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corresponding author: piotr.stawinski@wum.edu.pl

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Improving consistency of constitutional CNV classification through automated ACMG/ClinGen scoring

Piotr Stawiński

Department of Medical Genetics, Medical University of Warsaw, Warsaw, Poland

BACKGROUND

The ACMG/ClinGen technical standards established a quantitative framework for constitutional CNV classification [Riggs ER et al., PMID: 31690835].

Its application requires integration of multiple evidence sources, including gene content, dosage sensitivity, known pathogenic or benign regions and population data.

Manual evidence collection and scoring are time-consuming and may introduce inter-analyst variability, particularly for small, intragenic and partial-overlap CNVs.

OUR AIM

To extend the GeneBe variant interpretation framework with automated ACMG/ClinGen scoring for constitutional CNVs, providing transparent criteria activation, individual point contributions and reproducible final classification.

METHODS

1. Input and workflow: CNVs are submitted as genomic intervals and processed through the web interface or REST API. The workflow combines regional annotation with automated ACMG/ClinGen scoring.

2. Annotations: include cytoband, genes, MANE transcripts, exon/CDS overlap, dosage sensitivity and disease associations. Regional evidence is collected from ClinVar, gnomAD SV, ClinGen and AnnotSV-derived resources.

3. Evidence evaluation: The algorithm evaluates full, partial, intragenic, CDS and UTR overlaps, using separate logic for copy-number losses and gains. Computable evidence includes pathogenic or benign regions, dosage-sensitive genes, gene count and population CNV overlap.

4. Scoring: Activated ACMG/ClinGen criteria receive quantitative points, for example **LOSS_2A: 1.0** point and **LOSS_3B: 0.45** points. Their sum determines the final classification: Pathogenic, Likely pathogenic, VUS, Likely benign or Benign.

5. Transparent review: The output provides the final class, activated criteria, point contributions and a human-readable rationale, while leaving phenotype- and segregation-dependent evidence to expert review.

RESULTS AND CASES

Routine use
The module is routinely used at the Department of Medical Genetics, Medical University of Warsaw, to support expert CNV interpretation.

Confirmed cases
Three independently confirmed pathogenic exon-level deletions — **PALB2 exons 12–13, BRCA1 exon 2 and BRCA1 exons 4–5** — were evaluated. Two were classified as **Likely Pathogenic** and one as **Pathogenic**, consistent with independent expert assessment.

Systematic validation of larger deletions and duplications has not yet been performed.

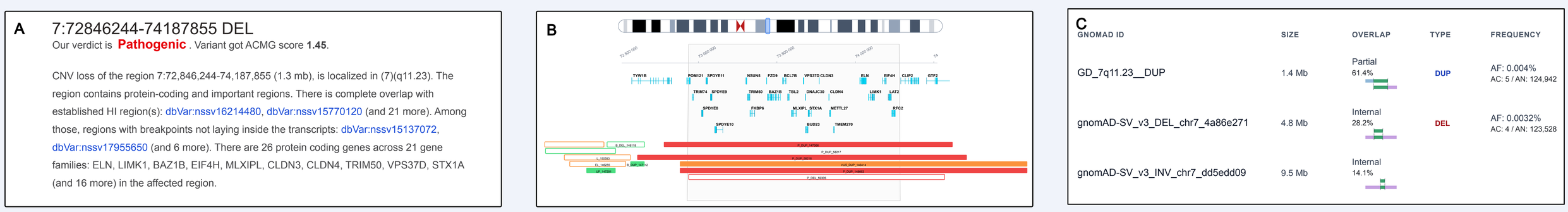

Figure 1. Interface for interpretation of a chromosome 7 deletion.
A: Human-readable summary of the automated ACMG/ClinGen CNV assessment, including activated criteria, point contributions and final classification.
B: Genome browser view of the affected region, showing the evaluated deletion, overlapping transcripts and previously reported ClinVar variants.
C: Table of overlapping gnomAD variants showing size, overlap type and frequency; analogous tables are available for ClinVar and other annotation sources.

DISCUSSION

CNV scoring depends strongly on the quality and curation of reference datasets; artefacts and questionable population records may affect benign/common-variant criteria.

CNV comparison remains challenging because breakpoints rarely match exactly and partial overlaps may affect different genes, exons or regulatory regions.

Standard loss/gain scoring does not fully capture exact copy number, while very small intragenic CNVs may require complementary gene-level ACMG interpretation.

Transparent visualization of annotations, overlaps and activated criteria is therefore essential for expert review.

CONCLUSIONS

Free access: GeneBe provides ACMG/ClinGen-based CNV annotation and scoring at no cost, with clear criteria and point values to support faster expert review.
Scalable analysis: CNVs can be assessed individually online or processed in larger batches.
Pipeline integration: the command-line client reads and returns VCF files, making it easier to include GeneBe in existing laboratory workflows.

Available at **https://genebe.net**

GeneBe

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The authors declare no conflicts of interests.