STUDENT CASE FILE | GENETICS DOMAIN | LESSONS 1 TO 20

The Baby Mateo Case

One observed structural difference. Twenty evidence updates. One bounded clinical synthesis.

Composite patient snapshot

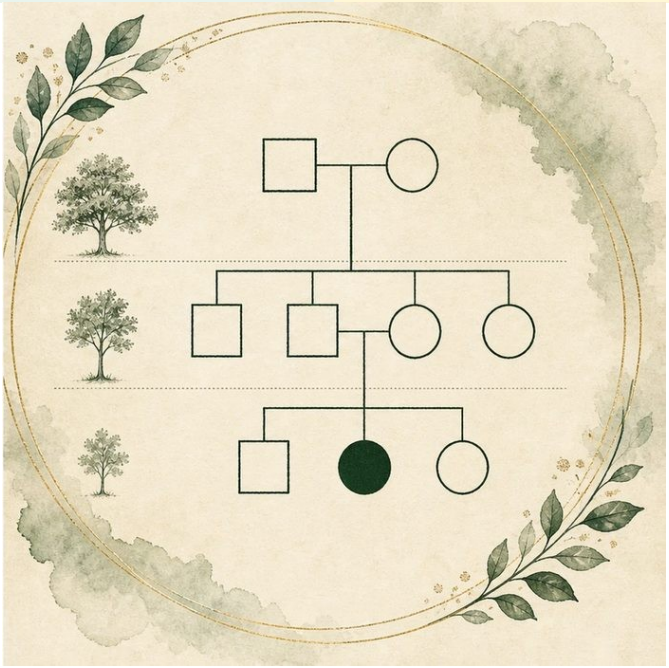
Patient	Mateo, a composite teaching case. No real patient data.
Birth	Term newborn. Breathing and tone are stable.
Observed structure	Complete unilateral left cleft lip and palate.
Initial whole-body exam	No additional congenital anomalies identified on the first structured examination.
Inquiry target	Is the cleft isolated or part of a syndrome? What evidence supports the cause model and care plan?
Evidence rule	Use only the labeled findings supplied in the lesson. Do not invent history, tests, symptoms, or family details.

EVIDENCE SUPPLIED

Every required finding has a stable ID.

EVIDENCE NOT SUPPLIED

Do not invent missing symptoms, tests, exposures, or family history.

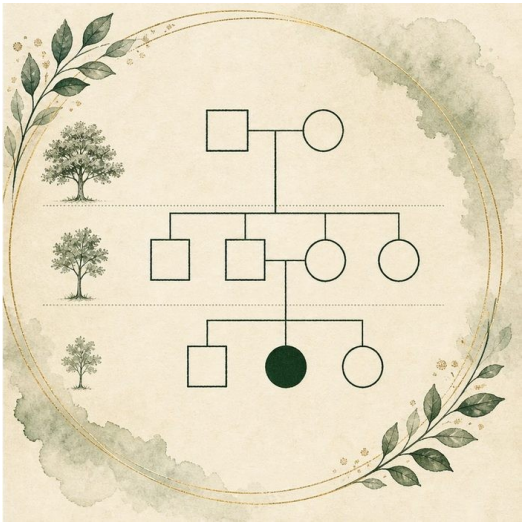


Illustration, not a clinical photograph. Composite craniofacial teaching model.

EVIDENCE UPDATE 1 OF 20 | INTAKE GENETICIST

Chance or Genetic? Reading Mateo's Family Tree

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



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

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.

Decision in this update: Choose the counseling statement and cite the pedigree plus its limit.

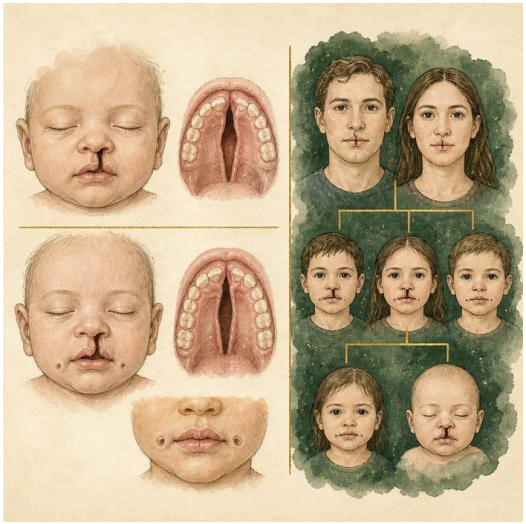
Claim ceiling: You may describe the observed family pattern. You may not exclude genetic contribution or name an inheritance model yet.

Handoff to the next update: Mateo's cleft looks isolated and his parents are unaffected, but a cleft can sometimes be one feature of a hidden syndrome. What would a syndrome look like, and how would we screen for one?

EVIDENCE UPDATE 2 OF 20 | CLINICAL GENETICIST

Screening for a Hidden Syndrome

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



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

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.

Decision in this update: Choose the chart language and cite the absent pattern evidence.

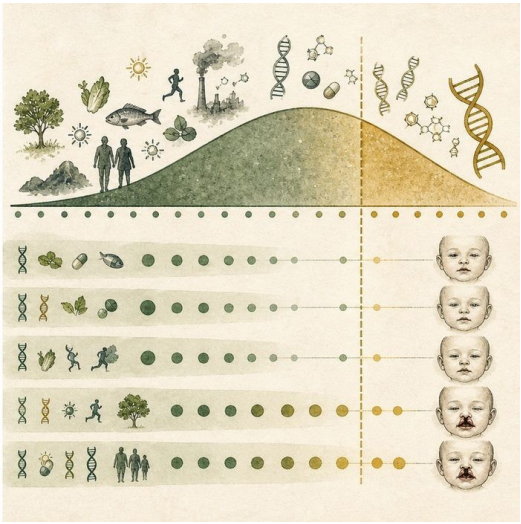
Claim ceiling: You may say the current screen is isolated-appearing. You may not establish or exclude every syndrome without appropriate testing.

Handoff to the next update: Mateo has no lip pits and no other features, so his cleft screens as isolated. But even an isolated cleft must follow some inheritance logic. Does an isolated cleft like Mateo's travel through families the clean way a single dominant gene would?

EVIDENCE UPDATE 3 OF 20 | CLINICAL GENETICIST

Does It Run in Families Like a Single Gene?

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



Biomedical teaching illustration: Model isolated cleft as multifactorial liability

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.

Decision in this update: Choose the model and cite both pedigree and population evidence.

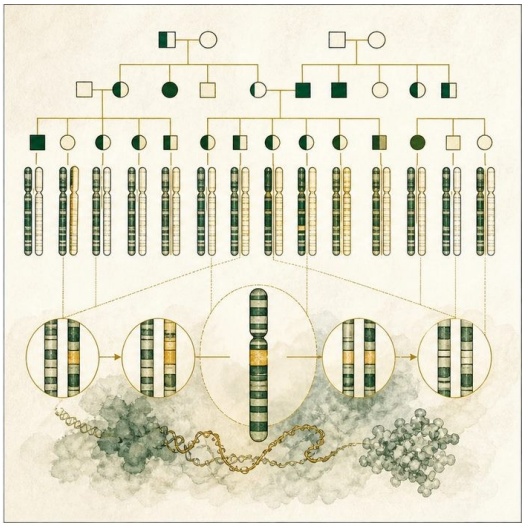
Claim ceiling: You may choose the best-fit model. You may not calculate Mateo's exact liability or identify each contributor.

Handoff to the next update: Mateo's cleft fits a multifactorial model where many small factors add up. But to understand cleft biology at all, scientists study the best-understood cleft gene in depth. Which gene is the best door into how clefts happen?

EVIDENCE UPDATE 4 OF 20 | GENE MAPPER

Hunting the Exemplar Cleft Gene: Linkage to 1q32

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



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

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.

Decision in this update: Choose the next step and cite what linkage can and cannot locate.

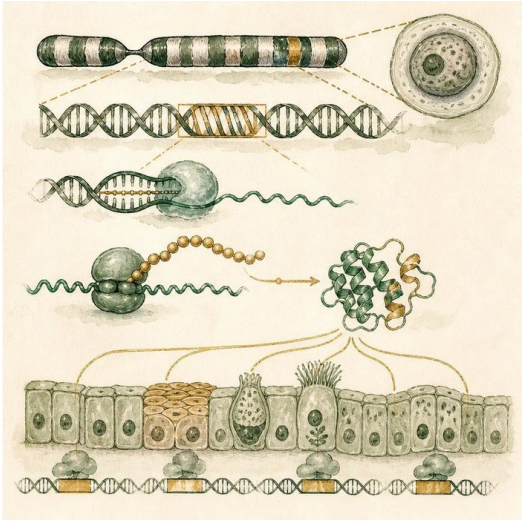
Claim ceiling: You may prioritize a locus. You may not call a marker causal or name IRF6 before sequence evidence.

Handoff to the next update: We have an address, chromosome 1q32, but an address is not a name. What is the actual gene sitting there, and what does it make?

EVIDENCE UPDATE 5 OF 20 | MOLECULAR GENETICIST

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

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



Biomedical teaching illustration: Trace IRF6 from gene to regulatory protein

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.

Decision in this update: 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.

Handoff to the next update: Now that we have the exemplar gene IRF6, where do we look up whether a given variant in it is already known, and whether it is harmful?

EVIDENCE UPDATE 6 OF 20 | BIOINFORMATICIAN

Looking Up a Variant

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

Biomedical teaching illustration: Read a ClinVar-style IRF6 record

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.

Decision in this update: Choose the report language and cite review-status plus frequency rules.

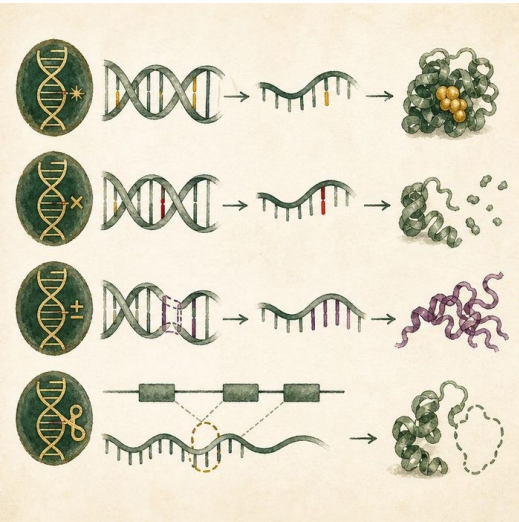
Claim ceiling: You may summarize database evidence. You may not independently diagnose from a weak or conflicting record.

Handoff to the next update: When we read variants we saw codes like R84C and R250X. What kinds of typos in DNA do those codes actually stand for?

EVIDENCE UPDATE 7 OF 20 | VARIANT ANALYST

Kinds of Typos in DNA

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



Biomedical teaching illustration: Translate four IRF6 variant types

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.

Decision in this update: Choose the annotation strategy and cite two distinct mechanisms.

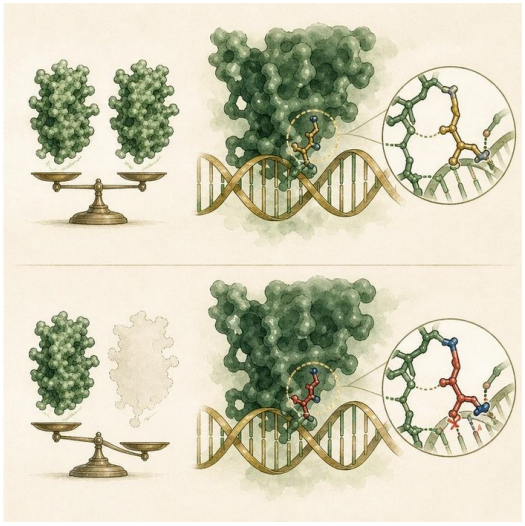
Claim ceiling: You may predict molecular consequences. You may not classify pathogenicity from variant type alone.

Handoff to the next update: We can sort IRF6 typos by type. But IRF6 causes two different diseases, a milder one and a more severe one. Why would one gene cause two diseases?

EVIDENCE UPDATE 8 OF 20 | VARIANT ANALYST

One Gene, Two Diseases

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



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

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.

Decision in this update: Choose the comparison and cite dosage plus domain evidence.

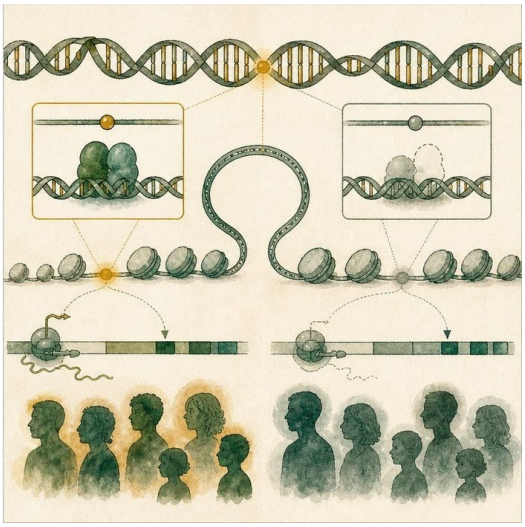
Claim ceiling: You may compare supported mechanisms. You may not guarantee syndrome severity from variant position alone.

Handoff to the next update: The harmful IRF6 changes we studied are rare and cause syndromes. Most clefts are isolated and common. Where is the common, hidden variant, and why have we not seen it in the protein code?

EVIDENCE UPDATE 9 OF 20 | VARIANT ANALYST

The Hidden Regulatory Variant

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



Biomedical teaching illustration: Map rs642961 to an IRF6 enhancer

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.

Decision in this update: Choose the interpretation and cite regulatory mechanism plus penetrance.

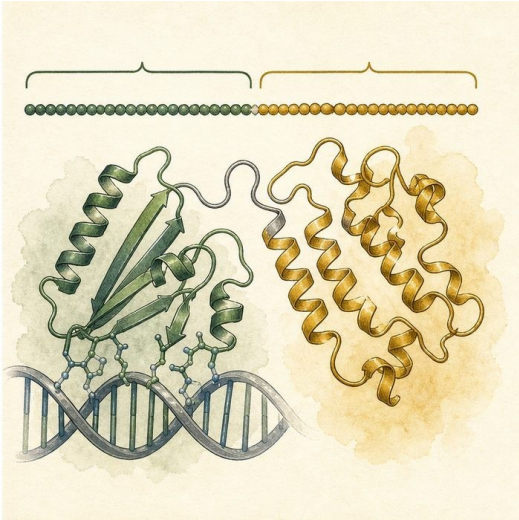
Claim ceiling: You may describe association and mechanism. You may not claim the allele alone caused Mateo's cleft.

Handoff to the next update: A regulatory variant lowers how MUCH IRF6 is made, while syndromic variants damage specific protein parts. To understand both, we need to see the protein itself. What does the IRF6 protein actually look like?

EVIDENCE UPDATE 10 OF 20 | PROTEIN SCIENTIST

What the IRF6 Protein Looks Like

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



Biomedical teaching illustration: Place variants on the IRF6 domain map

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.

Decision in this update: Choose the assay plan and cite the domain-function evidence.

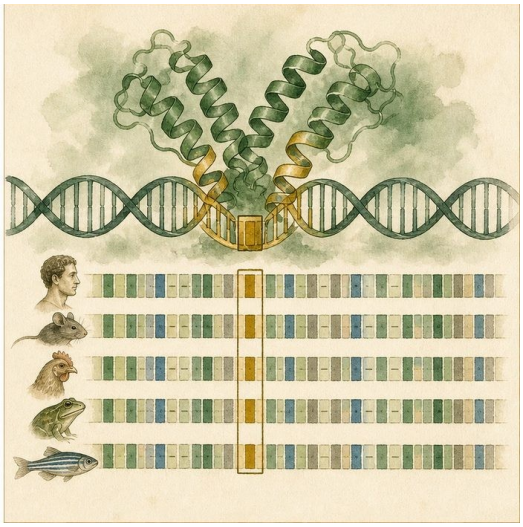
Claim ceiling: You may select assays from domain location. You may not classify a variant without results and other evidence.

Handoff to the next update: Our protein has critical domains. How can we tell which parts are so important that evolution never lets them change?

EVIDENCE UPDATE 11 OF 20 | BIOINFORMATICIAN

Is This Gene Important Across Species?

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



Biomedical teaching illustration: Read an IRF6 multispecies alignment

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.

Decision in this update: 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.

Handoff to the next update: 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.

EVIDENCE UPDATE 12 OF 20 | STRUCTURAL BIOLOGIST

How Does One Wrong Amino Acid Break the Protein?

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

Biomedical teaching illustration: Model an Arg84 substitution in IRF6

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.

Decision in this update: Choose the report language and cite prediction versus experiment.

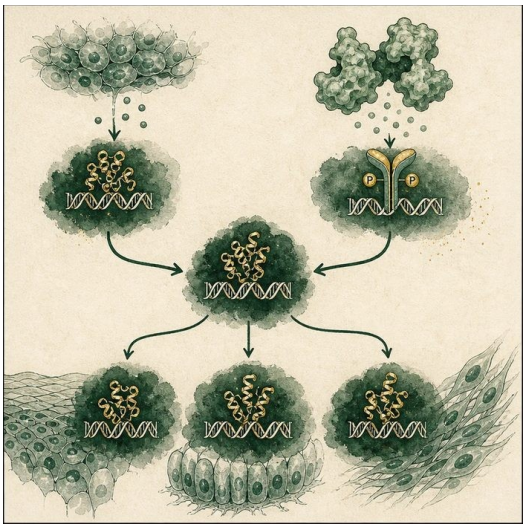
Claim ceiling: You may propose a structure-function mechanism. You may not present a prediction as measured protein behavior.

Handoff to the next update: We found that one wrong amino acid in the conserved domain can stop IRF6 from gripping DNA. But a transcription factor never works alone. Who switches IRF6 on, and who carries the signal once IRF6 has done its part? We chase that next.

EVIDENCE UPDATE 13 OF 20 | SYSTEMS GENETICIST

Does IRF6 Work Alone?

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



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

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.

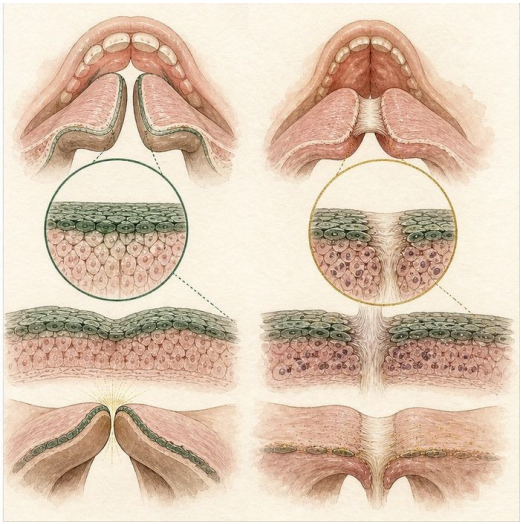
Decision in this update: Choose the next genetic strategy and cite network convergence.

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

Handoff to the next update: We placed IRF6 in a network with p63 above it and GRHL3 and the KLFs alongside and below. But a network of genes is just instructions. What does this network actually make the cells of the embryo do so the lip and palate can physically close? We chase that next.

What Does IRF6 Actually Do in the Embryo?

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



Biomedical teaching illustration: Connect IRF6 genotype to periderm cell behavior

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.

Decision in this update: Choose the sequence and cite cell plus tissue evidence.

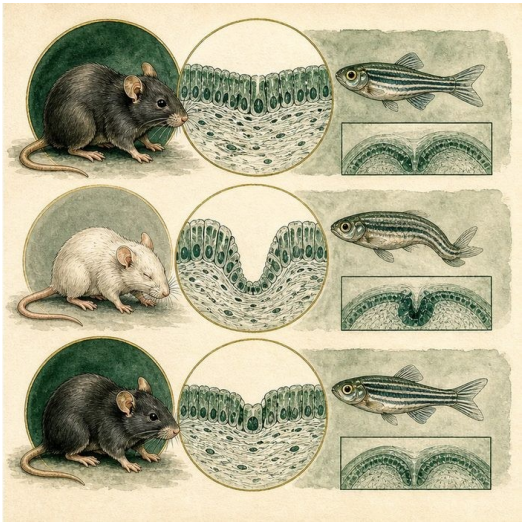
Claim ceiling: You may explain an established model mechanism. You may not claim Mateo has IRF6 loss without a result.

Handoff to the next update: We found that IRF6 makes periderm cells differentiate so the shelves can fuse, and without it they stick wrongly and stay open. But a strong story is not proof. How do scientists actually prove that losing IRF6 causes the cleft, rather than just appearing alongside it? We chase that next.

EVIDENCE UPDATE 15 OF 20 | MODEL RESEARCHER

How Do We Prove the Gene Causes It?

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



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

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.

Decision in this update: Choose the verdict and cite both improvement and remaining phenotype.

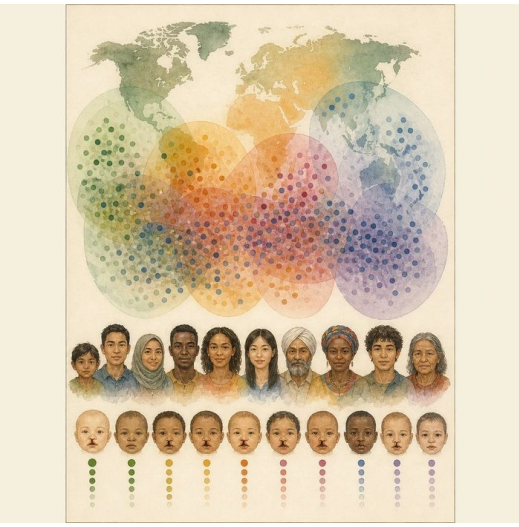
Claim ceiling: You may support causation and a tissue role. You may not claim complete rescue or human treatment.

Handoff to the next update: We proved IRF6 loss causes clefting using knockout and rescue in mouse and zebrafish, so we now understand how the cleft happens in one embryo. But why is cleft lip and palate far more common in some human populations than in others? We chase that next, when the population geneticist takes the seat.

EVIDENCE UPDATE 16 OF 20 | POPULATION GENETICIST

Why Is CL/P More Common in Some Groups?

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



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

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.

Decision in this update: 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.

Handoff to the next update: We found why CL/P differs across whole populations, but population averages are not a family. Mateo's parents now ask the practical question: if they have another child, what is the chance that child also has a cleft? That family recurrence risk is what we chase next.

EVIDENCE UPDATE 17 OF 20 | GENETIC COUNSELOR

What Is the Family's Recurrence Risk?

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

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

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.

Decision in this update: Choose the counseling approach and cite case fit plus uncertainty.

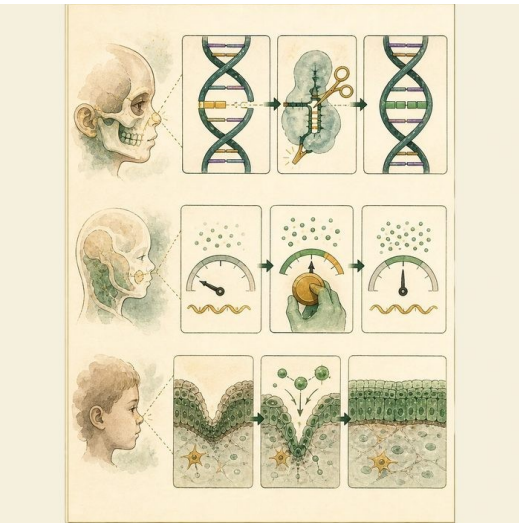
Claim ceiling: You may provide an educational empiric range from the supplied source. You may not personalize medical advice beyond the composite evidence.

Handoff to the next update: We can now counsel the family honestly about the odds, but giving a number does not change the gene. Sooner or later a family asks the bolder question: instead of measuring the risk, could we repair the underlying genetic problem itself? Can we fix the code? We chase that next.

EVIDENCE UPDATE 18 OF 20 | GENE THERAPIST

Can We Fix the Code?

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



Biomedical teaching illustration: Compare three preclinical intervention strategies

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.

Decision in this update: 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.

Handoff to the next update: These fixes work in animals today, and the science is moving. That raises a question no experiment can answer: if correcting a cleft gene in a human embryo ever became possible, should we do it, and who gets to decide? We chase that next.

EVIDENCE UPDATE 19 OF 20 | BIOETHICIST

Should We, and Who Decides?

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

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

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.

Decision in this update: Choose the panel decision and cite two ethical dimensions.

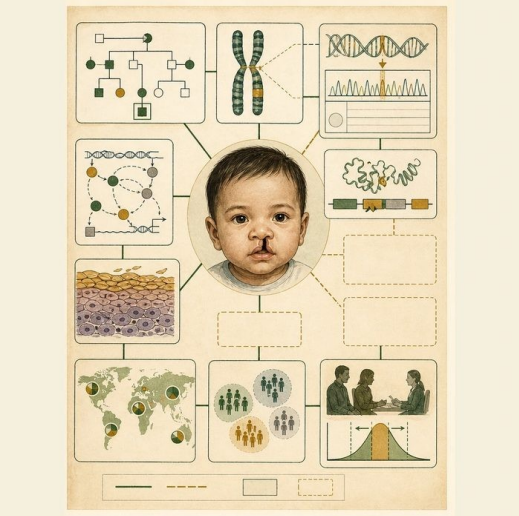
Claim ceiling: You may reason from the supplied case. You may not claim one universal moral answer for every family or future technology.

Handoff to the next update: We have now followed the gene from the first clue all the way to treatment and the ethics of treatment. Nothing is left to add: the only task remaining is to put the whole story together. What is Mateo's complete genetic story, start to finish? We assemble it next.

EVIDENCE UPDATE 20 OF 20 | WHOLE TEAM (HEAD MEDICAL GENETICIST AND ALL SPECIALIST SEATS)

What Is Mateo's Complete Genetic Story?

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



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

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.

Decision in this update: 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.

Handoff to the next update: The genetics team has now assembled Mateo's complete molecular story, from first clue to ethics. But genetics cannot finish his care alone. We hand the story across to the developmental, anatomical, clinical, and experimental-design teams, so each domain can do its part on how this gene shapes the embryo, the face, the surgery, and the care plan.