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# INTEGRATING GENOMICS AND MOLECULAR GENETICS TO EXPLAIN HUMAN GENETIC VARIATION

***Diyora Muxtoraliyeva***
*First-year undergraduate student*
*Central Asian University*

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**Abstract.** Human genome sequencing identifies differences in DNA, but the biological meaning of these differences requires further investigation. This extended abstract examines how genome assembly, population comparisons, gene expression analysis and functional experiments contribute to variant interpretation. Four primary studies are compared. The reviewed findings show that a more complete reference improves access to complex sequences, whereas a pangenome represents variation across individuals. Expression studies and genome editing address a separate question: whether and how a sequence difference changes cellular activity. The synthesis supports an integrated approach in which accurate detection, biological context and experimental evidence are evaluated together.

**Keywords:** genomics; molecular genetics; human genetic variation; pangenome; gene expression; functional analysis.

**Introduction.** Genomics examines DNA across an entire genome, while molecular genetics investigates how genes and their products function. The distinction matters because identifying a DNA variant is only the beginning of explaining its effect. A difference may alter a protein sequence, affect the processing of an RNA transcript, influence gene expression or have no measurable effect in the conditions examined. Consequently, an interpretation must connect sequence information with a plausible molecular mechanism rather than assume that every difference is biologically harmful.

Human variation also extends beyond single nucleotide changes. Insertions, deletions, duplications and rearrangements can modify larger genomic regions. Their detection depends partly on how well those regions are represented in the reference used for analysis [1, 2]. A

reference is therefore a practical comparison resource, not a definition of an ideal human genome. Combining genomics with molecular genetics helps researchers distinguish technical uncertainty about a sequence from biological uncertainty about its function. This separation supports more precise interpretation.

**Aim and Methodology**. A focused narrative review examines four selected primary publications from 2018 to 2023 [1–4] to explain how genome references and molecular evidence complement one another. The studies cover genome completeness, population diversity, RNA regulation and experimental variant assessment. Each is considered for its contribution and inferential limits. This illustrative synthesis reports no new laboratory or participant data

**Findings and Discussion.** Genome completeness determines which sequences can be examined reliably. Nurk et al. reported the T2T-CHM13 assembly, containing approximately 3.055 billion base pairs and gapless sequences for all chromosomes except the Y chromosome [1]. The study resolved regions that had remained difficult to assemble, including centromeric repeats and recent segmental duplications. Its value for molecular genetics is that previously inaccessible regions become available for further study. However, completeness and diversity are different properties: resolving one genome does not represent every sequence found across human populations.

The pangenome approach addresses representation across individuals. Liao et al. constructed a draft reference from 47 genetically diverse individuals, producing 94 haplotype assemblies [2]. A haplotype describes a set of variants carried together on a chromosome; separating the two parental copies preserves information that can be lost in a combined sequence. The study showed improved variant discovery compared with workflows using GRCh38. A pangenome can therefore reduce reference bias and reveal alternative sequences at complex loci. Nevertheless, the presence of a sequence in a reference collection does not establish its functional effect.

Gene expression adds evidence about how variation influences RNA. The GTEx

Consortium analysed 15,201 RNA sequencing samples from 49 tissues of 838 donors [3]. The study examined genetic associations with expression and splicing and showed that their interpretation depends on tissue context and cell composition. This explains why a DNA difference may be relevant in one biological setting but less informative in another. Expression associations can guide a mechanistic hypothesis, yet association alone does not prove that a particular variant causes the observed change.

Functional experiments provide a more direct test of variant effects within a defined model. Findlay et al. used saturation genome editing to assess nearly 4,000 single nucleotide variants in 13 functionally important BRCA1 exons [4]. The method introduces many sequence changes and measures their consequences in cells. The study demonstrated that experimental scores can distinguish variants with different effects on gene function and expression. However, its coverage was limited to selected exons and its evidence came from a particular cellular system. Such scores should be interpreted within the experimental context rather than treated as universal descriptions of whole organism biology.

Together, these studies support a sequence of questions for variant interpretation. First, is the difference real and measured accurately? Second, does the reference and comparison dataset represent the relevant sequence diversity? Third, which molecular process could be affected, and in which tissue or cell type? Finally, does a suitable experiment support that explanation? These questions separate evidence about detection from evidence about mechanism. As a synthesis of the reviewed work, the strongest interpretation is one in which independent types of evidence converge on the same explanation.

Disagreement between evidence types is also informative. A predicted effect may fail to appear in an assay because the prediction is incorrect, because the assay measures a different function or because the relevant biological context is absent. An uncertain result should therefore prompt a narrower claim and a better defined follow-up question. For example, an expression association could motivate testing whether the candidate sequence changes RNA processing. This is a proposed research strategy, not a result established for every variant by

the reviewed studies.

**Limitations and Research Implications.** The four studies use different datasets, biological materials and analytical endpoints, so their findings cannot be combined into a single accuracy estimate. They also do not establish how well any particular analysis performs in an unexamined population. An integrated investigation should therefore define its target population, biological context and functional question before selecting a method. A useful framework is to specify the question each method can answer and the additional evidence required for the next inference. This approach encourages precise explanations and avoids equating technical progress in sequencing with a complete understanding of gene function.

**Conclusion.** Genomics and molecular genetics make complementary contributions to understanding human variation. Genome assemblies and pangenomes improve the sequence framework, expression studies identify context-dependent relationships, and functional experiments test specific biological effects. The central conclusion of this review is that a defensible explanation requires both reliable sequence information and evidence appropriate to the proposed mechanism. Further progress depends on connecting these levels carefully, reporting uncertainty and testing hypotheses in relevant biological systems. This framework links the description of a DNA difference to a testable explanation of its biological effect.

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