

Is This Gene Important Across Species?

If we line up the IRF6 protein from many animals, which parts stay the same, and what does staying the same tell us about importance?

CARRY FORWARD

Protein domains are specialized working regions, so a variant's position helps predict which function may fail.

10-YEAR TAKEAWAY

Evolutionary conservation marks positions that tolerated little change, adding evidence that a new change may matter.

Cells differentiate	Development sculpts	Cells move	Development can go wrong
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1. Observe the analogy before naming the biology

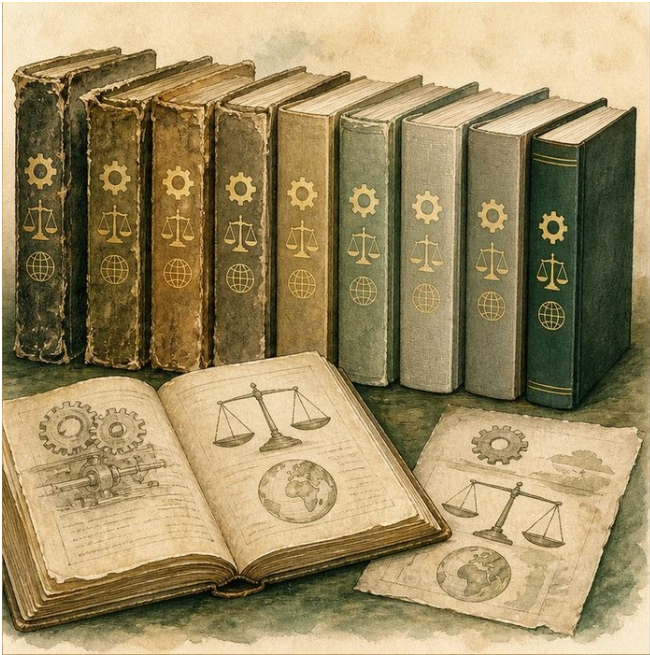


Illustration: Compare many editions to find the words no editor changes

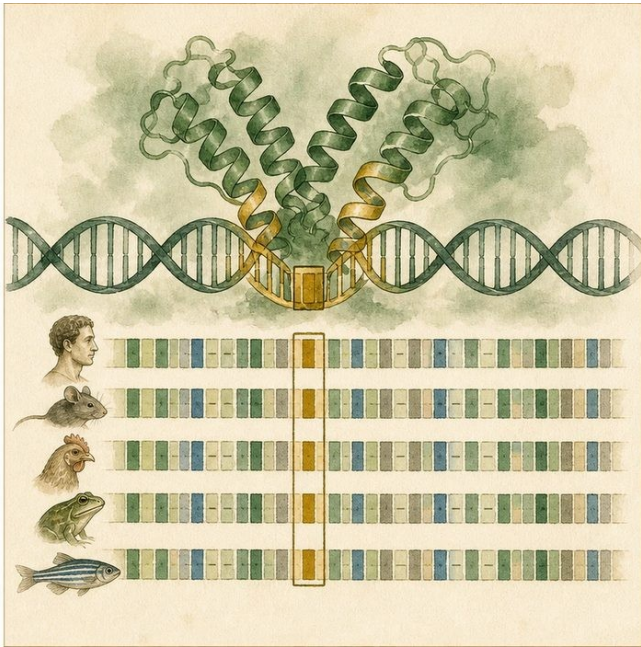
- 1. Which parts remain unchanged across every edition?
- 2. What does repeated preservation suggest?
- 3. Can preservation alone prove a new edit is harmful?

2. Turn observations into rules

- 1. Rule 1: Align orthologous sequences. Explain it in your own words.
- 2. Rule 2: High conservation suggests functional constraint. Explain it in your own words.
- 3. Rule 3: Conservation supports, but does not settle, variant classification. Explain it in your own words.

Where the analogy stops: Evolution selects organisms and populations, not words in a book.

3. Map the rules onto the biomedical example



Biomedical teaching illustration: Read an IRF6 multispecies alignment

Analogy step	Biology step	How the relationship stays the same
Edition	Species ortholog	_____
Unchanged phrase	Conserved amino-acid stretch	_____
Editorial constraint	Purifying selection	_____

4. Use the case evidence

ID	Finding supplied in the case	Why it matters
GEN11-E1	IRF6 orthologs occur across many vertebrate species.	The gene is evolutionarily shared.
GEN11-E2	The DNA-binding domain has highly conserved residues, including Arg84.	Those positions tolerated little change.
GEN11-E3	Some conserved-position variants have different clinical effects.	Conservation is one evidence line, not a complete verdict.

5. Make the clinical decision

You are reviewing a new missense variant at a conserved IRF6 residue. The residue is identical in five vertebrates, but no patient or functional data exist.

- A. Use conservation as supporting evidence and keep classification uncertain.
- B. Call it pathogenic from conservation alone.
- C. Call it benign because only one amino acid changed.

Decision. Choose the classification stance and cite both support and limit.

Claim ceiling: You may say the site is constrained. You may not make conservation the only pathogenicity criterion.

Claim. State the choice you can defend.

Evidence. Use these labeled IDs: GEN11-E1 + GEN11-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. Evolutionary conservation marks positions that tolerated little change, adding evidence that a new change may matter.

1. What does conservation suggest?
2. Why does it not finish classification?

Glossary

Term	Plain-English definition
BLAST	A search tool (Basic Local Alignment Search Tool) that compares a DNA or protein sequence against a database to find similar sequences and likely relatives.
ortholog	The matching version of a gene found in a different species, descended from the same gene in a common ancestor.
conservation	When a DNA or protein sequence stays similar across many species, a strong sign that it does an essential biological job.
percent identity	In a sequence comparison, the share of positions that exactly match between two DNA or protein sequences; a higher value means they are more alike.
purifying selection	Natural selection that removes harmful mutations over time, which is why important DNA and protein sequences stay highly conserved across species.

Next lesson unlock

We found that the DNA-binding domain is conserved across species, so it must be essential. But if those exact amino acids are protected across hundreds of millions of years, what actually happens to the protein when one of them, like position 84, is swapped for the wrong letter? We chase that next.

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.