVDs: an example is the determination of specific genomic hotspot regions such as the amino-terminal propeptide domain of DSG2 gene, where an overrepresentation of missense mutations has been observed in patients with arrhythmogenic right ventricular cardiomyopathy (PMID 21636032). We then collected two benchmark datasets: CardioDB (<http://cardiodb.org/>) with well-assessed CVDs-pathogenic variants and CLINVITAE (<http://clinvitae.invitae.com>) that gathers clinically-observed benign/pathogenic variants related to a broader set of genetic diseases.

VARIANTS



REPORT



RESULTS AND CONCLUSIONS

We implemented an automated approach (eVAI) to evaluate genomic variants and further specialized it for CVDs diagnosis. We tested eVAI on benchmark datasets reporting a high concordance both for pathogenic and benign variants. We compared eVAI to InterVar reporting a VUS reduction of about 80% and 45.3% in CardioDB and CLINVITAE respectively. Finally, we ran eVAI on 72 CVDs-related genes and created CardioVAI (<http://cardiovai.engenome.com>), a freely-accessible web-application to interpret every possible missense variants in CVDs genes.

	CardioDB (pathogenic)	CLINVITAE (pathogenic)	CLINVITAE (benign)
CardioVAI	84.9% (79/93)	76.2% (4310/5651)	88.5% (7499/8472)
InterVar	24.7% (23/93)	35.4% (2004/5651)	85.9% (7281/8472)

- Information about 72 genes analyzed
- Search variant by gene and HgvsP nomenclature.
- Results for query
- Other queries: search variant by gene and HgvsC nomenclature or by genomic coordinates

CardioVAI
ACMG/AMP Interpretation of genomic variants associated to Cardiovascular diseases

More about the Cardio Variant Interpreter

Gene: HgvsP:

Query by HGVS Protein Level

Query by HGVS DNA Level

- Adjust criteria and their level of evidence according to your knowledge
- Variant re-classification according to user change
- Download results in CSV format

#	HGVS	Gene	Phenotype	Class	Criteria
1	GCh37:11g.2466677C>T More Info	KCNQ1 ENST00000155840: p.Pro117Ser, c.349C>T (missense_variant)	Long QT syndrome 1 C0035828 Autosomal dominant	Pathogenic 10	PP2, PM2, PS1, PM5, PP3, PP5
2	GCh37:11g.2466677C>T More Info	KCNQ1 ENST00000155840: p.Pro117Ser, c.349C>T (missense_variant)	Atrial fibrillation, familial, 3 C1837014 Autosomal dominant	Likely pathogenic 6	PP2, PM2, PM5, PP3
3	GCh37:11g.2466677C>T More Info	KCNQ1 ENST00000155840: p.Pro117Ser, c.349C>T (missense_variant)	Jervell and Lange-Nielsen syndrome 1 CN034131 Autosomal recessive	Likely pathogenic 6	PP2, PM2, PM5, PP3

Criterion	Description	Active	Level of Evidence
PVS1	Null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease	<input checked="" type="checkbox"/>	Very Strong
PS1	Same amino acid change as a previously established pathogenic variant regardless of nucleotide change	<input type="checkbox"/>	Strong
PS2	De novo (both maternity and paternity confirmed) in a patient with the disease and no family history	<input type="checkbox"/>	Strong