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

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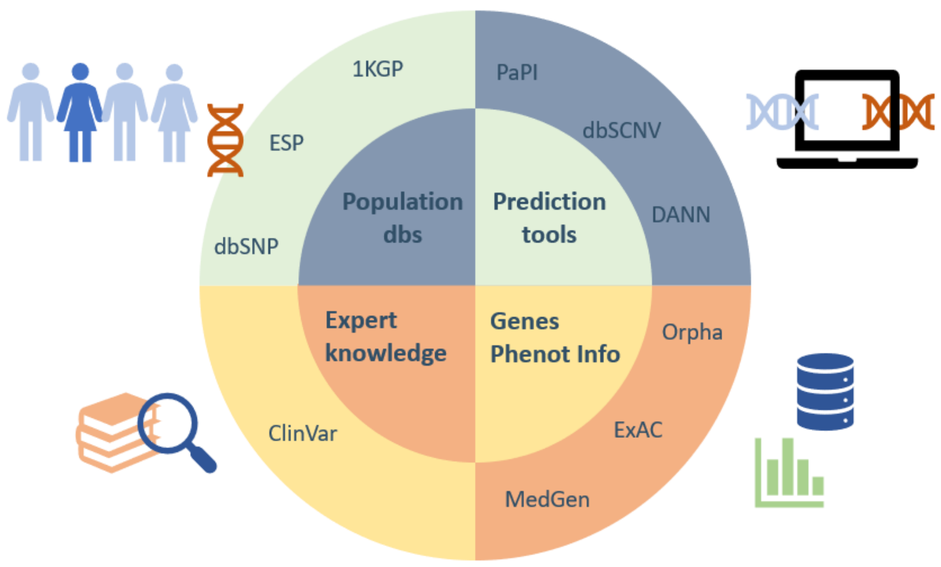
BACKGROUND

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

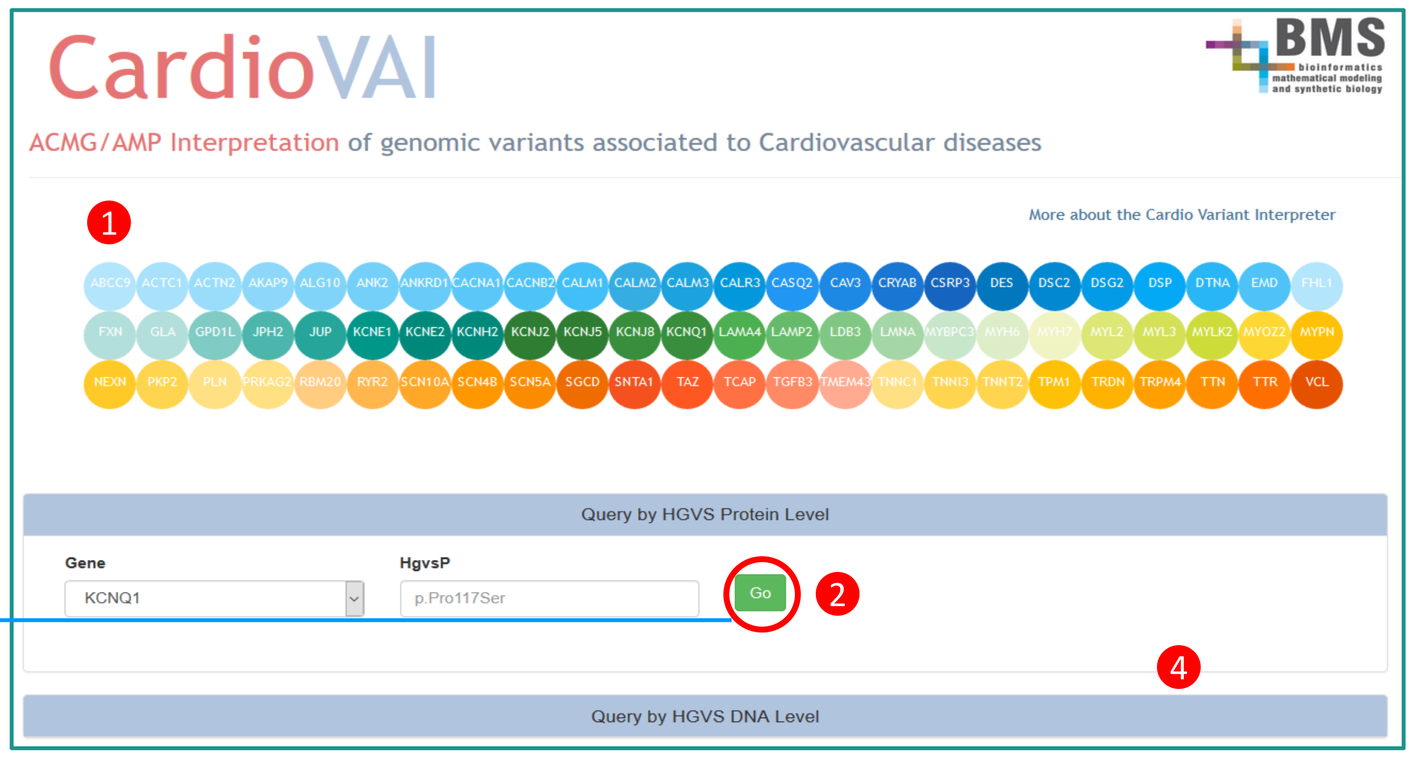
We designed a systematic approach to classify variants according to ACMG/AMP guidelines, developing the Variant Interpreter software (eVAI). ACMG/AMP criteria were implemented based on data integration of different omics-resources. Other criteria were tailored to CVDs: an example is the determination 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.



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 an 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)



1. Information about 72 genes analized
2. Search variant by gene and HgvsP nomenclature.
3. Results for query
4. Other queries: search variant by gene and HgvsC nomenclature or by genomic coordinates
5. Adjust criteria and their level of evidence according to your knowledge
6. Variant re-classification according to user change
7. Download results in CSV format