GENETICS DOMAIN | LESSON 6 OF 20 | BIOINFORMATICIAN

Looking Up a Variant

When we find a DNA change in a patient's gene, where do we look it up, and how do we decide if it is harmful, harmless, or unknown?

CARRY FORWARD

IRF6 encodes a transcription factor that changes cell behavior by controlling other genes.

10-YEAR TAKEAWAY

Variant interpretation combines clinical assertions, population frequency, molecular consequence, and evidence quality.

1. Observe the analogy before naming the biology

Illustration: A library catalog card needs several trust signals

1. Which card has the strongest review trail?

2. Why does a rare book not have to be harmful?

3. What should happen when reviewers disagree?

2. Turn observations into rules

1. Rule 1: Read classification with review status. Explain it in your own words.

2. Rule 2: Check population frequency and condition match. Explain it in your own words.

3. Rule 3: Treat uncertain and conflicting evidence honestly. Explain it in your own words.

Where the analogy stops: Variant databases are updated evidence systems, not static library verdicts.

3. Map the rules onto the biomedical example

Biomedical teaching illustration: Read a ClinVar-style IRF6 record

Analogy step	Biology step	How the relationship stays the same
Catalog claim	Clinical significance	_____
Review trail	Submission criteria and review status	_____
Circulation count	Population allele frequency	_____

4. Use the case evidence

ID	Finding supplied in the case	Why it matters
GEN06-E1	ClinVar stores submitted variant-condition classifications and review status.	A classification must be read with its evidence level.
GEN06-E2	A pathogenic IRF6 assertion should match an IRF6-related condition and supporting evidence.	Condition context matters.
GEN06-E3	A common population variant is unlikely to cause a rare fully penetrant syndrome by itself.	Frequency constrains pathogenic claims.

5. Make the clinical decision

You are the variant-review trainee. An IRF6 record says pathogenic but has one old submission and no assertion criteria; another lab calls it uncertain.

A. Report the conflict and seek stronger current evidence.

B. Treat the word pathogenic as final without review context.

C. Call every rare variant disease-causing.

Decision. Choose the report language and cite review-status plus frequency rules.

Claim ceiling: You may summarize database evidence. You may not independently diagnose from a weak or conflicting record.

Claim. State the choice you can defend.

Evidence. Use these labeled IDs: GEN06-E1 + GEN06-E2.

Reasoning. Explain why the evidence supports the claim and stays inside the claim ceiling.

6. Reduce the lesson to one lasting idea

Take-home. Variant interpretation combines clinical assertions, population frequency, molecular consequence, and evidence quality.

1. What should be read beside a ClinVar classification?

2. Why does rarity not prove pathogenicity?

Glossary

Term	Plain-English definition
ClinVar	An NIH database of reported DNA variants, the conditions they are linked to, and a clinical-significance call for each.
OMIM	Online Mendelian Inheritance in Man, a catalog of human genes and the inherited diseases they cause, each with a stable reference number.
pathogenic	Capable of causing disease; for a gene variant, classified as disease-causing based on the weight of scientific evidence.
benign	Not harmful or not cancerous; a benign tumor stays in one place and does not spread, and a benign gene variant does not cause disease.
variant of uncertain significance (VUS)	A genetic change whose effect on health is not yet known, leaving doctors unable to call it harmful or harmless.

Next lesson unlock

When we read variants we saw codes like R84C and R250X. What kinds of typos in DNA do those codes actually stand for?

The journal links on the lesson page are optional. Everything required for this guided-notes set is already supplied here and in the case file.