STUDENT READING PACK | GENETICS DOMAIN | NINTH-GRADE TARGET

The Genetics Domain Explainer

Short readings that supply every idea needed for each lesson decision.

REQUIRED	OPTIONAL
Read the three short paragraphs and use the labeled case evidence.	**Open the publication links only if you want to go deeper.**

How every reading is structured

- Why it matters
- The question
- Prior takeaway
- Analogy and rules
- Biomedical example
- Case evidence
- Decision
- Take-home
- Glossary
- Optional sources

Chance or Genetic? Reading Mateo's Family Tree

Is Mateo's cleft a one-time chance event, or is it written into his family?

START WITH

Mateo's developmental pathway is supported, but the composite file does not establish one cause.

REMEMBER

A pedigree shows how a trait travels through a family; it does not prove that an isolated case is non-genetic.

Why this matters

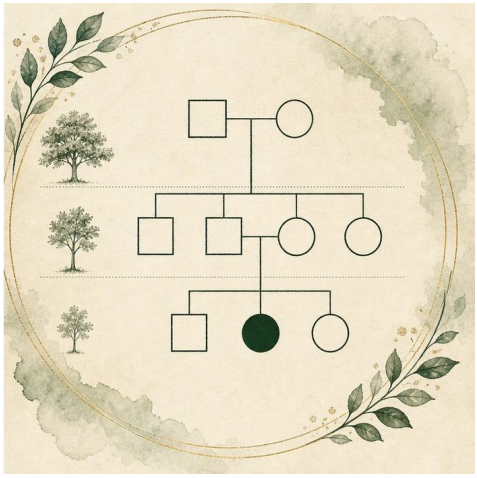
A pedigree is the first genetic model students can build from a clinical interview.

The biology in plain English

A pedigree is a family diagram that records relationships and traits across generations.

Mateo is the proband, the person who brings the family to genetic attention. No other clefts are reported.

An isolated pedigree can reflect many small risks, a new variant, incomplete penetrance, or missing family information.



Biomedical teaching illustration: Build Mateo's three-generation pedigree

Check your understanding

- What does Mateo's pedigree show?
- What genetic claim can it not close?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN01-E1	Mateo is the only reported relative with a cleft across three generations.	The pedigree appears sporadic rather than strongly familial.
GEN01-E2	Both parents are unaffected.	A simple fully penetrant dominant pattern is not supported.
GEN01-E3	Isolated clefts can still involve inherited and new genetic risk factors.	No family history does not mean no genetic contribution.

Concrete decision

You are the intake genetic counselor. Mateo's parents ask whether the empty family history means the cleft was only chance.

A. Say the pedigree looks isolated but cannot exclude genetic risk.

B. Say no relatives means genes played no role.

C. Diagnose a dominant syndrome from one affected child.

Decision prompt: Choose the counseling statement and cite the pedigree plus its limit.

Claim ceiling: You may describe the observed family pattern. You may not exclude genetic contribution or name an inheritance model yet.

Glossary

Term	Plain-English definition
pedigree	A family tree drawn with standard symbols (squares for males, circles for females, filled for affected) so any geneticist can read a family at a glance.
proband	The first affected person whose case brings a family in for genetic study, marked with an arrow on the pedigree.
isolated (sporadic) case	A trait that appears in just one person in a family, with no other clearly affected relatives.
familial case	An instance of a trait or condition that appears in more than one relative, often across several generations of a family.
generation	One layer of a family tree, such as grandparents, then parents, then children, shown as a row on a pedigree.

READING 2 OF 20 | CELLS DIFFERENTIATE

Screening for a Hidden Syndrome

What clue separates a syndrome from a lone cleft, and does Mateo show it?

START WITH

A pedigree shows how a trait travels through a family; it does not prove that an isolated case is non-genetic.

REMEMBER

A syndrome claim requires a repeatable pattern of features, not a cleft plus a familiar gene name.

Why this matters

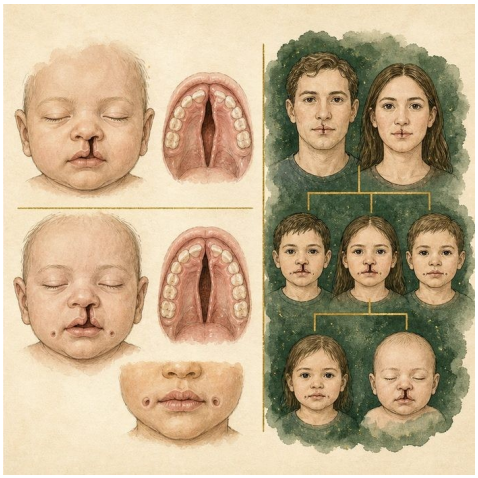
Students must separate an exemplar gene from a diagnosis in one patient.

The biology in plain English

A syndrome is a repeatable group of findings. Van der Woude syndrome often includes clefting, lower-lip pits, and a family pattern.

Mateo's composite file has no lip pits or broader anomaly pattern.

IRF6 is still useful to study because it reveals cleft biology, but studying IRF6 does not diagnose Mateo.



Biomedical teaching illustration: Compare isolated cleft with an IRF6-related syndrome pattern

Check your understanding

- What pattern raises Van der Woude suspicion?
- Why does studying IRF6 not diagnose Mateo?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN02-E1	Mateo has no lower-lip pits on repeated examination.	A classic Van der Woude clue is absent.
GEN02-E2	No additional anomaly pattern or affected relative is documented.	The current phenotype screen supports an isolated presentation.
GEN02-E3	IRF6-related disorders are established by suggestive findings plus a pathogenic IRF6 variant.	Phenotype and molecular evidence work together.

Concrete decision

You are presenting the genetics screen. A teammate wants to label Van der Woude syndrome because IRF6 will be studied later.

A. Keep the case isolated-appearing pending molecular evidence.

B. Assign Van der Woude syndrome from the cleft alone.

C. Ignore lip pits and family history.

Decision prompt: Choose the chart language and cite the absent pattern evidence.

Claim ceiling: You may say the current screen is isolated-appearing. You may not establish or exclude every syndrome without appropriate testing.

Glossary

Term	Plain-English definition
phenotype	The observable traits of an organism, such as appearance or function, that result from its genotype combined with environmental influences.
syndromic cleft	A cleft that comes packaged with other features as part of a named syndrome, accounting for roughly 30 percent of clefts.
nonsyndromic (lone) cleft	A cleft that occurs on its own without other birth differences, making up roughly 70 percent of all clefts.
Van der Woude syndrome (VWS)	The most common single-gene cause of cleft lip and palate, usually from an IRF6 change, whose hallmark is small lower-lip pits.
lip pits	Small paired depressions on the lower lip that serve as the hallmark sign flagging Van der Woude syndrome, a cleft-related disorder.

READING 3 OF 20 | DEVELOPMENT CAN GO WRONG

Does It Run in Families Like a Single Gene?

Does Mateo's isolated cleft fit clean single-gene (dominant) transmission, or something else?

START WITH

A syndrome claim requires a repeatable pattern of features, not a cleft plus a familiar gene name.

REMEMBER

Most isolated clefts fit a multifactorial threshold model in which many small influences add to risk.

Why this matters

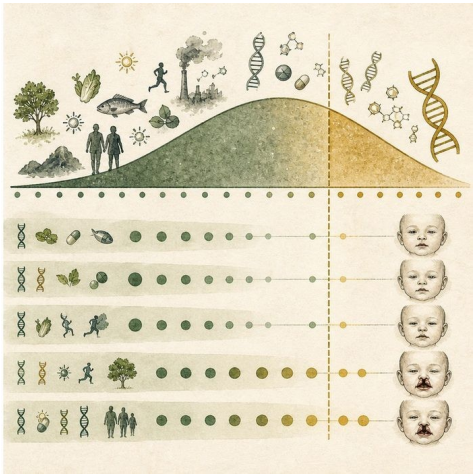
The threshold model explains how many small risks can create a discrete developmental outcome.

The biology in plain English

Multifactorial means that more than one factor contributes. Liability is the combined underlying tendency toward an outcome.

If total liability crosses a developmental threshold, a cleft can occur. Below the threshold, it does not.

The model explains risk patterns but does not give one exact cause for Mateo.



Biomedical teaching illustration: Model isolated cleft as multifactorial liability

Check your understanding

- Why is the outcome discrete even when liability is graded?
- What evidence makes simple dominant inheritance less likely?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN03-E1	Mateo's pedigree does not show clean vertical transmission.	A fully penetrant dominant model is a poor fit.
GEN03-E2	Isolated cleft risk is influenced by many genetic loci and non-genetic factors.	Multiple contributors are expected.
GEN03-E3	A person can carry risk factors without developing a cleft.	Penetrance is not all-or-none for each risk factor.

Concrete decision

You are selecting the inheritance model for the case board. The board offers either one dominant allele with complete penetrance or a multifactorial threshold model.

A. Choose the multifactorial threshold model.

B. Choose complete dominant inheritance despite unaffected parents.

C. Say genetics cannot affect isolated clefts.

Decision prompt: Choose the model and cite both pedigree and population evidence.

Claim ceiling: You may choose the best-fit model. You may not calculate Mateo's exact liability or identify each contributor.

Glossary

Term	Plain-English definition
autosomal dominant	A lesson term defined by the surrounding model and case evidence.
vertical transmission	A trait appearing in nearly every generation, passed directly from parent to child, the signature pattern of a dominant inheritance.
multifactorial inheritance	A trait caused by many small genetic and environmental factors adding up together, rather than by a single gene alone.
threshold model	The idea that a trait appears only when a person's combined liability from genes and environment crosses a set line.
liability	A person's total built-up risk for a trait from all their genetic and environmental factors combined, often pictured on a continuous scale.

READING 4 OF 20 | CELLS MOVE

Hunting the Exemplar Cleft Gene: Linkage to 1q32

How do you hunt a gene when you have no address for it?

START WITH

Most isolated clefts fit a multifactorial threshold model in which many small influences add to risk.

REMEMBER

Linkage follows inherited chromosome markers to narrow a gene's address before sequencing names the gene.

Why this matters

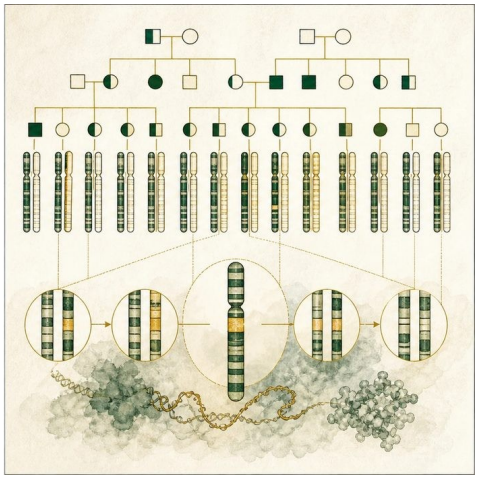
Linkage shows how scientists found genes before whole-genome sequencing became routine.

The biology in plain English

A DNA marker is an inherited sequence position that can be followed through a family.

Nearby markers and a disease locus tend to travel together because recombination separates close sites less often.

Linkage narrowed Van der Woude syndrome to chromosome 1q32. Sequencing was still needed to identify IRF6.



Biomedical teaching illustration: Follow a linked marker to chromosome 1q32

Check your understanding

- What does co-segregation mean?
- Why is a linked marker not automatically causal?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN04-E1	In large Van der Woude families, certain chromosome 1 markers co-segregated with the phenotype.	The disease locus was linked to that region.
GEN04-E2	Recombination events narrowed the shared interval to 1q32.	Family crossovers set region boundaries.
GEN04-E3	The interval still contained more than one possible gene.	Linkage gives an address range, not a gene name.

Concrete decision

You are the linkage analyst for a historical gene hunt. A marker travels with the syndrome in nearly every informative relative, but several genes lie nearby.

A. Prioritize the linked interval for sequencing.

B. Declare the marker itself the causal gene.

C. Ignore recombination boundaries.

Decision prompt: Choose the next step and cite what linkage can and cannot locate.

Claim ceiling: You may prioritize a locus. You may not call a marker causal or name IRF6 before sequence evidence.

Glossary

Term	Plain-English definition
DNA marker	A known, variable spot in the genome used as a trackable signpost near a gene, even though the marker itself is not the disease gene.
linkage	The tendency of two spots close together on a chromosome to be inherited together.
co-segregation	When a marker version and a disease are inherited together in every affected family member, evidence that the responsible gene sits nearby.
recombination	The shuffling of chromosome pieces during egg and sperm formation, which can occasionally separate a marker from a nearby gene.
locus	The specific address of a gene or marker on a chromosome, such as the band 1q32.

The Gene at 1q32 Has a Name: IRF6, From DNA to Protein

What is the gene at 1q32, and what does it make?

START WITH

Linkage follows inherited chromosome markers to narrow a gene's address before sequencing names the gene.

REMEMBER

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

Why this matters

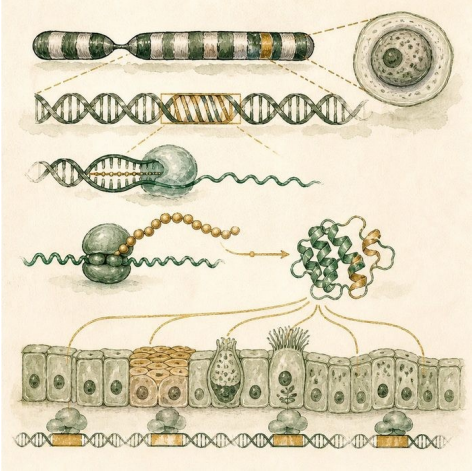
Students need the central dogma before they can interpret variant consequences.

The biology in plain English

IRF6 is a gene on chromosome 1q32.2. Cells copy the gene into messenger RNA.

Ribosomes translate the RNA into the IRF6 protein, which is 467 amino acids long.

IRF6 is a transcription factor. It helps control other genes that guide epithelial cells toward the right differentiated state.



Biomedical teaching illustration: Trace IRF6 from gene to regulatory protein

Check your understanding

- What molecule is translated?
- Why is transcription factor more accurate than structural lip protein?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN05-E1	Sequencing the linked 1q32 interval identified damaging variants in IRF6.	IRF6 was the gene supported by molecular evidence.
GEN05-E2	IRF6 is transcribed into mRNA and translated into a 467-amino-acid protein.	The gene produces a specific protein product.
GEN05-E3	IRF6 contains a DNA-binding domain and regulates epithelial differentiation genes.	Its main job is control of gene activity.

Concrete decision

You are explaining the gene discovery to a molecular team. A new intern says IRF6 is a piece of lip tissue made directly from DNA.

A. Correct the path to DNA, RNA, transcription factor, target genes, and cell behavior.

B. Agree that DNA becomes lip tissue directly.

C. Say IRF6 is only a chromosome marker.

Decision prompt: Choose the correction and cite gene-product and protein-job evidence.

Claim ceiling: You may describe IRF6's molecular role. You may not say one IRF6 result explains Mateo without a case test.

Glossary

Term	Plain-English definition
transcription	The first step of making a protein: copying a DNA gene into messenger RNA.
mRNA (messenger RNA)	The working copy of a gene that carries its instructions out of the nucleus to the ribosome to be read into protein.
translation	The second step of making a protein: the ribosome reads the mRNA and builds a chain of amino acids.
transcription factor	A protein that binds DNA and turns specific genes on or off, controlling what a cell becomes and does.
IRF6	Interferon Regulatory Factor 6, a transcription factor needed by the skin-like cells that let the lip and palate fuse; a leading cleft gene.

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?

START WITH

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

REMEMBER

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

Why this matters

Students must learn that databases organize claims rather than replace reasoning.

The biology in plain English

ClinVar collects variant interpretations from laboratories and expert groups. The same variant may have one or several submissions.

Review stars, dates, condition names, and assertion criteria help users judge confidence.

Population frequency from resources such as gnomAD adds another check. Rare does not automatically mean harmful, and uncertain means uncertain.

Biomedical teaching illustration: Read a ClinVar-style IRF6 record

Check your understanding

- What should be read beside a ClinVar classification?
- Why does rarity not prove pathogenicity?

Case evidence supplied for this lesson

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.

Concrete 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 prompt: 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.

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.

Kinds of Typos in DNA

What kinds of typos can occur in DNA?

START WITH

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

REMEMBER

DNA variants change proteins in different ways, so variant type is evidence about mechanism, not a verdict by itself.

Why this matters

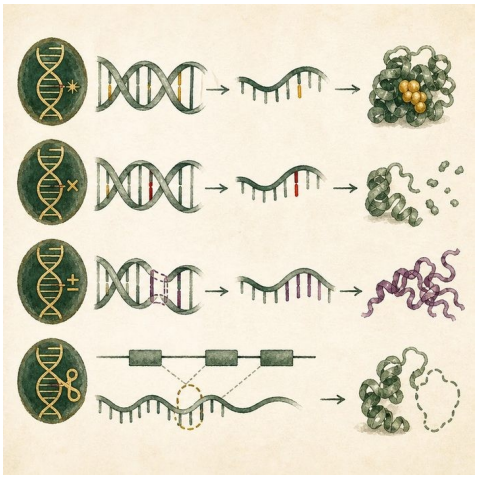
Variant vocabulary becomes useful when it connects a DNA edit to a testable protein or RNA effect.

The biology in plain English

A missense change replaces one amino acid. Its effect depends on the amino acid, location, and protein structure.

Nonsense and frameshift changes may shorten the protein. Cells sometimes destroy RNA containing an early stop.

Splice-site changes can alter how exons are joined. Laboratory, clinical, and population evidence are still needed.



Biomedical teaching illustration: Translate four IRF6 variant types

Check your understanding

- Which variant type shifts later codons?
- Why is variant type not a final classification?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN07-E1	A missense variant replaces one amino acid.	The rest of the reading frame can remain intact.
GEN07-E2	A nonsense or frameshift variant can create a premature stop.	The protein may be shortened or its RNA degraded.
GEN07-E3	A splice-site variant can alter exon joining.	The mature mRNA can lose or gain sequence.

Concrete decision

You are annotating three IRF6 lab reports. Report A is missense, B is an early nonsense, and C is a splice-site change near an exon boundary.

A. Predict different possible consequences and request location-specific evidence.

B. Call all three identical.

C. Call every missense benign.

Decision prompt: Choose the annotation strategy and cite two distinct mechanisms.

Claim ceiling: You may predict molecular consequences. You may not classify pathogenicity from variant type alone.

Glossary

Term	Plain-English definition
missense	A DNA change that swaps one amino acid in a protein, leaving it full length but possibly altering how it works.
nonsense	A DNA change that creates an early stop codon, halting translation so the protein is cut short and usually nonfunctional.
frameshift	An insertion or deletion not a multiple of three that re-groups every codon after it, scrambling the rest of the protein.
splice-site variant	A change at an intron and exon boundary that disrupts mRNA splicing, so the wrong pieces are joined and the protein is altered.
reading frame	The set of three-letter codons the ribosome reads in order along messenger RNA; a frameshift mutation throws this grouping off.

READING 8 OF 20 | CELLS DIFFERENTIATE

One Gene, Two Diseases

Why does one gene cause two different diseases?

START WITH

DNA variants change proteins in different ways, so variant type is evidence about mechanism, not a verdict by itself.

REMEMBER

Variant location can change mechanism: reduced dosage and altered DNA binding can produce different IRF6-related outcomes.

Why this matters

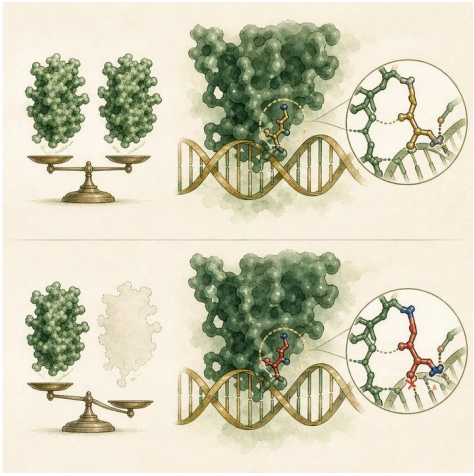
Genotype-phenotype reasoning is strongest when students name both pattern and uncertainty.

The biology in plain English

Haploinsufficiency means one working copy does not make enough functional product for typical development.

Some IRF6 missense variants alter the DNA-binding domain, including variants at amino acid 84.

Variant location helps, but the exact substitution, family data, and experiments still matter.



Biomedical teaching illustration: Compare IRF6 haploinsufficiency and domain-specific disruption

Check your understanding

- How is reduced dosage different from an interfering protein?
- Why can two changes at the same position have different outcomes?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN08-E1	Many Van der Woude variants reduce the amount of functional IRF6.	Haploinsufficiency is a supported disease mechanism.
GEN08-E2	Some severe PPS-associated variants cluster at Arg84 in the DNA-binding domain.	Location can alter protein behavior and phenotype.
GEN08-E3	Different substitutions at Arg84 do not always produce the same phenotype.	Position alone does not erase the exact amino-acid effect.

Concrete decision

You are comparing two IRF6 variant reports. One creates an early stop. The other changes Arg84 in the DNA-binding domain.

A. Discuss dosage loss versus domain-specific altered function.

B. Call both mechanisms identical without evidence.

C. Predict Mateo's phenotype from the gene name alone.

Decision prompt: Choose the comparison and cite dosage plus domain evidence.

Claim ceiling: You may compare supported mechanisms. You may not guarantee syndrome severity from variant position alone.

Glossary

Term	Plain-English definition
haploinsufficiency	When one working copy of a gene cannot make enough product on its own, so losing the second copy causes the trait.
dominant-negative	A faulty protein that not only fails at its own job but also blocks the working protein made from the normal gene copy.
DNA-binding domain	The part of a transcription factor that grips DNA so it can switch target genes on or off.
loss of function	A genetic change that reduces or removes a protein's normal activity, so the cell loses what that protein usually does.
genotype-phenotype correlation	A link between which gene variant a person carries and which features or how severe a condition they show.

READING 9 OF 20 | DEVELOPMENT CAN GO WRONG

The Hidden Regulatory Variant

Where is the common, hidden variant?

START WITH

Variant location can change mechanism: reduced dosage and altered DNA binding can produce different IRF6-related outcomes.

REMEMBER

A regulatory variant changes when or how much a gene is used without changing the protein sequence.

Why this matters

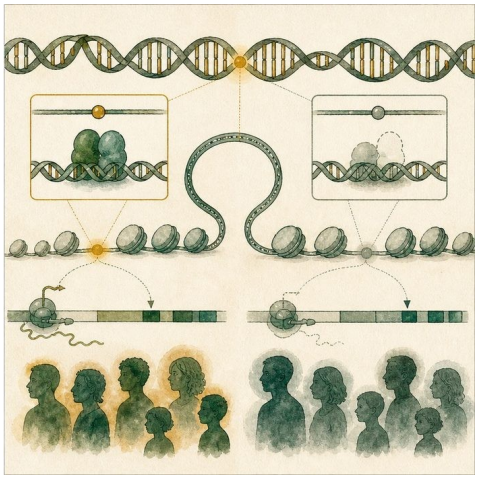
Regulatory DNA connects genetics to the timing and location of development.

The biology in plain English

Enhancers are DNA regions that help control when and where a gene is active.

The IRF6 variant rs642961 changes an AP-2alpha binding site in an enhancer. It does not change the IRF6 protein sequence.

The allele is associated with higher cleft risk in some populations, but many carriers are unaffected.



Biomedical teaching illustration: Map rs642961 to an IRF6 enhancer

Check your understanding

- What changes in a regulatory variant?
- Why is risk allele more accurate than causal mutation here?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN09-E1	rs642961 lies in an IRF6 enhancer rather than a protein-coding exon.	The variant does not change an IRF6 amino acid.
GEN09-E2	The risk allele disrupts an AP-2alpha binding site in laboratory assays.	A molecular regulatory mechanism is supported.
GEN09-E3	The allele is associated with increased cleft-lip risk but is found in unaffected people.	It is a risk allele, not a deterministic syndrome mutation.

Concrete decision

You are reviewing an isolated-cleft research result. A report finds one rs642961 risk allele and no pathogenic coding variant.

A. Describe a modest regulatory risk contribution, not a diagnosis.

B. Call it a guaranteed cause.

C. Dismiss it because the protein sequence is unchanged.

Decision prompt: Choose the interpretation and cite regulatory mechanism plus penetrance.

Claim ceiling: You may describe association and mechanism. You may not claim the allele alone caused Mateo's cleft.

Glossary

Term	Plain-English definition
coding variant	A DNA change located inside the protein-coding part of a gene, which can alter the protein the gene builds.
regulatory variant	A DNA change outside a gene's coding region that alters when or how strongly the gene is switched on.
enhancer	A stretch of regulatory DNA that boosts how strongly a nearby gene is transcribed, even from some distance away.
transcription factor	A protein that binds DNA and turns specific genes on or off, controlling what a cell becomes and does.
risk allele	A common version of a gene that nudges the chance of a trait up a little, without causing the trait by itself.

READING 10 OF 20 | CELLS DIFFERENTIATE

What the IRF6 Protein Looks Like

What does the IRF6 protein actually look like?

START WITH

A regulatory variant changes when or how much a gene is used without changing the protein sequence.

REMEMBER

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

Why this matters

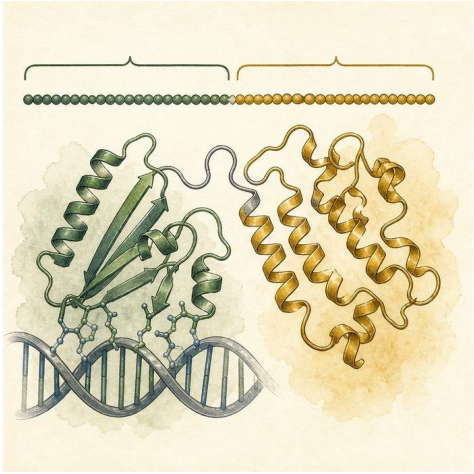
A domain map turns an amino-acid coordinate into a testable mechanism.

The biology in plain English

A protein domain is a region that folds or functions as a unit.

IRF6 has an N-terminal DNA-binding domain and a C-terminal region that supports protein interactions.

Location helps researchers choose experiments. It does not by itself prove that a variant is harmful.



Biomedical teaching illustration: Place variants on the IRF6 domain map

Check your understanding

- Which IRF6 domain binds DNA?
- What does a domain map help researchers choose?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN10-E1	IRF6 is 467 amino acids long.	Variant position can be recorded precisely.
GEN10-E2	The N-terminal DNA-binding domain spans roughly residues 7 to 115.	Variants there may alter DNA recognition.
GEN10-E3	The C-terminal SMIR/IAD region supports protein interactions.	Different domains support different molecular jobs.

Concrete decision

You are choosing a functional assay for an IRF6 variant. Variant A lies in the DNA-binding domain; variant B lies in the C-terminal interaction region.

A. Test DNA binding for A and partner interaction for B.

B. Use the same unrelated assay for both.

C. Classify both from location alone.

Decision prompt: Choose the assay plan and cite the domain-function evidence.

Claim ceiling: You may select assays from domain location. You may not classify a variant without results and other evidence.

Glossary

Term	Plain-English definition
protein domain	A distinct part of a protein that folds and works on its own, such as the DNA-binding domain of IRF6.
DNA-binding domain	The part of a transcription factor that grips DNA so it can switch target genes on or off.
protein-binding domain	The part of a protein that attaches to other proteins to do its job.
SMIR / IAD domain	A lesson term defined by the surrounding model and case evidence.
structure-function	The principle that a molecule's three-dimensional shape determines what it can do, so breaking the shape breaks the job.

READING 11 OF 20 | CELLS DIFFERENTIATE

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?

START WITH

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

REMEMBER

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

Why this matters

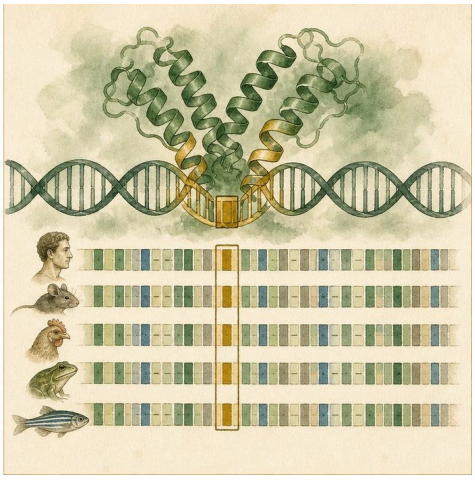
Comparative biology helps students ask why one position may be more important than another.

The biology in plain English

Orthologs are related genes in different species that came from a shared ancestral gene.

Sequence alignment places comparable amino acids in columns. Positions that remain the same across distant species are conserved.

Conservation suggests importance, but classification also needs population, clinical, computational, or functional evidence.



Biomedical teaching illustration: Read an IRF6 multispecies alignment

Check your understanding

- What does conservation suggest?
- Why does it not finish classification?

Case evidence supplied for this lesson

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.

Concrete 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 prompt: 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.

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.

How Does One Wrong Amino Acid Break the Protein?

How can changing one single amino acid in a 467-amino-acid protein stop the whole protein from doing its job?

START WITH

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

REMEMBER

A missense variant matters when its side-chain change disrupts a specific protein interaction or fold.

Why this matters

Students learn to keep computational evidence in its proper lane.

The biology in plain English

A missense variant replaces one amino acid with another. Side chains differ in charge, size, and shape.

If the change occurs at a DNA-contact or folding site, it may disrupt function. Protein models help visualize that possibility.

AlphaFold predicts a likely fold. A laboratory assay is needed to test binding or activity directly.

Biomedical teaching illustration: Model an Arg84 substitution in IRF6

Check your understanding

- What chemical features can change in a missense variant?
- What can a model not measure?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN12-E1	Arg84 lies in the conserved IRF6 DNA-binding domain.	The position is functionally plausible.
GEN12-E2	Replacing arginine changes side-chain chemistry and may alter DNA contact or local folding.	A structural mechanism can be proposed.
GEN12-E3	AlphaFold predicts structure but does not measure variant function.	Experimental validation remains necessary.

Concrete decision

You are deciding whether a structure image completes a variant report. The model predicts an altered DNA-contact surface, but no binding experiment has been run.

A. Report a supported hypothesis and request functional testing.

B. Call the prediction direct proof.

C. Ignore position and chemistry.

Decision prompt: Choose the report language and cite prediction versus experiment.

Claim ceiling: You may propose a structure-function mechanism. You may not present a prediction as measured protein behavior.

Glossary

Term	Plain-English definition
AlphaFold	An artificial intelligence system from DeepMind that predicts a protein's three-dimensional folded shape directly from its amino acid sequence.
missense variant	A DNA change that swaps one amino acid for another in the protein, such as the IRF6 R84C change.
protein folding	How a chain of amino acids settles into its specific three-dimensional shape, which determines what the protein can do.
side chain	The variable part of an amino acid that gives it its chemistry, so changing it can alter how a protein folds or works.
structure-function	The principle that a molecule's three-dimensional shape determines what it can do, so breaking the shape breaks the job.

READING 13 OF 20 | CELLS DIFFERENTIATE

Does IRF6 Work Alone?

Is IRF6 a lone actor, or one link in a chain of genes, and how would we tell from the patterns in patients?

START WITH

A missense variant matters when its side-chain change disrupts a specific protein interaction or fold.

REMEMBER

IRF6 works in a regulatory network, so similar phenotypes can arise when different connected genes fail.

Why this matters

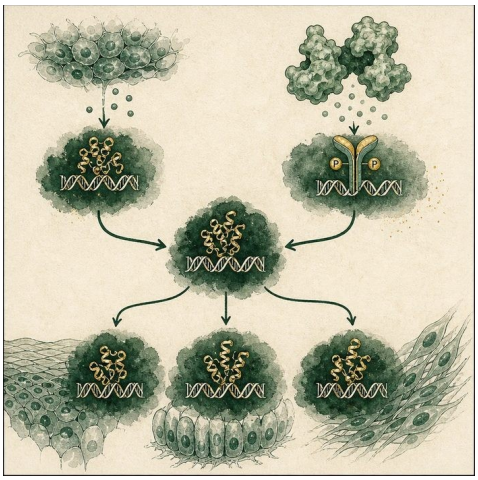
Networks prevent students from treating one famous gene as the entire biology.

The biology in plain English

Transcription factors work in networks. Upstream signals affect IRF6, and IRF6 helps regulate other differentiation genes.

GRHL3, KLF4, and KLF17 are examples of connected genes in oral epithelial development.

Because different nodes can affect the same pathway, a negative IRF6 result does not erase a strong phenotype.



Biomedical teaching illustration: Place p63, IRF6, GRHL3, and KLF genes in a network

Check your understanding

- What do upstream and downstream mean?
- Why can different genes produce similar phenotypes?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN13-E1	p63 and TGF-beta signaling influence IRF6 expression or activity in oral epithelium.	IRF6 has upstream regulators.
GEN13-E2	IRF6 promotes GRHL3, KLF4, and KLF17-related differentiation programs.	IRF6 connects to downstream targets.
GEN13-E3	GRHL3 variants can also cause Van der Woude-like phenotypes.	Different network nodes can converge on similar outcomes.

Concrete decision

You are explaining a negative IRF6 test in a family with lip pits and clefting. IRF6 sequencing is negative, but the phenotype remains strongly suggestive of the network.

A. Consider other connected genes and broader testing.

B. Conclude the phenotype is impossible.

C. Invent an IRF6 variant.

Decision prompt: Choose the next genetic strategy and cite network convergence.

Claim ceiling: You may broaden the candidate network. You may not diagnose a specific second gene without evidence.

Glossary

Term	Plain-English definition
gene regulatory network	The web of genes that turn each other on and off to control a process such as palate fusion.
transcription factor	A protein that binds DNA and turns specific genes on or off, controlling what a cell becomes and does.
upstream	Genes or events that come earlier in a pathway and control what happens later, downstream.
downstream	Describing genes or events that come later in a pathway, controlled by something acting earlier, or upstream, of them.
redundancy	When more than one gene can perform the same job, so losing one is partly covered by another and the effect is softened.

READING 14 OF 20 | CELLS DIFFERENTIATE

What Does IRF6 Actually Do in the Embryo?

What job do the cells controlled by IRF6 perform, and how does losing that job cause the shelves to fail to fuse?

START WITH

IRF6 works in a regulatory network, so similar phenotypes can arise when different connected genes fail.

REMEMBER

The IRF6 network helps oral epithelial cells form periderm, preventing wrong adhesions before correct fusion.

Why this matters

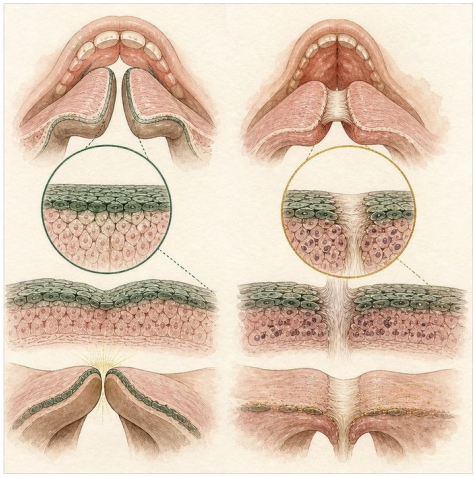
A causal story needs intermediate cell behavior, not a jump from gene to anatomy.

The biology in plain English

IRF6 helps oral epithelial cells differentiate. A temporary surface layer called periderm prevents tissues from sticking to the wrong neighbor.

In Irf6-deficient models, periderm is abnormal or missing and oral adhesions form.

The adhesions can block palatal shelf movement. This is a model mechanism, not a molecular diagnosis for Mateo.



Biomedical teaching illustration: Connect IRF6 genotype to periderm cell behavior

Check your understanding

- What cell behavior links IRF6 to palate closure?
- Which claim about Mateo remains unsupported?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN14-E1	IRF6 is active in oral epithelium and periderm differentiation.	The gene acts in a relevant cell type.
GEN14-E2	Irf6-deficient models lose normal periderm and develop abnormal oral adhesions.	Gene loss changes a specific cell behavior.
GEN14-E3	Those adhesions can block palatal elevation and closure.	The cell defect connects to the tissue phenotype.

Concrete decision

You are building the molecular-to-anatomy chain for the case board. The board requires one sequence from gene to cell to tissue outcome.

A. IRF6 network failure, periderm defect, wrong adhesion, blocked closure.

B. IRF6 instantly creates a hole in the palate.

C. Periderm has no relationship to fusion.

Decision prompt: Choose the sequence and cite cell plus tissue evidence.

Claim ceiling: You may explain an established model mechanism. You may not claim Mateo has IRF6 loss without a result.

Glossary

Term	Plain-English definition
periderm	A thin temporary outer cell layer of the embryo; if it sticks where it should not, the growing edges cannot fuse.
epithelium	A sheet of tightly joined surface cells, such as the lining whose edges must clear away for the palatal shelves to fuse.
differentiation	The process by which an unspecialized cell turns on specific genes and becomes a specialized cell type with a defined job.
fusion	When two growing tissue edges meet at the midline and join into one continuous structure, as the lip and palate do during development.
cell-autonomous	Describing an effect that plays out inside the very cell carrying the change, rather than in its neighbors.

READING 15 OF 20 | DEVELOPMENT CAN GO WRONG

How Do We Prove the Gene Causes It?

How can a scientist prove that losing IRF6 causes clefting, instead of just appearing alongside it?

START WITH

The IRF6 network helps oral epithelial cells form periderm, preventing wrong adhesions before correct fusion.

REMEMBER

Knockout and rescue experiments strengthen causation when loss creates a defect and restoration reverses part of it.

Why this matters

Partial rescue teaches students to measure degrees of evidence rather than force yes-or-no conclusions.

The biology in plain English

A knockout removes or disables a gene in a model. If the predicted defect appears, the gene is necessary for the tested process.

A rescue restores the gene or pathway. Partial rescue can show that the restored tissue matters while other requirements remain.

IRF6 rescue evidence is preclinical and does not establish prenatal therapy for people.

Biomedical teaching illustration: Read IRF6 knockout and partial-rescue evidence

Check your understanding

- What does knockout test?
- Why is a partial rescue still informative?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN15-E1	Irf6 knockout models develop abnormal epithelium, oral adhesions, and cleft palate.	Loss of function produces the predicted phenotype.
GEN15-E2	Restoring epithelial IRF6 reduces some adhesions but does not fully rescue every defect.	The rescue supports an epithelial role and reveals limits.
GEN15-E3	Zebrafish rescue experiments add evidence in a second model.	Cross-model replication strengthens the mechanism while remaining preclinical.

Concrete decision

You are judging whether the rescue proves complete correction. The rescue group has fewer adhesions but still has cleft palate in several regions.

A. Call it a partial mechanistic rescue.

B. Call it a complete cure.

C. Ignore the improvement because it was incomplete.

Decision prompt: Choose the verdict and cite both improvement and remaining phenotype.

Claim ceiling: You may support causation and a tissue role. You may not claim complete rescue or human treatment.

Glossary

Term	Plain-English definition
model organism	A species, such as zebrafish or mouse, studied because its biology is similar enough to ours to teach us about human development and disease.
knockout	An organism or cell engineered to have a specific gene switched off, used to reveal what that gene normally does.
rescue experiment	Adding a working gene back into a mutant to see if it restores the normal trait, which proves that gene was responsible.
causation	When one factor actually brings about another, shown by controlled evidence rather than by the two simply appearing together.
correlation	Two things tending to occur together, which does not by itself prove that one causes the other.

Why Is CL/P More Common in Some Groups?

Why is cleft lip and/or palate far more common in some human populations than in others?

START WITH

Knockout and rescue experiments strengthen causation when loss creates a defect and restoration reverses part of it.

REMEMBER

Population differences reflect allele frequencies, effect sizes, environments, and sampling, not biological ranking of groups.

Why this matters

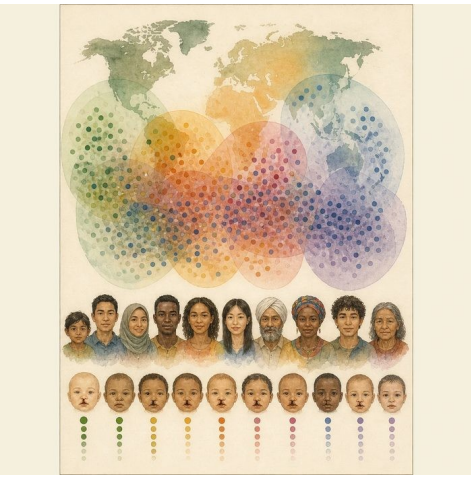
Population genetics must be scientifically precise and socially responsible.

The biology in plain English

Allele frequency is how common a variant is in a studied population. An odds ratio compares relative odds, not certainty.

Human ancestry reflects shared and mixed population history. Broad race labels are poor substitutes for detailed ancestry and context.

Population differences can involve genetics, environment, access, measurement, and sampling. Replication matters.



Biomedical teaching illustration: Interpret cleft prevalence and IRF6 risk across populations

Check your understanding

- Why is ancestry not destiny?
- What evidence should accompany a population difference?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN16-E1	Cleft prevalence differs among studied populations.	Population pattern is real but descriptive.
GEN16-E2	Risk-allele frequencies and effect estimates can differ by ancestry and study.	Genetic contribution is population-context dependent.
GEN16-E3	Within-group variation is large and ancestry groups overlap.	Population averages do not determine an individual outcome.

Concrete decision

You are reviewing a public-health infographic. The draft says one ancestry group is genetically destined to have more clefts.

A. Replace it with frequency, context, overlap, and replication language.

B. Keep the destiny claim.

C. Erase population data entirely.

Decision prompt: Choose the correction and cite both difference and overlap evidence.

Claim ceiling: You may discuss population statistics. You may not rank groups biologically or predict an individual from ancestry alone.

Glossary

Term	Plain-English definition
allele frequency	How common a particular version of a gene is in a population, written as the share of all copies that are that version.
ancestry	A person's population background inherited from earlier generations, which can affect how common certain DNA variants are.
odds ratio	A number comparing the odds of having a factor in affected versus unaffected people; above 1 suggests the factor is associated.
liability threshold	The point on a scale of combined genetic and environmental risk above which a trait such as a cleft actually appears.
gene-environment interaction	When a genetic risk and an environmental factor such as smoking or low folate combine to raise risk more than either alone.
replication	Repeating a study to see if the result holds; a key test of whether a finding is real.

What Is the Family's Recurrence Risk?

What is the recurrence risk for Mateo's family, and how do you communicate it honestly?

START WITH

Population differences reflect allele frequencies, effect sizes, environments, and sampling, not biological ranking of groups.

REMEMBER

Recurrence counseling uses empiric family data and uncertainty; it gives a range, not a promise.

Why this matters

Good counseling combines numbers, uncertainty, and respect for family choices.

The biology in plain English

Recurrence risk is the chance that a trait occurs again in a family. Empiric estimates come from many similar families.

The best estimate depends on the cleft pattern, affected relatives, ancestry, and any confirmed molecular diagnosis.

A range is more honest than a promise. A real family receives individualized counseling from qualified clinicians.

Biomedical teaching illustration: Build a recurrence-risk conversation for Mateo's family

Check your understanding

- What evidence could refine recurrence risk?
- Why is an empiric estimate not a guarantee?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN17-E1	Mateo's case is isolated-appearing with unaffected parents.	Syndrome-specific dominant risk is not established.
GEN17-E2	Empiric recurrence estimates come from outcomes in similar families.	The number is evidence-based but population-level.
GEN17-E3	A confirmed pathogenic familial variant would change the counseling model.	Molecular results can refine recurrence risk.

Concrete decision

You are the genetic counselor meeting Mateo's parents. They ask for one guaranteed percentage before deciding about future pregnancy.

A. Give a sourced empiric range and explain what could refine it.

B. Promise an exact outcome.

C. Refuse to discuss uncertainty.

Decision prompt: Choose the counseling approach and cite case fit plus uncertainty.

Claim ceiling: You may provide an educational empiric range from the supplied source. You may not personalize medical advice beyond the composite evidence.

Glossary

Term	Plain-English definition
recurrence risk	The chance that a future child in the same family will also be affected by a given condition.
empiric risk	A recurrence risk estimated from observed family and population data rather than from a single-gene inheritance calculation.
multifactorial inheritance	A trait caused by many small genetic and environmental factors adding up together, rather than by a single gene alone.
nonpenetrance	When a person carries a disease-linked variant but never shows the associated trait or condition.
genetic counselor	A specialist who explains genetic test results and recurrence risk to families and supports them in making their own decisions.
informed consent	Agreeing to a treatment or study only after truly understanding its purpose, risks, benefits, and alternatives; the understanding, not the signature, is the ethics.

READING 18 OF 20 | DEVELOPMENT CAN GO WRONG

Can We Fix the Code?

Can we fix the genetic code behind a cleft, and if so, how far along is that work, really?

START WITH

Recurrence counseling uses empiric family data and uncertainty; it gives a range, not a promise.

REMEMBER

Gene editing, pathway rescue, and gene-dosage modulation are different strategies with different targets and risks.

Why this matters

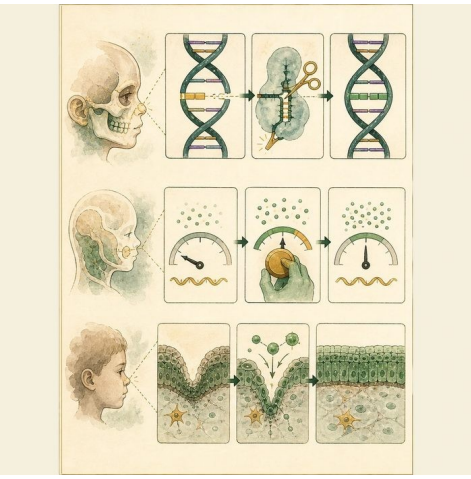
Students need to separate exciting mechanism from clinical readiness.

The biology in plain English

CRISPR changes DNA sequence. Gene-dosage strategies change how much product is made. Pathway rescue supplies or changes a downstream signal.

All three require a target tissue, delivery method, dose, and developmental window.

Animal rescue can support mechanism. Human use requires extensive safety, effectiveness, ethical, and regulatory evidence.



Biomedical teaching illustration: Compare three preclinical intervention strategies

Check your understanding

- How do the three strategies differ?
- What four gaps block a clinic-ready claim?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN18-E1	Animal studies have rescued some cleft-related model phenotypes through pathway or gene restoration.	Preclinical proof of mechanism exists.
GEN18-E2	The face forms during early, short developmental windows.	Delivery would need precise timing and tissue targeting.
GEN18-E3	No established prenatal gene-editing treatment prevents common human cleft lip and palate.	Clinical readiness is not established.

Concrete decision

You are evaluating a startup claim. The company says animal rescue results mean fetal CRISPR for clefts is clinic-ready.

A. Reject clinic-ready language and list delivery, timing, safety, and evidence gaps.

B. Approve the claim from animal rescue alone.

C. Say all preclinical work is meaningless.

Decision prompt: Choose the evaluation and cite mechanism evidence plus readiness limits.

Claim ceiling: You may compare preclinical strategies. You may not claim an available or proven human prenatal treatment.

Glossary

Term	Plain-English definition
gene therapy	Treating disease by adding, silencing, or correcting a gene in a patient's cells.
CRISPR	A gene-editing tool that uses a guide RNA to bring the Cas9 protein to a chosen DNA site and cut it so the sequence can be changed.
gene-dosage modulation	Tuning how much product a gene makes, raising or lowering it, as a possible way to treat or prevent a condition.
preclinical	Research done in cells and animals to test safety and effect before a treatment is ever tried in people.
somatic	Relating to the ordinary body cells other than egg and sperm; changes in these cells affect only the individual and are not inherited.
germline	The egg, sperm, and the cells that make them; changes in these cells can be passed to a person's children.

READING 19 OF 20 | DEVELOPMENT CAN GO WRONG

Should We, and Who Decides?

Should we genetically intervene in clefting, and who has the right to make that decision?

START WITH

Gene editing, pathway rescue, and gene-dosage modulation are different strategies with different targets and risks.

REMEMBER

An ethical decision weighs benefit, harm, autonomy, heritability, access, and alternatives before technical possibility.

Why this matters

Biomedical expertise includes knowing who should decide, not only what can be done.

The biology in plain English

Somatic editing affects treated cells in one person. Germline editing can pass changes to future generations.

Beneficence asks about benefit; nonmaleficence asks about harm; autonomy asks who chooses; justice asks who gains access.

Cleft care already includes effective surgery and team support. New interventions must be compared with those options and shaped with affected communities.

Biomedical teaching illustration: Apply an ethics matrix to a future cleft intervention

Check your understanding

- Why is germline editing ethically different?
- How does existing care change the benefit-harm comparison?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN19-E1	Cleft lip and palate already have effective multidisciplinary treatments, though access is unequal.	A genetic intervention must be compared with real alternatives.
GEN19-E2	Germline editing could affect future generations who cannot consent.	Heritability changes the ethical stakes.
GEN19-E3	Access to cleft care and new technology is uneven.	Equity is part of benefit and harm.

Concrete decision

You are chairing a future hospital ethics panel. A proposed germline intervention may reduce cleft risk but has uncertain off-target effects and high cost.

A. Pause approval and require stronger safety, governance, community input, and access planning.

B. Approve because editing is technically possible.

C. Exclude people born with clefts from the discussion.

Decision prompt: Choose the panel decision and cite two ethical dimensions.

Claim ceiling: You may reason from the supplied case. You may not claim one universal moral answer for every family or future technology.

Glossary

Term	Plain-English definition
bioethics	The study of what we should and should not do in medicine and research, weighing benefit, risk, consent, and fairness.
somatic editing	Editing the DNA of one patient's body cells to treat a condition, with the change not passed on to their children.
germline editing	Changing the DNA of eggs, sperm, or embryos so the edit can be inherited by future generations, which is ethically restricted.
equity	The bioethics principle that the benefits, risks, and access of research and care should be shared fairly across all groups of people.
autonomy	A patient's right to make their own informed decisions about their care, a core principle of bioethics and one of the hardest to honor.
beneficence	The bioethics principle of acting to benefit the patient and promote their well-being, weighing likely good against possible harm.

READING 20 OF 20 | DEVELOPMENT CAN GO WRONG

What Is Mateo's Complete Genetic Story?

Can your team assemble every piece of evidence into one clear, well-supported genetic story for Mateo?

START WITH

An ethical decision weighs benefit, harm, autonomy, heritability, access, and alternatives before technical possibility.

REMEMBER

Mateo's strongest genetic story is multifactorial and evidence-bounded: IRF6 explains a pathway, not a proven individual cause.

Why this matters

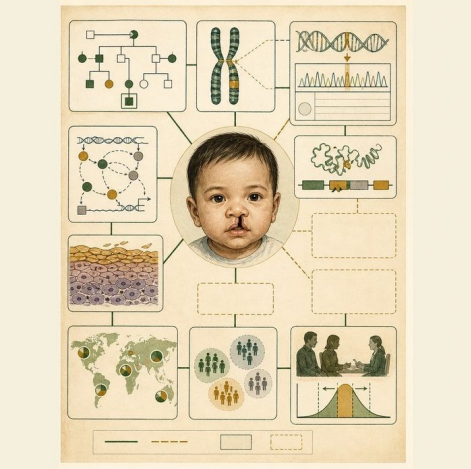
The final lesson rewards scientific restraint and prepares anatomy, clinical care, and experimental design.

The biology in plain English

Mateo's pedigree and phenotype are direct case evidence. They support an isolated-appearing, multifactorial model.

IRF6 research provides a detailed example from gene and enhancer to periderm and tissue fusion.

The case file does not include a proven pathogenic variant for Mateo. The responsible conclusion uses IRF6 to explain possibility, not to invent diagnosis.



Biomedical teaching illustration: Assemble Mateo's complete genetic evidence chain

Check your understanding

- What is direct evidence about Mateo?
- What useful IRF6 claim remains below the ceiling?

Case evidence supplied for this lesson

ID	Finding supplied in the case	Why it matters
GEN20-E1	Mateo has an isolated-appearing cleft and no strong family pattern in the composite file.	The case fits a multifactorial model better than a proven dominant syndrome.
GEN20-E2	IRF6 coding and regulatory studies explain how epithelial differentiation and cleft risk can change.	IRF6 is a strong pathway exemplar.
GEN20-E3	No pathogenic IRF6 result or single causal exposure is supplied for Mateo.	The individual cause remains open.

Concrete decision

You are the lead geneticist at the final conference. The team must approve one conclusion that will be shared with every other domain.

A. Use a multifactorial, IRF6-informed model while stating that Mateo's cause is unproven.

B. Declare a pathogenic IRF6 variant that was never tested.

C. Say genetics contributes no useful information.

Decision prompt: Choose the conclusion and cite case evidence plus the molecular limit.

Claim ceiling: You may synthesize the best-supported model. You may not add a molecular diagnosis absent from the case file.

Glossary

Term	Plain-English definition
synthesis	Building a molecule in the cell, as in protein synthesis (making a protein from mRNA).
domain report	A focused summary of the current research and evidence within one specific topic area, used to organize knowledge before drawing conclusions.
gene regulatory network	The web of genes that turn each other on and off to control a process such as palate fusion.
haploinsufficiency	When one working copy of a gene cannot make enough product on its own, so losing the second copy causes the trait.
multifactorial inheritance	A trait caused by many small genetic and environmental factors adding up together, rather than by a single gene alone.