

Application of qualifying variants for genomic analysis

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Abstract

Motivation:

Qualifying variants (QVs) are genomic alterations selected by defined criteria within analysis pipelines. Although crucial for both research and clinical diagnostics, QVs are often seen as simple filters rather than dynamic elements that influence the entire workflow. While best practices follow variant classification standards and standardised workflows, a unified framework to integrate and optimise QVs for advanced applications is missing.

Results:

Our aim is to embed the concept of a “QV” into the genomic analysis vernacular, moving beyond a single filtering step. By decoupling QV criteria from other pipeline variables and code, our approach facilitates easier discussion and application. Our framework, with its new terminology and reference model, offers a flexible approach for integrating QVs into analysis pipelines, thereby enhancing reproducibility, interpretability, and interdisciplinary communication. A validation case study implementing ACMG criteria in a disease cohort shows that our approach matches conventional methods while offering improved clarity and scalability.

Availability:

The source code and data are accessible at <https://github.com/DylanLawless/qv2025lawless>. The QV file used in this work is available from <https://doi.org/10.5281/zenodo.15105594> (qv_acmg_svindel_criteria_20250225.yaml). The QV framework is available under the MIT licence, and the dataset will be maintained for at least two years following publication.

Acronyms

ACMG American College of Medical Genetics and Genomics	5
CNV Copy Number Variant	6
GWAS Genome Wide Association Study	4
IRI Internationalised Resource Identifier	6
HPO Human Phenotype Ontology	10
MAF Minor Allele Frequency	8
PPIE Public and Patient Involvement and Engagement	6
PRS Polygenic Risk Score	4
QC Quality Control	4
QV Qualifying variant	4
RDF Resource Description Framework	6
SF Secondary Findings	5
SHA-256 Secure Hash Algorithm 256	6
SNV/INDEL Single Nucleotide Variant / Insertion Deletion	6
SNOMED CT Systematized Nomenclature of Medicine-Clinical Terms . . .	6
SNP Single Nucleotide Polymorphism	11
UUID Universally Unique Identifier	6
VCF Variant Call Format	10
VEP Variant Effect Predictor	8
WGS Whole Genome Sequencing	4

1 Introduction

Qualifying variant (QV)s are genomic alterations selected by specific criteria within genome processing pipelines, serving as dynamic elements essential for both research and clinical diagnostics. QVs are not merely static filters applied at a single step in an analysis pipeline; rather, they are dynamic, multifaceted elements that permeate the entire workflow, from initial data quality control to final result interpretation. This nuanced perspective underscores that QVs play an integral role in shaping the fidelity and reproducibility of genomic analyses, enabling the iterative refinement of data and facilitating the integration of diverse analytical strategies throughout the pipeline.

Often, QV selection adheres to established variant classification and reporting standards (1–5) and standardised workflows (6–8). However a unified framework for QVs is lacking, despite the recognised benefits of similar initiatives, such as Polygenic Risk Score (PRS) reporting standards (9; 10). For instance, tools like *vcfexpress* (11) enable flexible, rapid filtering and formatting of VCF files using user-defined expressions. The application of independently defined QV criteria would complement such tools. This role is particularly important for reproducibility across distributed computing environments (12) and would also integrate with workflow managers such as Snakemake (13) or Nextflow (14), streamlining genomic processing tasks.

The criteria for QV selection vary by application. For example, Genome Wide Association Study (GWAS) may focus on common variants, while clinical analyses usually target rare or known pathogenic variants. Previous studies have demonstrated the utility of QVs (15; 16), yet no common approach exists. Here, we detail four typical applications of QV sets:

1. **QV passing Quality Control (QC) only:** Generates large datasets (e.g. > 500,000 variants per subject) for GWAS or initial Whole Genome Sequencing (WGS) pre-processing.
2. **Flexible QV:** Balances between QC and false positives, yielding intermediate datasets (e.g. fewer than 100,000 variants per subject) for uses such as rare variant association testing.
3. **QV for rare disease:** Applies stringent filtering to produce smaller datasets (e.g. < 1,000 variants per subject), targeting known genes or single causal variants.

4. **Known disease panel QV set:** Focuses on well-established gene panels with pathogenic variants (e.g. the American College of Medical Genetics and Genomics (ACMG) Secondary Findings (SF) set) for clinical reporting (17).

These examples illustrate a few common applications without providing an exhaustive classification of all possible QV uses. The careful selection and categorisation of QVs are thus critical for accurate reporting and reproducibility, sometimes even more so than the choice of the analysis pipeline itself (18).

As WGS becomes standard for large cohorts (19; 20), the integration of diverse QV protocols is critical for data cleaning and analysis. During sequencing analysis several layers can be responsible for triggering QV protocols, including pre-existing metadata, technical QC results, and post-calling annotations, highlighting the need for a clear, unified approach.

We propose treating the QV as a standalone entity, independent from other pipeline variables. We suggest structured human- and machine-readable criteria, aligned with FAIR principles (21) to facilitate integration across databases (22; 23). We advocate for the use of standard vocabularies, unique identifiers, and flexible file formats to support this integration.

2 Methods

2.1 Implementation

Implementation configurations and roles within analysis pipelines include, for example: theoretical pipelining of QV sets, establishing public or standardised QV sets for specific analytical scenarios, and recognition that QVs are integral throughout the analysis pipeline rather than confined to a single end-stage. We introduce a simple framework for the effective use of QV protocols, comprising four components as illustrated in **Figure 1 (A)**:

- **1. Variables:** The criteria variables sourced as part of the pipeline (see **Box 2**).
- **2a. Technical description:** An optional narrative detailing each step within the overall QV set (see **Box 2**).

- **2b. Public and Patient Involvement and Engagement (PPIE) description:** An optional narrative providing a patient-focused interpretation of the protocol, incorporating preferences and priorities.
- **3. QV set ID:** A unique identifier that links analysis records.
- **4. Source code:** The implementation of the variables file within the pipeline code, for example through custom scripts or workflow managers.

We propose the QV set ID as a unique identifier linking variant sets used in analyses. This facilitates integration into databases, by representing data in formats such as Resource Description Framework (RDF) schemas (23), and allows for features including Secure Hash Algorithm 256 (SHA-256) hash functions, Universally Unique Identifier (UUID)s, semantic combinations, Internationalised Resource Identifier (IRI) incorporation, registry-based allocation, and standard mapping such as Systematized Nomenclature of Medicine-Clinical Terms (SNOMED CT). The results can be used alongside other genomic-specific concepts spanning from sample processing to the sequencing run (22).

This framework efficiently manages QV-specific variables (e.g. allele frequency thresholds) separately from general pipeline settings, ensuring clarity and specificity. Its versatile format supports applications across genomic analyses and by linking the QV set ID to both results and raw data sources in a database for downstream interpretation and reporting.

2.2 Example application of qualifying variants in WGS analysis

Multiple QV protocols can be combined to generate progressively filtered datasets tailored to specific analytical needs. Often, different QV sets are applied sequentially, with the final outcomes merged to address distinct objectives. For instance, a comprehensive analysis pipeline might integrate:

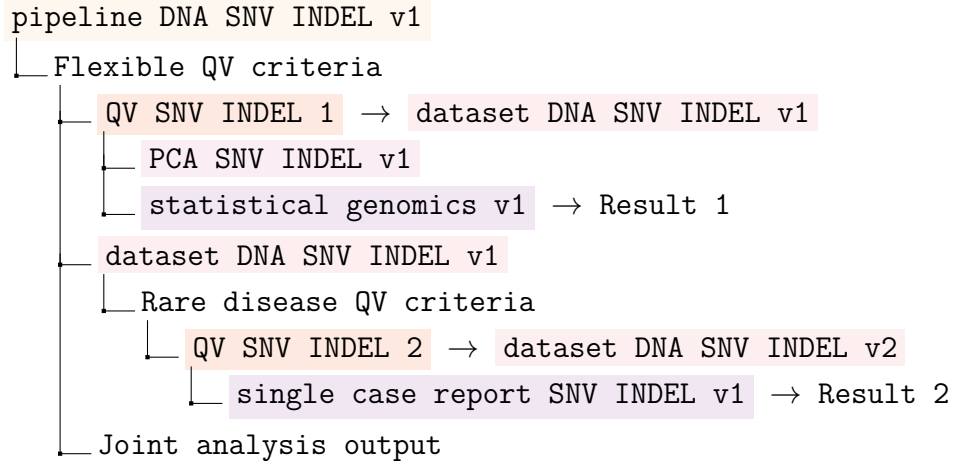
- **QV SNV/INDEL** Single Nucleotide Variant / Insertion Deletion (SNV/INDEL),
- **QV CNV** Copy Number Variant (CNV),
- **QV structural variation**,
- **QV rare disease known**, and

- QV statistical association QC.

The final analysis yields (1) a joint cohort disease association (e.g. variant P-values) and (2) individual single-case results (e.g. clinical genetics diagnosis for a patient) (24; 25). As an example, in **Figure 1 (A)** we focus on a SNV/INDEL pipeline employing two QV sets: **QV SNV INDEL 1** for flexible cohort-level filtering, and **QV SNV INDEL 2** for stricter filtering in subsequent single-case analysis. The pipeline is illustrated in **Box 1**, and can be summarised as follows:

“A cohort of patient WGS data was analysed to identify genetic determinants for phenotype X. Initially, a flexible QV set was applied using the **pipeline DNA SNV INDEL v1**, which implements the **QV SNV INDEL 1** criteria to produce the prepared dataset (**dataset DNA SNV INDEL v1**). This dataset was then analysed alongside other modules (e.g. **PCA SNV INDEL v1** and **statistical genomics v1**) to derive a cohort-level association signal (Result 1). Next, the same prepared dataset was re-filtered with the stricter **QV SNV INDEL 2** criteria to identify known causal variants for each patient, yielding the final dataset (**dataset DNA SNV INDEL v2**) and resulting in individual case reports (Result 2).”

Box 1: Example diagrammatic representation



Joint analysis output from:

Result 1 = Cohort-level association signal (e.g. variant P-value).

Result 2 = Single variant report per patient.

2.3 Usage in a rare disease validation study

In a validation study, we demonstrate the use of our QV criteria framework compared to the conventional manual approach. This analysis was performed on an in-house rare disease cohort of 940 individuals, which had been pre-processed for QC. We used genome-wide set of variants which was filtering to target rare variants (Minor Allele Frequency (MAF) < 0.01) restricted to known disease genes based on the Genomics England panel “Primary immunodeficiency or monogenic inflammatory bowel disease,” retrieved using our PanelAppRex R repository (<https://github.com/DylanLawless/PanelAppRex>) (26). This provided us with a prepared dataset of 6026 candidate variants annotated with 376 information sources. The dataset was prepared in R using GuRu, our variant interpretation tool that consolidates all annotation sources and scores variants as candidate causal, and was imported from gVCF format as output by Variant Effect Predictor (VEP).

We selected the first eight ACMG criteria for assigning pathogenicity scores to variants (1); six of these were relevant for this cohort. First, the analysis was performed manually by hard-coding each criterion in the pipeline script, reflecting a typical workflow. Second, the same criteria were imported from the QV YAML file for the new framework approach, using the file “qv acmg svindel criteria 20250225.yaml” (see **Box 2** or <https://doi.org/10.5281/zenodo.15105594>). The outputs from both methods were captured and compared.

Additional details of the YAML criteria in this QV set included definitions for ACMG_PS1 (identifying previously established pathogenic amino acid changes), ACMG_PS3 (supporting functional studies with matching inheritance patterns), and ACMG_PS5 (covering compound heterozygosity with high-impact variants). The criteria for ACMG_PM2 and ACMG_PM3 assess variant frequency and in trans occurrences, respectively, while PS2 and PS4 were not applicable to this cohort.

Box 2: qv_files/acmg_criteria.yaml

```
qv_set_id: qv_acmg_svnindel
criteria:
  ACMG_PVS1:
    conditions:
      - field: IMPACT
        operator: '=='
        value: HIGH
      - group: any_of:start
      - field: genotype
        operator: '=='
        value: 2
      - field: Inheritance
        operator: '=='
        value: AD
      - field: comp_het_flag
        operator: '=='
        value: 1
      - group: any_of:end
    description: 'Null variants (IMPACT == HIGH) in genes where
loss of function causes disease. Includes homozygous variants,
compound heterozygous cases, or dominant inheritance.
Warning to phase check compound heterozygosity.'
    logic: and

...
shasum -a 256 acmg_criteria.yaml | fold -w 32
d91fde41a5fff48631adecba38773d61
9ae8cd5cff9b9b42ef7f5efbd6bbfcdf
acmg_criteria.yaml
```

2.4 Usage in a GWAS validation study

We next applied the QV criteria framework to a genome-wide association study using HapMap3 Phase 3 (R3) consensus genotypes. The analysis was performed twice: first as a conventional hard coded pipeline and second using an externalised QV YAML

configuration file. Both pipelines used the same data and processing stages, ensuring comparability.

The hard coded implementation embedded all filtering and analysis thresholds directly in the bash scripts, while the QV-based implementation sourced them from the file “qv_gwas_common_v1_20250826.yaml” (see <https://doi.org/10.5281/zenodo.XXXXXXX>). This QV set defines common GWAS thresholds: restriction to autosomal, biallelic SNPs; minimum sample call rate of 95%; variant call rate of 95%; minor allele frequency $\geq 1\%$; and Hardy–Weinberg equilibrium $p \geq 1 \times 10^{-6}$. After quality control, variants were LD-pruned and principal components (PC1–PC10) were computed, with sex included as an additional covariate. Logistic regression under an additive model was then performed with PLINK.

The outputs of the two pipelines were captured and compared across each main PLINK stage: step 1 autosomal biallelic SNPs, step 2 sample call rate, step 3 variant call rate, step 4 minor allele frequency, step 5 Hardy–Weinberg equilibrium, and step 6 association results. Manhattan plots, PCA plots, and md5 checksums were used to confirm exact reproducibility between the hard coded and QV-driven analyses.

2.5 Usage in a WGS validation study with GIAB and Exomiser

We next validated the QV approach on the Genome In A Bottle Chinese Trio (HG005-HG007, PRJNA200694, GRCh38 v4.2.1) using a two-phase trio pipeline that differs only in how parameters are provided: phase 1 hard coded thresholds in scripts, while phase 2 externalised the same thresholds in a QV YAML file. Both phases applied identical QC and study filters and additionally demonstrated gene-panel style analysis using the paediatric disorders panel ((26) panel_486; 3,853 genes). The upstream processing demonstrated a range of QV settings used, including region restriction by BED overlap, site-level thresholds on QUAL and INFO/DP with computed site depth from per-sample FORMAT/DP if absent, per-sample thresholds on FORMAT/DP and FORMAT/GQ with exclusion of missing GT, and composite criteria that require either all samples to pass or at least one sample to pass. Upstream processing used BCFtools for region filtering, tag filling, site depth range, and per-sample filters. The downstream filtered trio Variant Call Format (VCF) was analysed with Exomiser using a trio .ped and without input for Human Phenotype Ontology (HPO).

3 Results

3.1 Validation rare disease case study

We validated our QV protocol using ACMG-based criteria for a rare disease cohort of 940 individuals. We then conducted the variant classification using two approaches: a conventional manual method with hard-coded criteria, and our new YAML-based implementation. As shown in **Figure 1 (B)**, the outputs from both methods were identical, demonstrating a 100% match. This confirmed that our framework of a standalone, shareable, QV criteria file can be imported and applied programmatically with equivalent accuracy, providing a reproducible resource that is adaptable across different pipelines and programming environments.

3.2 Validation in a common variant GWAS

we dont need redundant repetition of values and steps 1-6. just leave it in methods.

We validated the QV approach in a standard HapMap3 Phase 3 GWAS by running two equivalent analyses: a hard coded pipeline and a QV YAML driven pipeline that externalised all quality control and analysis thresholds. Both used autosomal biallelic Single Nucleotide Polymorphism (SNP)s with sample call rate $\geq 95\%$, variant call rate $\geq 95\%$, minor allele frequency $\geq 1\%$, and Hardy–Weinberg equilibrium $p \geq 1 \times 10^{-6}$, followed by LD pruning and inclusion of sex and PC1-PC10 as covariates in logistic regression. As shown in **Figure 2** panels A and B, the Manhattan and PCA plots were indistinguishable between methods. Panel C shows identical md5 checksums for the main PLINK outputs across stages: step 1 (autosomal biallelic SNPs), step 2 (sample call rate), step 3 (variant call rate), step 4 (minor allele frequency), step 5 (Hardy–Weinberg equilibrium), and step 6 (association results). These results demonstrate exact reproducibility of the hard coded workflow using a shareable QV criteria file, confirming that QV parameterisation preserves analytic intent while improving clarity and reuse.

3.3 Validation in a WGS study with GIAB and Exomiser

We conducted the trio analysis using a standard filtering approach and the Exomiser tool for variant annotation and interpretation (27). Both analyses were identical except for the way thresholds were defined: Phase 1 used hard coded criteria, while

Phase 2 externalised the same thresholds in a QV YAML file. Upstream, both pipelines applied identical QC and study filters and restricted analysis to the PanelAppRex paediatric disorders panel, which includes 3,853 genes. Outputs were identical across phases. Upstream file-level variant counts matched at every filtering step, and Exomiser annotation and filtering metrics were equivalent, yielding the same candidate genes and reported variants. **Figure 3** illustrates the agreement: panel (A) summarises upstream processing counts by file, panel (B) compares Exomiser metrics, and panel (C) presents the key variant fields for the two variants identified in this study. This validation demonstrates that a shareable QV file reproduces the full variant interpretation workflow exactly, consistent with established variant effect predictors (28) and interpretation frameworks including Exomiser and VarFish (27; 29).

3.4 Implications

Across the validation studies, the QV framework achieved exact reproducibility of conventional hard coded workflows while externalising all analytic thresholds into a portable, shareable format. This demonstrates that QV is not a variant calling, annotation, or interpretation method, but a formal layer for defining and reusing the qualifying variables that underlie these analyses. It complements existing variant effect predictors such as Ensembl VEP, SnpEff, FAVOR, and WGSa (28), and interpretation platforms such as Exomiser and VarFish (27; 29), by specifying their operational criteria explicitly and reproducibly.

In practice, the QV file enables identical pipelines to be run across environments or institutions without ambiguity in parameterisation. This improves traceability, clarity, and interoperability while maintaining complete compatibility with established genomic analysis tools. By defining variant qualifying logic in a structured and transparent way, the QV framework strengthens analytical reproducibility and provides a foundation for regulated, auditable genomic workflows.

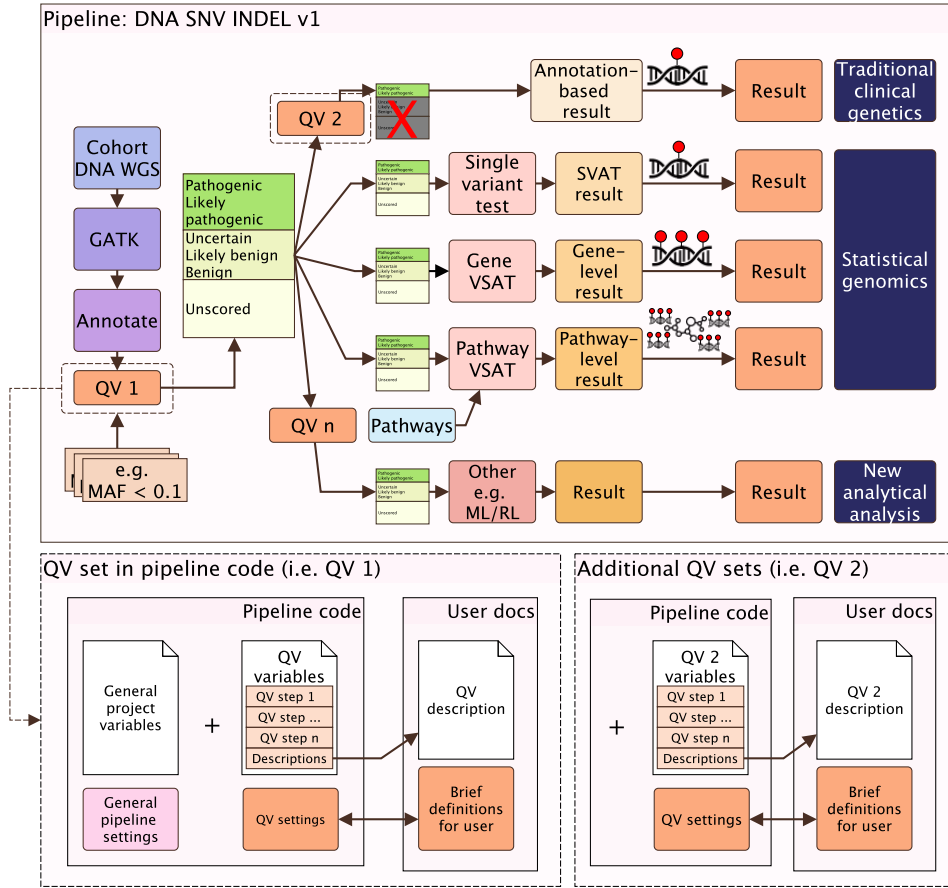
In the first validation study, we applied ACMG criteria for variant interpretation. In clinical genetics, for instance, the resulting output can be used to retrieve candidate pathogenic variants using ACMG scoring methods (1; 5). Application of additional QV sets, such as the widely used ACMG SF set for clinical reporting (17), can be used to confirm any secondary findings.

In a clinical setting it is necessary to bridge the gap between technical detail and lay understanding. By explicitly documenting variant qualifying criteria and making

QV data accessible, our framework builds trust and supports meaningful PPIE (30). The QV file adapts by integrating the main criteria variables with optionally dedicated fields for both technical description and PPIE description. This approach captures the analysis intent defined by the QV set creator and embeds patient preferences from the start.

For example, patient preferences recorded in the PPIE description can be automatically incorporated into a genetic report without additional interpretation, ensuring clarity and consistency throughout the analysis. This transparency guarantees that both experts and laypersons receive information in a format suited to their needs, thereby improving diagnostic traceability and accelerating the translation of genetic research into clinical practice.

A



B

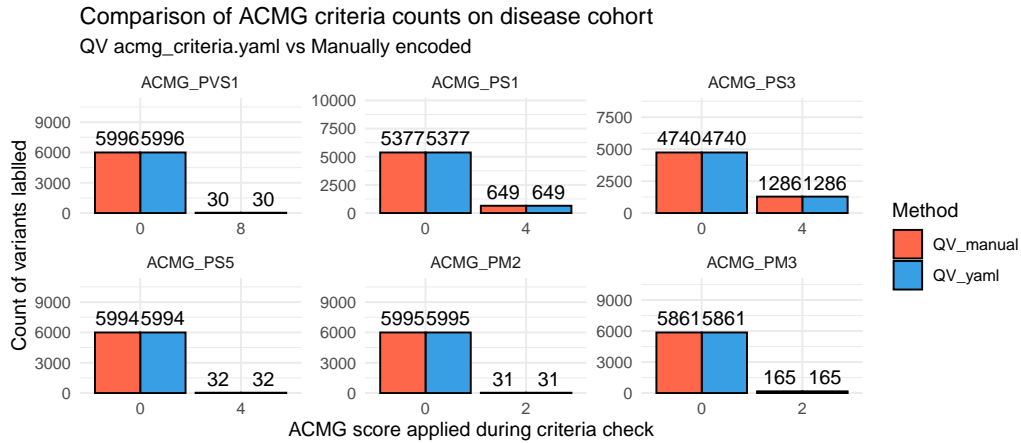


Figure 1: Summary of the QV application for a WGS pipeline. In panel (A), QV1 and QV2 are presented as sequentially piped protocol steps. In this example, QV2 differs from QV1 by retaining only likely/pathogenic variants (indicated by a red X). The QV file loaded by the analysis pipeline comprise a description field (optional) and a variables field (mandatory). The QV criteria may be spread throughout the pipeline. (B) Validation case study using an ACMG criteria subset, demonstrating a 100% match between manually encoded and standalone YAML-based QV (qv_files/acmg_criteria.yaml) for assigning pathogenicity scores.

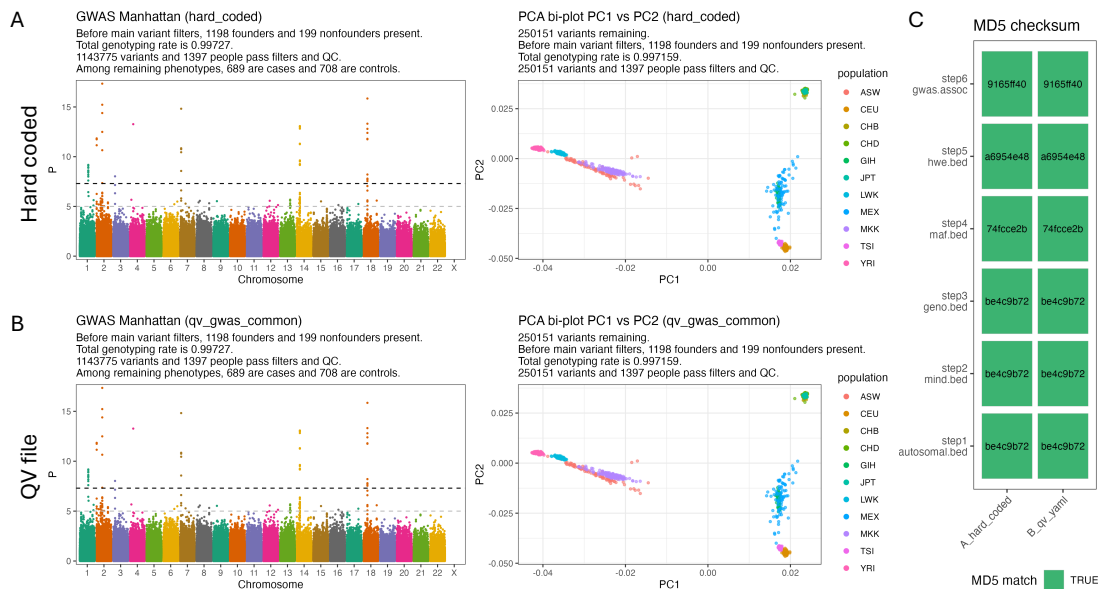


Figure 2: Reproducible GWAS using QV parameterisation. (A) GWAS of simulated binary phenotypes in HapMap3 Phase 3 (R3) using a hard-coded pipeline. Shown are the Manhattan plot of logistic regression results (left) and the correction for population structure with principal component analysis (PC1 vs PC2, right). (B) Identical GWAS using a QV YAML configuration file to supply quality-control and analysis thresholds. Manhattan and PCA results are indistinguishable from panel A. (C) Verification of reproducibility. MD5 checksums of the main PLINK outputs — step1 (autosomal, biallelic SNPs), step2 (sample call rate), step3 (variant call rate), step4 (minor allele frequency), step5 (Hardy–Weinberg equilibrium), and step6 (association results) — are identical between phases A and B. The QV file encodes these thresholds (sample call rate $\geq 95\%$, variant call rate $\geq 95\%$, MAF $\geq 1\%$, HWE $p \geq 1e-6$, autosomal biallelic SNPs only) together with covariates (sex and PC1-PC10) and logistic regression settings. This demonstrates that a shareable QV file reproduces hard-coded pipelines exactly while improving transparency and reusability.

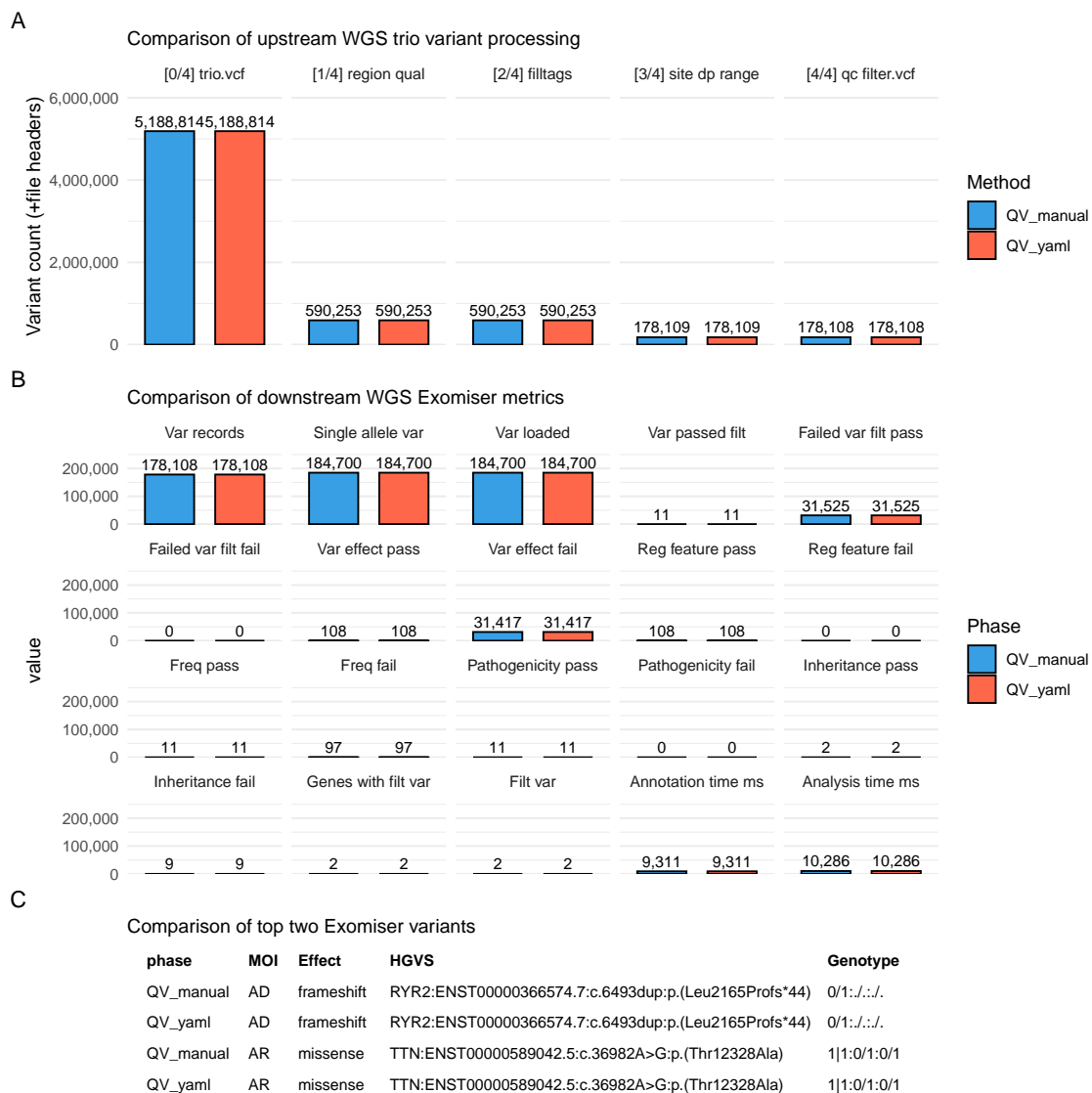


Figure 3: Validation of a trio Exomiser pipeline using QV parameterisation. Panels A, B, and C correspond to upstream processing counts, downstream Exomiser metrics, and final variants detected, respectively.

4 Summary

This paper introduces a framework for integrating qualifying variants into genomic analysis pipelines, enhancing reproducibility, interpretability and the seamless translation of research findings into clinical practice.

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7 Contributions

DL designed the work and contributed to the manuscript. AS, SB, VS, DH, SÖ, JA contributed to the manuscript. JF, SF, LJS supervised the work, manuscript, and applied for funding.

8 Competing interests

The authors declare no competing interests.

9 Ethics statement

Summary statistics were used from studies which have been previously reported and approved by the respective ethics committees of all participating centers (Cantonal

Ethics Committee Bern, approval number KEK-029/11) and the study was conducted in accordance with the Declaration of Helsinki.

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