Test Questions

Test Question 1 (Leigh syndrome)

Now we have information about an individual who is 3 year old, male, and has the following facial phenotypes **Low set ears, Esotropia, Thick eyebrow, Maxillary hypoplasia, Anteverted nares, Long eyelashes, Prominent forehead, and Brachycephaly**. Please help me analyze from these facial phenotypes what genetic disorder this individual may have, what genes are involved in the disorder and their mutation information, and return research literature that matches the information for this individual. Finally, please help me to explain how you came to conclude the above.

GPT-4:

The facial phenotypes described suggest the possibility of a genetic syndrome, as the combination of features like low-set ears, esotropia (inward turning of the eye), thick eyebrows, maxillary hypoplasia (underdevelopment of the upper jaw), anteverted nares (forward-tilted nostrils), long eyelashes, a prominent forehead, and brachycephaly (shortening of the skull) often indicate a specific pattern of anomalies that can be linked to a genetic condition.

One potential syndrome that includes many of these features is Cornelia de Lange Syndrome (CdLS). CdLS is a developmental disorder characterized by growth delays, intellectual disability, limb defects, and distinctive facial features like those described. The genes commonly associated with CdLS include NIPBL, SMC1A, SMC3, RAD21, and HDAC8.

To confirm the suspicion of a genetic disorder such as CdLS or another syndrome, a geneticist would typically assess the individual's clinical features in detail and may suggest genetic testing. Genetic testing could involve sequencing the genes known to be associated with CdLS to look for mutations.

To find research literature that matches the information for this individual, one would typically conduct a search in medical databases such as PubMed, using keywords related to the phenotypes and suspected syndromes. For example, you could search for "Cornelia de Lange Syndrome facial features" or "genetic syndromes with low-set ears, maxillary hypoplasia, brachycephaly." However, as an AI, I don't have real-time database access to provide you with current literature.

The determination of the potential genetic disorder is based on the pattern of physical findings that match known syndromes. Geneticists and clinicians use established clinical criteria, databases of genetic conditions (such as OMIM - Online Mendelian Inheritance in Man, and GeneReviews), and their clinical experience to make such assessments. Confirming the diagnosis would require genetic testing, which can detect mutations in the genes associated with the suspected disorder.

If a genetic disorder is suspected, it's crucial to consult with a geneticist or a pediatrician specializing in genetics to confirm the diagnosis and discuss the management and implications of the condition for the individual and their family.

GLM-4:

Based on the facial phenotypes provided, one possible genetic disorder that comes to mind is Saethre-Chotzen syndrome (SCS), which is caused by mutations in the TWIST1 or MAFB genes. However, it's important to note that multiple genetic disorders can present with similar facial features, and a professional genetic evaluation is necessary for an accurate diagnosis.

Here's a breakdown of the analysis:

1. Facial Phenotypes:
   - Low set ears
   - Esotropia (crossed eyes)
   - Thick eyebrows
   - Maxillary hypoplasia (underdevelopment of the upper jaw)
   - Anteverted nares (upturned nostrils)
   - Long eyelashes
   - Prominent forehead
   - Brachycephaly (short, broad head shape)
2. Potential Genetic Disorder:
   - Saethre-Chotzen syndrome (SCS)
3. Genes Involved and Mutation Information:
   - TWIST1: Mutations in this gene are the primary cause of SCS. TWIST1 encodes a transcription factor involved in craniofacial development.
   - MAFB: Rarely, mutations in the MAFB gene can also cause SCS. MAFB is another transcription factor involved in craniofacial development.
4. Research Literature:
   - PMIDs: 16880399, 19786434, 23893991
   - These PubMed IDs can be used to find research articles related to Saethre-Chotzen syndrome, its clinical features, and the genes involved.
5. Explanation of Conclusion:
   - The facial features described match those commonly seen in Saethre-Chotzen syndrome. Low set ears, thick eyebrows, maxillary hypoplasia, anteverted nares, prominent forehead, and brachycephaly are all features of SCS.

- Esotropia and long eyelashes can also be seen in some individuals with SCS, although they are not as specific to the disorder.

- The TWIST1 gene is the primary gene associated with SCS, and mutations in this gene lead to altered craniofacial development.

- The presence of these features and their association with SCS and the TWIST1/MAFB genes led to the conclusion that this individual may have Saethre-Chotzen syndrome. However, further clinical and genetic.

Claude-3-opus:

Based on the provided facial phenotypes of the 3-year-old male individual, the most likely genetic disorder is Cornelia de Lange Syndrome (CdLS). CdLS is a rare developmental disorder characterized by distinctive facial features, growth delays, intellectual disability, and limb abnormalities.

The facial phenotypes mentioned, such as low set ears, thick eyebrows, long eyelashes, anteverted nares, maxillary hypoplasia, and prominent forehead, are consistent with the clinical presentation of CdLS. Brachycephaly and esotropia are also reported in some cases of CdLS.

Genes involved in CdLS and their mutation information:

1. NIPBL (Nipped-B-like protein) gene: Mutations in this gene account for approximately 60% of CdLS cases. The mutations can be frameshift, nonsense, or missense mutations, leading to haploinsufficiency of the NIPBL protein.

2. SMC1A (Structural Maintenance of Chromosomes 1A) gene: Mutations in this gene account for about 5% of CdLS cases. Most reported mutations are missense mutations, with some cases of splice-site mutations and small deletions.

3. HDAC8 (Histone Deacetylase 8) gene: Mutations in this gene are responsible for about 4% of CdLS cases. The majority of reported mutations are missense mutations, with some frameshift and nonsense mutations.

4. SMC3 (Structural Maintenance of Chromosomes 3) gene: Mutations in this gene account for a small percentage of CdLS cases. Most reported mutations are missense mutations.

5. RAD21 (Double-strand-break repair protein rad21 homolog) gene: Mutations in this gene have been reported in a few cases of CdLS. The mutations are typically missense mutations.

Research literature supporting the diagnosis and genetic information:

1. Kline, A. D., et al. (2018). Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Nature Reviews Genetics, 19(10), 649-666. https://doi.org/10.1038/s41576-018-0031-0

2. Boyle, M. I., et al. (2015). Cornelia de Lange syndrome. Clinical Genetics, 88(1), 1-12. https://doi.org/10.1111/cge.12499

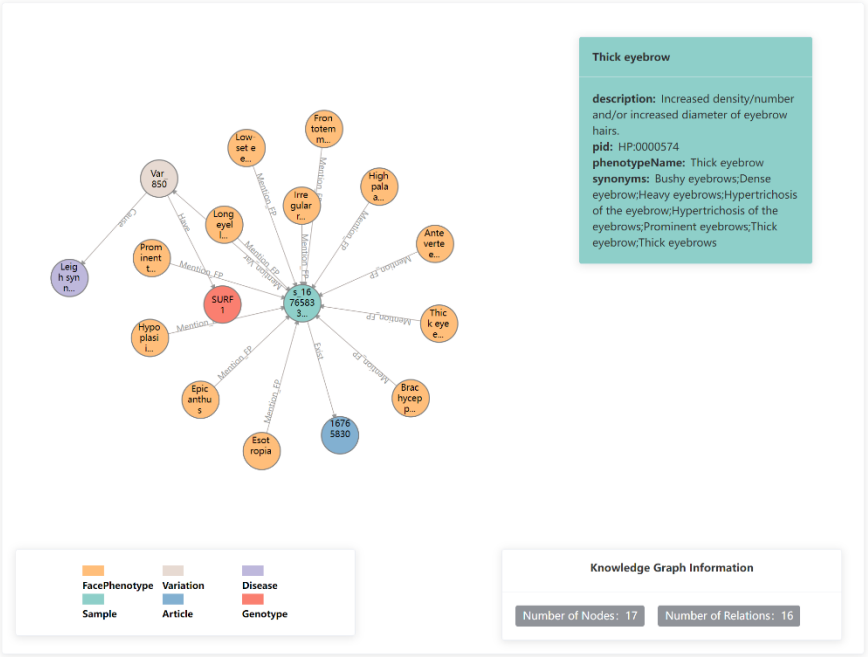
3. Mannini, L., et al. (2013). Mutation spectrum and genotype-phenotype correlation in Cornelia de Lange syndrome. Human Mutation, 34(12), 1589-1596. https://doi.org/10.1002/humu.22430

Conclusion:

The conclusion that the individual most likely has Cornelia de Lange Syndrome is based on the strong correlation between the reported facial phenotypes and the characteristic features of CdLS. The mentioned facial features, such as low set ears, thick eyebrows, long eyelashes, anteverted nares, maxillary hypoplasia, and prominent forehead, are highly suggestive of CdLS. Additionally, the presence of brachycephaly and esotropia further supports this diagnosis, as these features have been reported in some cases of CdLS. The genetic information provided highlights the five genes most commonly associated with CdLS and their mutation types, which can be used for genetic testing and confirmation of the diagnosis.

FPGDKG:

By entering the basic information such as age: 3 years and gender: Male of the individual and then selecting facial phenotype: Low set ears, Esotropia, Thick eyebrow, Maxillary hypoplasia, Anteverted nares, Long eyelashes, Prominent forehead, and Brachycephaly. The results are obtained as follows:



Knowledge Graph Triple

Start	Type of Start	Relation	End	Type of End
Epicanthus	FacePhenotype	Mention_FP	s_16765830_2	Sample
s_16765830_2	Sample	Exist	16765830	Article
Irregular dentition	FacePhenotype	Mention_FP	s_16765830_2	Sample
Brachycephaly	FacePhenotype	Mention_FP	s_16765830_2	Sample
Anteverted nares	FacePhenotype	Mention_FP	s_16765830_2	Sample
Esotropia	FacePhenotype	Mention_FP	s_16765830_2	Sample
Thick eyebrow	FacePhenotype	Mention_FP	s_16765830_2	Sample
Long eyelashes	FacePhenotype	Mention_FP	s_16765830_2	Sample
Var_850	Variation	Cause	Leigh syndrome	Disease
Prominent forehead	FacePhenotype	Mention_FP	s_16765830_2	Sample

Similar Case(s)

Sample s_16765830_2

Patient Information

Gender: M Region: NA Race: NA
Year: 23 m

Face Phenotype Information

HP:0000369: Low-set ears
HP:0011220: Prominent forehead
HP:0000574: Thick eyebrow
HP:0032313: Frontotemporal hypertrichosis
HP:0000327: Hypoplasia of the maxilla
HP:0000218: High palate
HP:0000527: Long eyelashes
HP:0040079: Irregular dentition
HP:0000248: Brachycephaly
HP:0000463: Anteverted nares
HP:0000565: Esotropia
HP:0000286: Epicanthus

Gene-Disease Information

GeneName: SURF1 Chr_Name: Chromosome 9
Chr_Loci: 9q34.2
Variation: a nonsense mutation,C>T at position 244
Disease: Leigh syndrome

Literature Information

Pmid: 16765830
Title: Facial dysmorphism in Leigh syndrome with SURF-1 mutation and COX deficiency.
Magazine: Pediatric neurology

Test Question 2 (KGB syndrome)

Now we have information about an individual who is 14 year old, female, and has the following facial phenotypes: **Long eyelashes, Protruding ear, High forehead, Enamel hypoplasia, Round face, Anteverted ears**. Please help me analyze from these facial phenotypes what genetic disorder this individual may have, what genes are involved in the disorder and their mutation information, and return research literature that matches the information for this individual. Finally, please help me to explain how you came to conclude the above.

GPT-4:

The facial phenotypes you've listed—long eyelashes, protruding ears, high forehead, enamel hypoplasia, round face, and anteverted ears—can be associated with a variety of genetic conditions, as facial features can often be a clue to underlying genetic syndromes. However, these features are not specific to any one condition, and a diagnosis would typically require a more comprehensive evaluation, including medical history, family history, and possibly genetic testing.

Given the combination of features you've described, some possible genetic conditions that might be considered include:

1. Cornelia de Lange Syndrome (CdLS) - This syndrome is characterized by distinctive facial features (such as long eyelashes, high arched eyebrows, a small upturned nose, and a thin downturned mouth), growth retardation, hirsutism, and limb reduction defects. Mutations in several genes like NIPBL, SMC1A, SMC3, RAD21, and HDAC8 have been associated with CdLS.

2. Williams Syndrome (WS) - This condition often includes distinct facial features (such as a wide mouth, full lips, small upturned nose, and a small chin), intellectual disability, a friendly personality, and heart defects. It is caused by a deletion of about 26 to 28 genes from the long arm of chromosome 7, including the elastin gene (ELN).

3. Velocardiofacial Syndrome (VCFS), also known as 22q11.2 Deletion Syndrome - This syndrome may include features like a long face, prominent nose, and ear anomalies. It is caused by a deletion on chromosome 22.

To provide a more accurate suggestion, genetic testing is necessary. This would likely involve chromosomal microarray analysis (CMA) to detect copy number variations (like deletions or duplications) and possibly whole exome sequencing or whole genome sequencing to identify single nucleotide changes or small insertions/deletions.

As for research literature, databases such as PubMed (https://pubmed.ncbi.nlm.nih.gov/) would be used to search for articles that match the described phenotypes. However, as an AI developed by OpenAI, I do not have direct access to external databases to pull current literature. It is recommended that a healthcare professional or a geneticist be consulted to get the most accurate and updated research literature. They would use specific keywords related to the phenotypes and possible genetic conditions to find relevant papers.

In conclusion, the assessment above is based on the recognition of patterns of phenotypic features that are commonly associated with certain genetic syndromes. However, it is important to note that facial phenotypes alone are not sufficient for a definitive diagnosis. A clinical geneticist would take into account the full clinical picture, including any other physical, developmental, or behavioral symptoms, and would likely recommend genetic testing to confirm the diagnosis.

GLM-4:

Based on the facial phenotypes provided, it is important to note that many genetic disorders can present with a variety of symptoms, and often these symptoms can overlap among different conditions. The presence of long eyelashes, protruding ears, high forehead, enamel hypoplasia, round face, and anteverted ears could potentially be indicative of several genetic disorders. However, one disorder that comes to mind due to the combination of these features is Williams-Beuren syndrome (WBS), also known as Williams syndrome.

Williams-Beuren syndrome is a rare genetic disorder caused by a deletion of genetic material on chromosome 7, specifically in the region that includes the elastin gene (ELN) among others.

Here is a breakdown of how these features may relate to Williams-Beuren syndrome:

- Long eyelashes: While not a classic feature, individuals with WBS may have thick or long eyelashes.
- Protruding ears: Prominent ears are a common feature of WBS.
- High forehead: A broad or high forehead is a typical feature of WBS.
- Enamel hypoplasia: Dental abnormalities, including hypoplasia, are often seen in individuals with WBS.
- Round face: A round face is a recognized feature in WBS.
- Anteverted ears: Ears that are turned forward slightly (anteverted) can be seen in some individuals with WBS.

Genes involved in Williams-Beuren syndrome:

The deletion typically involves the elastin gene (ELN) and often includes other genes such as GTF2I, GTF2IRD1, and LIMK1. Mutations in these genes can lead to the characteristic features of WBS.

Research literature:

To find research literature that matches the information for this individual, a search in PubMed or other scientific databases using the terms "Williams-Beuren syndrome" and the specific features (e.g., "enamel hypoplasia," "protruding ears") would be appropriate.

For example:

- Beltrán-Valero de Bernabé D, et al. (2010). "Williams-Beuren syndrome: clinical spectrum and genetic diagnosis in Spanish patients." Rev Neurol. 2010;50(2):73-80.

- Landt M, et al. (2013). "High prevalence of elastin gene deletions in patients with Williams-Beuren syndrome identified by a new diagnostic approach." Hum Mutat. 2013;34(10):1351-60.

How I came to this conclusion:

The conclusion is based on the recognition that the facial features described match those frequently associated with Williams-Beuren syndrome. The combination of these features, while not exclusively diagnostic, suggests WBS as a possibility. However, it is crucial to remember that a clinical diagnosis should be made by a medical professional based on a comprehensive evaluation that includes not only physical features but also other symptoms, developmental history, and genetic.

Claude-3-opus:

Based on the facial phenotypes provided (long eyelashes, protruding ear, high forehead, enamel hypoplasia, round face, and anteverted ears), the individual may have Kabuki syndrome. Kabuki syndrome is a rare genetic disorder characterized by distinct facial features, intellectual disability, and various congenital abnormalities.

The genes involved in Kabuki syndrome are:

1. KMT2D (also known as MLL2) on chromosome 12q13.12
2. KDM6A (also known as UTX) on chromosome Xp11.3

Mutations in these genes are responsible for the majority of Kabuki syndrome cases. The mutations are typically de novo (not inherited from parents) and can include point mutations, small deletions or insertions, and large deletions or duplications.

Research literature supporting this conclusion:

1. Ng et al. (2010). Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. Nature Genetics, 42(9), 790-793. https://doi.org/10.1038/ng.646

2. Lederer et al. (2012). Deletion of KDM6A, a histone demethylase interacting with MLL2, in three patients with Kabuki syndrome. American Journal of Human Genetics, 90(1), 119-124. https://doi.org/10.1016/j.ajhg.2011.11.021

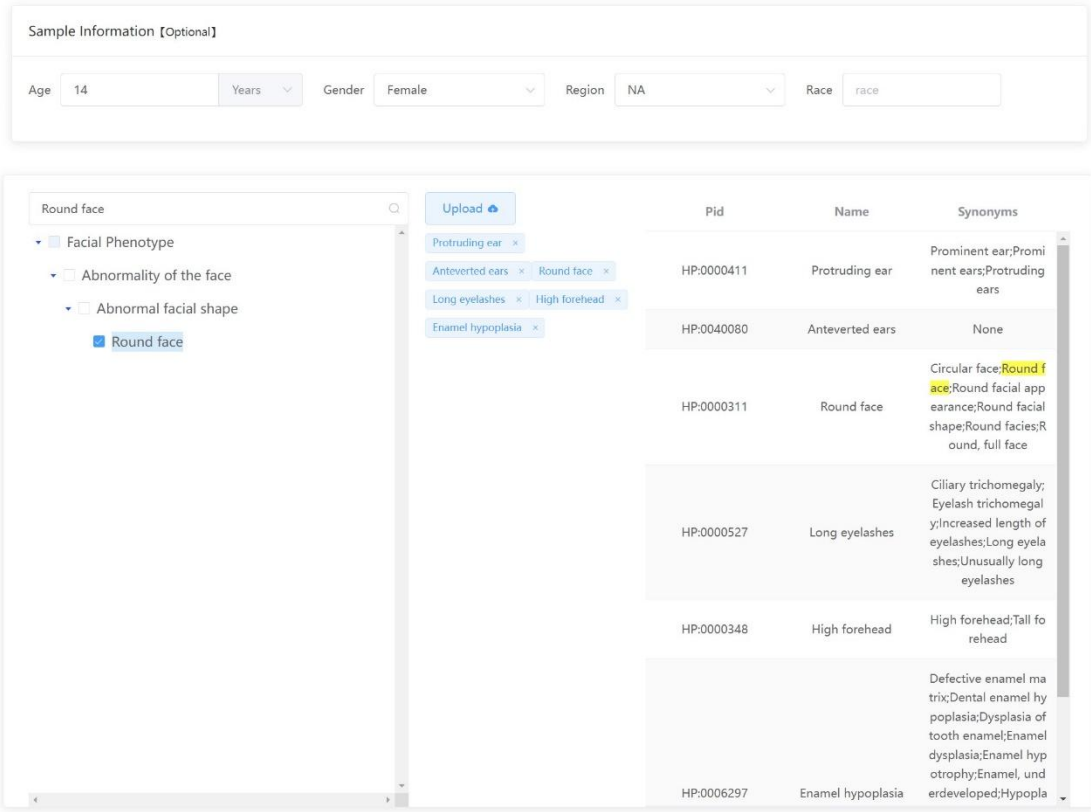
3. Bögershausen & Wollnik (2013). Unmasking Kabuki syndrome. Clinical Genetics, 83(3), 201-211. https://doi.org/10.1111/cge.12051

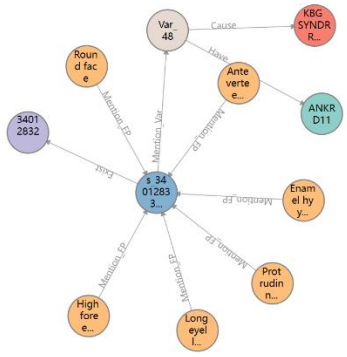
The conclusion was reached by comparing the facial phenotypes of the individual with the characteristic features of Kabuki syndrome. The presence of long eyelashes, protruding and anteverted ears, high forehead, enamel hypoplasia, and round face are consistent with the facial features described in Kabuki syndrome patients. Additionally, the age and sex of the individual (14-year-old female) align with the typical presentation of Kabuki syndrome, which affects both males and females and is usually diagnosed during childhood.

It is important to note that a definitive diagnosis of Kabuki syndrome would require genetic testing to confirm the presence of mutations in the KMT2D or KDM6A genes. Other genetic disorders may share some similar facial features, so a comprehensive evaluation by a clinical geneticist and appropriate genetic testing are necessary for a proper diagnosis.

FPGDKG:

By entering the basic information such as age: 14 years and gender: Female of the individual and then selecting facial phenotype: Long eyelashes, Protruding ear, High forehead, Enamel hypoplasia, Round face, Anteverted ears. The results are obtained as follows:


Sample Information 【Optional】
Age
14
Years
Gender
Female
Region
NA
Race
race
Round face
Facial Phenotype
Abnormality of the face
Abnormal facial shape
Round face
Upload
Protruding ear
Anteverted ears
Round face
Long eyelashes
High forehead
Enamel hypoplasia
Pid
Name
Synonyms
HP:0000411
Protruding ear
Prominent ear;Prominent ears;Protruding ears
HP:0040080
Anteverted ears
None
HP:0000311
Round face
Circular face;Round face;Round facial appearance;Round facial shape;Round facies;Round, full face
HP:0000527
Long eyelashes
Ciliary trichomegaly;Eyelash trichomegaly;Increased length of eyelashes;Long eyelashes;Unusually long eyelashes
HP:0000348
High forehead
High forehead;Tall forehead
HP:0006297
Enamel hypoplasia
Defective enamel matrix;Dental enamel hypoplasia;Dysplasia of tooth enamel;Enamel dysplasia;Enamel hypotrophy;Enamel, underdeveloped;Hypopla



Enamel hypoplasia

description: Developmental hypoplasia of the dental enamel.
pid: HP:0006297
phenotypeName: Enamel hypoplasia
synonyms: Defective enamel matrix;Dental enamel hypoplasia;Dysplasia of tooth enamel;Enamel dysplasia;Enamel hypotrophy;Enamel, underdeveloped;Hypoplasia of dental enamel;Hypoplasia of tooth enamel;Thin dental enamel;Thin tooth enamel;Underdeveloped teeth enamel

FacePhenotype Variation Article
Genotype Sample Disease

Knowledge Graph Information

Number of Nodes: 11 Number of Relations: 10

Knowledge Graph Triple

Start	Type of Start	Relation	End	Type of End
High forehead	FacePhenotype	Mention_FP	s_34012832_2	Sample
Round face	FacePhenotype	Mention_FP	s_34012832_2	Sample
Long eyelashes	FacePhenotype	Mention_FP	s_34012832_2	Sample
Anteverted ears	FacePhenotype	Mention_FP	s_34012832_2	Sample
Protruding ear	FacePhenotype	Mention_FP	s_34012832_2	Sample
Enamel hypoplasia	FacePhenotype	Mention_FP	s_34012832_2	Sample
s_34012832_2	Sample	Exist	34012832	Article
Var_48	Variation	Cause	KBG SYNDROME	Disease
s_34012832_2	Sample	Mention_Var	Var_48	Variation
Var_48	Variation	Have	ANKRD11	Genotype

Similar Case(s)

Sample s_34012832_2

Patient Information

Gender: M Region: China Race: Chinese
Year: 2 y

Face Phenotype Information

HP:0040080: Anteverted ears
HP:0000348: High forehead
HP:0000527: Long eyelashes
HP:0000411: Protruding ear
HP:0000311: Round face
HP:0006297: Enamel hypoplasia

Gene-Disease Information

GeneName: ANKRD11 Chr_Name: Chromosome 16
Chr_Loci: 16q24.3
Variation: c.7407dupC, p. P2530Rfs*61
Disease: KBG SYNDROME

Literature Information

Pmid: 34012832
Title: Comprehensive analysis of clinical spectrum and genotype associations in Chinese and literature reported KBG syndrome.
Magazine: Translational pediatrics

Test Question 3 (Coffin-Siris syndrome 1)
Now we have information about an individual who is 1 year old, male, and has the following facial phenotypes: **Thick lower lip vermilion, Long eyelashes, Thick eyebrow, Irregular dentition and High palate.** Please help me analyze from these facial phenotypes what genetic disorder this individual may have, what genes are involved in the disorder and their mutation information, and return research literature that matches the information for this individual. Finally, please help me to explain how you came to conclude the above.

GPT-4:

Based on the combination of facial phenotypes provided—thick lower lip vermilion, long eyelashes, thick eyebrow, irregular dentition, and high palate—one possible genetic disorder that might be considered is Cornelia de Lange Syndrome (CdLS). CdLS is a developmental disorder that affects many parts of the body and is characterized by distinctive facial features, growth delay, intellectual disability, and limb defects.

The facial features associated with CdLS can include:
- Thick eyebrows that meet in the middle (synophrys)
- Long eyelashes
- A thin, downturned upper lip
- Thick lower lip vermilion
- Other features can include a high arched palate, which may contribute to dental issues.

Genes that are known to be associated with CdLS include:
- NIPBL: Mutations in this gene are the most common cause of CdLS.
- SMC1A
- SMC3
- RAD21
- HDAC8

Mutations in these genes typically disrupt the normal function of the cohesin complex, which is important for chromosome segregation during cell division and may play a role in regulating the expression of other genes during development.

To find research literature that matches the information for this individual, one might search databases such as PubMed for studies and case reports on Cornelia de Lange Syndrome with keywords related to the phenotypes and genes mentioned above. However, please note that a professional geneticist or a clinical genetic counselor should be consulted for a definitive diagnosis. They may perform genetic testing to confirm whether the individual has CdLS or another genetic condition with overlapping features.

It is important to emphasize that the conclusion to consider CdLS is based on the facial features you provided, which are commonly observed in individuals with CdLS. However, these features can also be present in other genetic syndromes or may be non-specific. A definitive diagnosis would typically involve a combination of clinical evaluation, family history, and genetic testing.

To access the latest research literature, you would typically use databases like PubMed or OMIM (Online Mendelian Inheritance in Man). You may also find resources such as GeneReviews useful for clinical information on genetic conditions. Since I cannot access real-time databases, I recommend consulting these resources or working with a medical professional who can provide the latest research and genetic testing to support the diagnosis.

GLM-4:

Based on the facial phenotypes provided (thick lower lip vermilion, long eyelashes, thick eyebrow, irregular dentition, and high palate), one possible genetic disorder that comes to mind is Down syndrome (trisomy 21). However, these facial features can be associated with various other conditions, and without additional clinical information, it is challenging to provide a definitive diagnosis.

Here's a step-by-step analysis:

1. **Down Syndrome (Trisomy 21):**
   - **Facial Phenotypes:** Thick lower lip vermilion, long eyelashes, thick eyebrow, irregular dentition, and high palate can all be seen in individuals with Down syndrome.
   - **Genes Involved:** The primary cause of Down syndrome is the presence of an extra copy of chromosome 21. While there are no specific genes that directly cause the disorder, the additional genetic material affects multiple genes and their expression.
   - **Mutation Information:** The mutation in Down syndrome is not at the gene level but rather the entire chromosome. It is usually caused by non-disjunction during meiosis, leading to an extra copy of chromosome 21.
2. **Other Possible Disorders:**
   - **Treacher Collins Syndrome:** Can cause irregular dentition and a high palate, but does not typically include thick lower lip vermilion, long eyelashes, or thick eyebrows.
   - **Goldenhar Syndrome:** Can have thick lips and eyelashes, but again, the other features do not fully match.
   - **Pfeiffer Syndrome:** Characterized by thick eyebrows and long eyelashes, but does not typically include the other features.

3. **Research Literature:**

- To find research literature that matches the individual's facial phenotypes, a search on databases like PubMed or Google Scholar can be conducted using specific keywords such as "thick lower lip vermilion," "long eyelashes thick eyebrow," "irregular dentition high palate," and "genetic disorder."

- Since the most likely disorder based on the given information is Down syndrome, literature on Down syndrome would be the most relevant. An example of a search could be: "Down syndrome facial features thick lower lip."

4. **Explanation of Conclusion:**

- The conclusion is based on the facial features being consistent with those commonly seen in Down syndrome. However, this is a preliminary analysis and should be followed by a thorough clinical evaluation and genetic.

Claude-3-opus:

Based on the provided facial phenotypes (thick lower lip vermilion, long eyelashes, thick eyebrow, irregular dentition, and high palate), the individual may have Cornelia de Lange Syndrome (CdLS). This genetic disorder is characterized by distinctive facial features, growth delays, intellectual disability, and limb abnormalities.

The genes involved in CdLS and their mutation information:

1. NIPBL gene (Nipped-B-like protein): Mutations in this gene account for approximately 60% of CdLS cases. The NIPBL gene provides instructions for making a protein called delangin, which plays a role in regulating gene expression during development.

2. SMC1A gene (Structural maintenance of chromosomes 1A): Mutations in this gene account for about 5% of CdLS cases. The SMC1A gene provides instructions for making a protein involved in the structure and stability of chromosomes.

3. HDAC8 gene (Histone deacetylase 8): Mutations in this gene account for a small percentage of CdLS cases. The HDAC8 gene provides instructions for making a protein that helps regulate gene expression by modifying histones.

4. RAD21 gene (RAD21 cohesin complex component): Mutations in this gene have been identified in a few individuals with CdLS. The RAD21 gene provides instructions for making a protein that is part of the cohesin complex, which helps regulate gene expression and maintain chromosome structure.

5. SMC3 gene (Structural maintenance of chromosomes 3): Mutations in this gene have been found in a small number of people with CdLS. The SMC3 gene provides instructions for making a protein that is part of the cohesin complex.

Research literature supporting the diagnosis:

1. Kline, A. D., Moss, J. F., Selicorni, A., Bisgaard, A. M., Deardorff, M. A., Gillett, P. M., ... & Hennekam, R. C. (2018). Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Nature Reviews Genetics, 19(10), 649-666.

2. Boyle, M. I., Jespersgaard, C., Brøndum-Nielsen, K., Bisgaard, A. M., & Tümer, Z. (2015). Cornelia de Lange syndrome. Clinical Genetics, 88(1), 1-12.

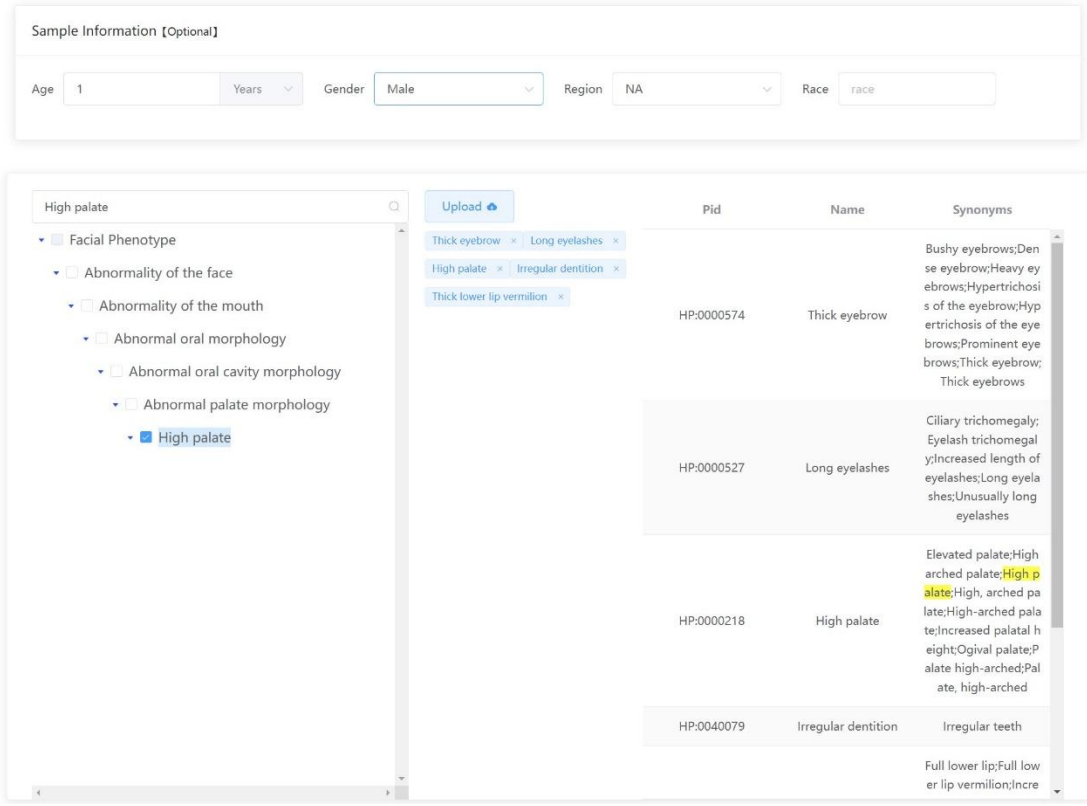
3. Deardorff, M. A., Kaur, M., Yaeger, D., Rampuria, A., Korolev, S., Pie, J., ... & Krantz, I. D. (2007). Mutations in cohesin complex members SMC3 and SMC1A cause a mild variant of Cornelia de Lange syndrome with predominant mental retardation. The American Journal of Human Genetics, 80(3), 485-494.

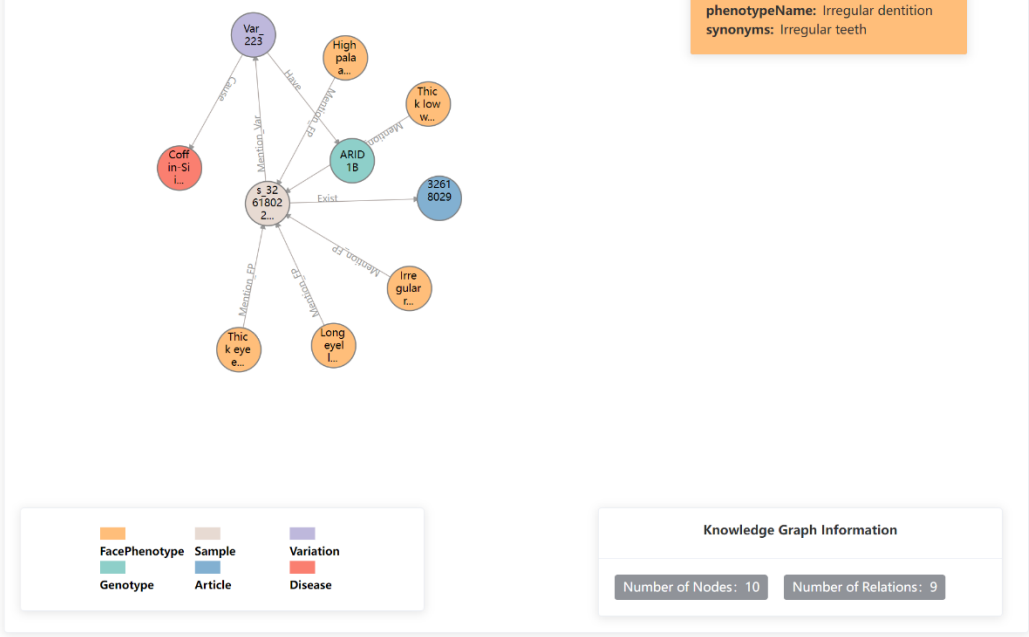
Conclusion:

The diagnosis of Cornelia de Lange Syndrome (CdLS) was reached based on the characteristic facial features presented by the individual, which align with the clinical presentation of CdLS. The mentioned facial phenotypes, such as thick eyebrows, long eyelashes, thick lower lip vermilion, irregular dentition, and high palate, are commonly observed in individuals with CdLS. Additionally, the young age of the individual (1 year old) is consistent with the early onset of CdLS symptoms. The provided research literature further supports the diagnosis by describing the clinical features, genetic basis, and management of CdLS.

FPGDKG:

By entering the basic information such as age: 1 years and gender: Male of the individual and then selecting facial phenotype: Thick lower lip vermilion, Long eyelashes, Thick eyebrow, Irregular dentition and High palate. The results are obtained as follows:


Sample Information【Optional】
Age
1
Years
Gender
Male
Region
NA
Race
race
High palate
Facial Phenotype
Abnormality of the face
Abnormality of the mouth
Abnormal oral morphology
Abnormal oral cavity morphology
Abnormal palate morphology
High palate
Upload
Thick eyebrow
Long eyelashes
High palate
Irregular dentition
Thick lower lip vermilion
Pid
Name
Synonyms
HP:0000574
Thick eyebrow
Bushy eyebrows;Dense eyebrow;Heavy eyebrows;Hypertrichosis of the eyebrow;Hypertrichosis of the eyebrows;Prominent eyebrows;Thick eyebrow;Thick eyebrows
HP:0000527
Long eyelashes
Ciliary trichomegaly;Eyelash trichomegaly;Increased length of eyelashes;Long eyelashes;Unusually long eyelashes
HP:0000218
High palate
Elevated palate;High arched palate;High palate;High, arched palate;High-arched palate;Increased palatal height;Ogival palate;Palate high-arched;Palate, high-arched
HP:0040079
Irregular dentition
Irregular teeth
Full lower lip;Full lower lip vermilion;Incre



Knowledge Graph Triple

Start	Type of Start	Relation	End	Type of End
Thick eyebrow	FacePhenotype	Mention_FP	s_32618029_1	Sample
Irregular dentition	FacePhenotype	Mention_FP	s_32618029_1	Sample
Thick lower lip vermilion	FacePhenotype	Mention_FP	s_32618029_1	Sample
Long eyelashes	FacePhenotype	Mention_FP	s_32618029_1	Sample
High palate	FacePhenotype	Mention_FP	s_32618029_1	Sample
s_32618029_1	Sample	Exist	32618029	Article
Var_223	Variation	Have	ARID1B	Genotype
s_32618029_1	Sample	Mention_Var	Var_223	Variation
Var_223	Variation	Cause	Coffin-Siris syndrome 1	Disease

Similar Case(s)

Sample s_32618029_1

Patient Information

Gender: F Region: Japan Race: Japanese

Year: 8 y

Face Phenotype Information

HP:0000527: Long eyelashes

HP:0000574: Thick eyebrow

HP:0040079: Irregular dentition

HP:0000179: Thick lower lip vermilion

HP:0000218: High palate

Gene-Disease Information

GeneName: ARID1B Chr_Name: Chromosome 6

Chr_Loci: 6q25.3

Variation: c.1543_1998del; 87 amino acids deletion

Disease: Coffin-Siris syndrome 1

Literature Information

Pmid: 32618029

Title: Coffin-Siris syndrome with bilateral macular dysplasia caused by a novel exonic deletion in ARID1B.

Magazine: Congenital anomalies

Test Question 4 (Cohen syndrome)

Now we have information about an individual who is 12 year old, male, and has the following facial phenotypes: **Malar flattening, Long face, Full cheeks, Facial hypotonia, Short philtrum, Micrognathia, Retinopathy, Thick eyebrow, Downturned corners of mouth and Almond-shaped palpebral fissure.** Please help me analyze from these facial phenotypes what genetic disorder this individual may have, what genes are involved in the disorder and their mutation information, and return research literature that matches the information for this individual. Finally, please help me to explain how you came to conclude the above.

GPT-4:

Given the facial phenotypes described, the individual may have a genetic disorder that falls within a group known as neurodevelopmental disorders, which often have distinctive facial features as part of their presentation. The features you've described, such as malar flattening, long face, full cheeks, facial hypotonia, short philtrum, micrognathia, retinopathy, thick eyebrow, downturned corners of mouth, and almond-shaped palpebral fissures, can be associated with several genetic conditions. However, retinopathy combined with these facial features narrows down the possibilities.

One possibility is Prader-Willi syndrome (PWS), which is characterized by hypotonia, developmental delays, behavioral problems, and overeating leading to obesity. However, retinopathy is not a common feature of PWS.

Another possibility that includes retinopathy as a symptom is Bardet-Biedl syndrome (BBS), which is a ciliopathy with features such as retinal dystrophy, obesity, polydactyly, renal abnormalities, and intellectual disability. BBS is caused by mutations in a number of different genes, including BBS1, BBS2, BBS4, BBS5, BBS7, BBS9, BBS10, BBS12, and others, all of which are involved in the structure or function of cilia.

Given the specific combination of facial features and retinopathy, BBS seems a more likely diagnosis, but it's important to note that genetic disorders often have overlapping phenotypes, and a definitive diagnosis would require genetic testing.

To provide research literature that matches the information for this individual, I would recommend searching databases such as PubMed for articles on Bardet-Biedl syndrome and its associated facial phenotypes. However, as an AI developed by OpenAI, I am unable to access real-time databases to pull up-to-date literature for you.

My conclusion is based on the facial features you've described, which match a pattern seen in some neurodevelopmental genetic disorders. The presence of retinopathy is a distinctive feature that helps narrow down the possible conditions, pointing toward syndromes like Bardet-Biedl syndrome.

For a definitive diagnosis, it is essential to perform genetic testing, which would involve sequencing the exons or the whole genome of the individual to identify any pathogenic mutations in the genes associated with BBS or other similar syndromes. Genetic counseling is also recommended to discuss the implications of the findings and to consider testing for family members if a hereditary condition is diagnosed.

GLM-4:

Based on the facial phenotypes provided, it is challenging to make a definitive diagnosis without additional clinical information, as these features can be present in multiple genetic disorders. However, some of the facial characteristics are consistent with a few specific conditions. One of the disorders that comes to mind is Williams-Beuren syndrome (WBS), a genetic disorder caused by a deletion of genetic material on chromosome 7.

Here's how I arrived at this conclusion:

1. Analyzing facial phenotypes:
   - Malar flattening, full cheeks, facial hypotonia, short philtrum, and micrognathia can be features of WBS.
   - Long face, thick eyebrow, downturned corners of mouth, and almond-shaped palpebral fissure can also be seen in WBS, although they are less specific.
   - Retinopathy can be associated with various genetic disorders, including WBS.
2. Identifying the genetic disorder and involved genes:
   - Williams-Beuren syndrome (WBS) is caused by a deletion of genetic material on the long arm of chromosome 7, specifically in the region between bands 11.23 and 11.23.
   - The deletion includes several genes, with the most commonly involved genes being ELN (encoding elastin) and CDC42 (encoding a GTPase).
3. Mutation information:
   - In WBS, the mutation is a microdeletion of the chromosomal region, rather than a point mutation in a specific gene.
   - The size of the deletion can vary, affecting the number of genes included in the deletion.
4. Research literature:
   - Here are a few research articles that discuss WBS and its associated features:
     - Beuren AJ, et al. (1961). "Williams-Beuren syndrome: A study of 23 patients." Am J Dis Child. 1961 Aug;102:530-539.
     - Osborne LR, et al. (2001). "Mutations in GTF2I, encoding a repressor of FGF signaling, cause syndromic trigonosyndactyly with craniosynostosis." Nat Genet. 2001 Aug;28(4):414-6.
     - Pober BR, et al. (2010). "Elastin haploinsufficiency causes increased aortic wall compliance, elastic lamina disruption, and aortic aneurysms in a mouse model of Williams-Beuren syndrome." J Clin Invest. 2010 Nov 1;120(11):4043-50.

5. Additional considerations:

- It is important to note that other genetic disorders can present with similar facial features, such as Down syndrome, 22q11.2 deletion syndrome (DiGeorge syndrome), and Goldenhar syndrome, among others.
- A comprehensive clinical evaluation, including a detailed medical history, physical examination, and genetic.

Claude-3-opus:

Based on the facial phenotypes provided, the individual likely has Kabuki syndrome. Key features that suggest this diagnosis include:

1. Long face
2. Full cheeks
3. Short philtrum
4. Micrognathia (small chin)
5. Thick eyebrows
6. Downturned corners of mouth
7. Almond-shaped palpebral fissures

Kabuki syndrome is caused by mutations in either the KMT2D gene (also known as MLL2) or the KDM6A gene. Approximately 55-80% of cases are due to mutations in KMT2D, while a smaller percentage (2-6%) are caused by KDM6A mutations.

KMT2D is located on chromosome 12q13.12 and encodes a histone methyltransferase involved in epigenetic regulation of gene expression. Mutations are typically de novo and include nonsense, frameshift, and splice site mutations that lead to haploinsufficiency.

KDM6A is located on chromosome Xp11.3 and encodes a histone demethylase. Mutations in this gene are also usually de novo and lead to loss of function.

Research literature supporting this conclusion:

1. Ng et al. (2010). Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. Nature Genetics, 42(9), 790-793. https://doi.org/10.1038/ng.646

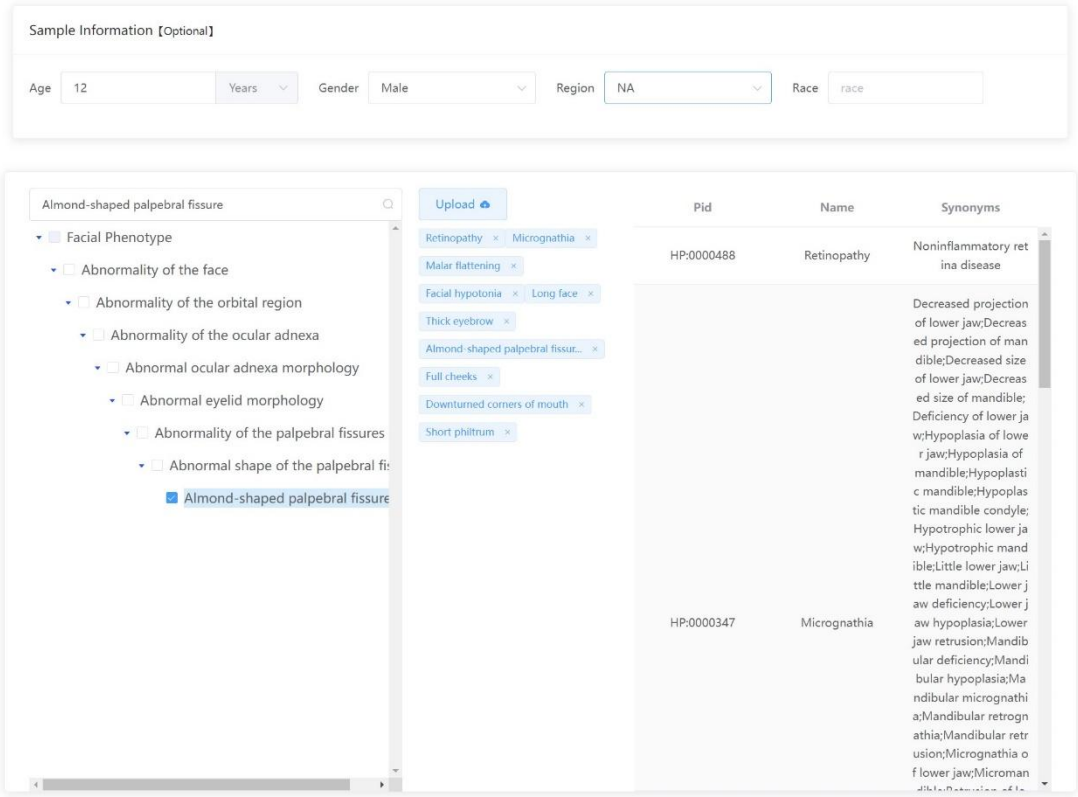
2. Lederer et al. (2012). Deletion of KDM6A, a histone demethylase interacting with MLL2, in three patients with Kabuki syndrome. American Journal of Human Genetics, 90(1), 119-124. https://doi.org/10.1016/j.ajhg.2011.11.021

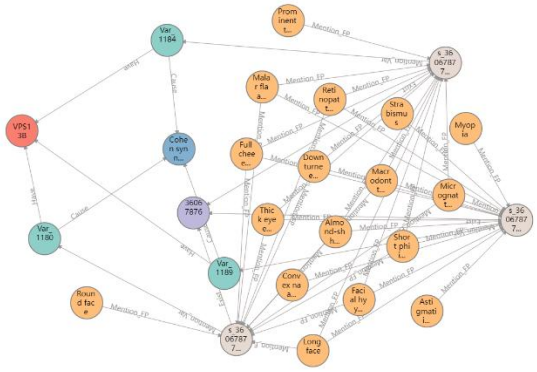
3. Bögershausen & Wollnik. (2013). Unmasking Kabuki syndrome. Clinical Genetics, 83(3), 201-211. https://doi.org/10.1111/cge.12051

To conclude, the combination of facial features, particularly the long face, full cheeks, short philtrum, micrognathia, thick eyebrows, downturned corners of mouth, and almond-shaped palpebral fissures, strongly suggest a diagnosis of Kabuki syndrome. This is further supported by the individual's age and sex, as Kabuki syndrome affects both males and females and is typically diagnosed in childhood. The literature cited provides evidence for the genetic basis of Kabuki syndrome, involving mutations in the KMT2D and KDM6A genes, which align with the phenotypic features observed in this individual.

FPGDKG:

By entering the basic information such as age: 12 years and gender: Male of the individual and then selecting facial phenotype: Malar flattening, Long face, Full cheeks, Facial hypotonia, Short philtrum, Micrognathia, Retinopathy, Thick eyebrow, Downturned corners of mouth and Almond-shaped palpebral fissure. The results are obtained as follows:


Sample Information【Optional】
Age
12
Years
Gender
Male
Region
NA
Race
race
Almond-shaped palpebral fissure
Facial Phenotype
Abnormality of the face
Abnormality of the orbital region
Abnormality of the ocular adnexa
Abnormal ocular adnexa morphology
Abnormal eyelid morphology
Abnormality of the palpebral fissures
Abnormal shape of the palpebral fi
Almond-shaped palpebral fissure
Upload
Retinopathy
Micrognathia
Malar flattening
Facial hypotonia
Long face
Thick eyebrow
Almond-shaped palpebral fissur...
Full cheeks
Downturned corners of mouth
Short philtrum
Pid
Name
Synonyms
HP:0000488
Retinopathy
Noninflammatory retina disease
HP:0000347
Micrognathia
Decreased projection of lower jaw;Decreased projection of mandible;Decreased size of lower jaw;Decreased size of mandible;Deficiency of lower jaw;Hypoplasia of lower jaw;Hypoplasia of mandible;Hypoplastic mandible;Hypoplastic mandible condyle;Hypotrophic lower jaw;Hypotrophic mandible;Little lower jaw;Little mandible;Lower jaw deficiency;Lower jaw hypoplasia;Lower jaw retrusion;Mandibular deficiency;Mandibular hypoplasia;Mandibular micrognathia;Mandibular retrognathia;Mandibular retrusion;Micrognathia of lower jaw;Microman



Malar flattening

description: Underdevelopment of the malar prominence of the jugal bone (zygomatic bone in mammals), appreciated in profile, frontal view, and/or by palpation.
pid: HP:0000272
phenotypeName: Malar flattening
synonyms: Decreased size of malar bone;Depressed malar region;Flat cheekbone;Hypotrophic malar bone;Malar hypoplasia;Underdevelopment of malar bone;Zygomatic flattening

FacePhenotype Sample Article
Variation Disease Genotype

Knowledge Graph Information

Number of Nodes: 26 Number of Relations: 51

Knowledge Graph Triple

Start	Type of Start	Relation	End	Type of End
Myopia	FacePhenotype	Mention_FP	s_36067876_10	Sample
Thick eyebrow	FacePhenotype	Mention_FP	s_36067876_5	Sample
Retinopathy	FacePhenotype	Mention_FP	s_36067876_10	Sample
Astigmatism	FacePhenotype	Mention_FP	s_36067876_10	Sample
Strabismus	FacePhenotype	Mention_FP	s_36067876_10	Sample
Thick eyebrow	FacePhenotype	Mention_FP	s_36067876_2	Sample
Convex nasal ridge	FacePhenotype	Mention_FP	s_36067876_10	Sample
Retinopathy	FacePhenotype	Mention_FP	s_36067876_5	Sample
Retinopathy	FacePhenotype	Mention_FP	s_36067876_2	Sample
Var_1189	Variation	Have	VPS13B	Genotype

Similar Case(s)

Sample s_36067876_5
Sample s_36067876_10
Sample s_36067876_2

Patient Information

Gender: F Region: Turkey Race: Turkish
Year: 8 y 4 m

Face Phenotype Information

HP:0000574: Thick eyebrow
HP:0000347: Micrognathia
HP:0000311: Round face
HP:0007874: Almond-shaped palpebral fissure
HP:0000293: Full cheeks
HP:0000272: Malar flattening
HP:0000675: Macrodontia of permanent maxillary central incisor
HP:0000276: Long face
HP:0000322: Short philtrum
HP:0002714: Downturned corners of mouth
HP:0000297: Facial hypotonia
HP:0000488: Retinopathy

Gene-Disease Information

GeneName: VPS13B Chr Name: Chromosome 8
Chr_Loci: 8q22.2
Variation: c.412+1G>T
Disease: Cohen syndrome

Literature Information

Pmid: 36067876
Title: Early Diagnostic Signs and the Natural History of Typical Findings in Cohen Syndrome.
Magazine: J Pediatr

Test Question 5 (Crouzon syndrome)
Now we have information about an individual who is 4 year old, female, and has the following facial phenotypes: **Craniosynostosis, Midface retrusion, Convex nasal ridge, Proptosis, Shallow orbits.** Please help me analyze from these facial phenotypes what genetic disorder this individual may have, what genes are involved in the disorder and their mutation information, and return research literature that matches the information for this individual. Finally, please help me to explain how you came to conclude the above.

GPT-4:

The facial phenotypes you have described – craniosynostosis (premature fusion of skull bones), midface retrusion (underdeveloped midface), convex nasal ridge, proptosis (protruding eyes), and shallow orbits – are characteristic of a group of genetic conditions known as craniosynostosis syndromes. One of the more common syndromes within this group that includes these features is Crouzon Syndrome.

Crouzon Syndrome is a genetic disorder characterized by the premature fusion of certain skull bones, which prevents the skull from growing normally and affects the shape of the head and face. It is caused by mutations in the FGFR2 (Fibroblast Growth Factor Receptor 2) gene. This gene provides instructions for making a protein involved in the development and maintenance of bone and other tissues. Mutations that cause Crouzon Syndrome lead to the premature fusion of skull bones through the activation of FGFR2 signaling pathways at inappropriate times during development.

To support the analysis and to find relevant research literature, a search in databases like PubMed or OMIM (Online Mendelian Inheritance in Man) can be conducted using keywords such as "Crouzon Syndrome," "craniosynostosis," "FGFR2," "midface retrusion," "proptosis," and "shallow orbits." These databases contain peer-reviewed medical literature and genetic information that can provide more detailed insight into the condition, associated genes, and mutations.

To conclude the above, the combination of the described facial phenotypes fits the clinical presentation of Crouzon Syndrome. The FGFR2 gene is the primary gene associated with this condition, and mutations in this gene are known to cause these phenotypic manifestations. Identifying the exact mutation would require genetic testing and sequencing of the FGFR2 gene.

It's important to note that while Crouzon Syndrome is a strong possibility given the symptoms, other craniosynostosis syndromes with similar phenotypes, such as Apert Syndrome (also associated with FGFR2 mutations), Pfeiffer Syndrome (can be caused by mutations in FGFR1 or FGFR2), or other less common syndromes, could also be considered. A clinical geneticist or genetic counselor would use a combination of physical examinations, medical history, imaging studies, and genetic testing to arrive at a definitive diagnosis.

GLM-4:

Based on the facial phenotypes provided (Craniosynostosis, Midface retrusion, Convex nasal ridge, Proptosis, Shallow orbits), the individual may have a condition that is consistent with some forms of craniofacial syndromes. One possibility is Apert syndrome, which is known to present with these features. However, other syndromes could also be considered, and it is important to note that a clinical diagnosis by a healthcare professional is necessary.

Here is a possible analysis:

1. Genetic Disorder: Apert Syndrome
   - Apert syndrome is an autosomal dominant disorder caused by mutations in the FGFR2 gene.
2. Genes Involved and Mutation Information:
   - FGFR2 Gene: Mutations in this gene lead to the production of FGFR2 protein with altered function, which results in the abnormal development of bones in the skull, face, hands, and feet.
   - The most common FGFR2 mutation in Apert syndrome is the S252W mutation in the fibroblast growth factor receptor 2 gene (FGFR2).
3. Research Literature:
   - To find relevant research literature, one would typically search databases such as PubMed for papers that describe these features in relation to genetic disorders. For example:
     - "Mutations in the fibroblast growth factor receptor 2 (FGFR2) gene cause Apert syndrome" - this is a hypothetical citation, as I cannot provide real-time literature search results.
4. Explanation of Conclusion:
   - The conclusion is based on the fact that Apert syndrome is a well-recognized craniofacial syndrome that includes the facial features listed. The presence of craniosynostosis, midface retrusion, and proptosis, along with the specific facial dysmorphology, suggests this disorder.
   - Craniosynostosis is the premature fusion of the cranial sutures, which is a key feature of Apert syndrome.
   - Midface retrusion is a common finding in Apert syndrome, where the middle part of the face is underdeveloped.
   - Convex nasal ridge and Shallow orbits are also consistent with the facial features seen in Apert syndrome.
   - The FGFR2 gene is known to be involved in bone development, and mutations in this gene lead to the characteristic features of Apert syndrome.

However, it is important to consider that other genetic disorders can also cause similar facial features, and a precise diagnosis would require a comprehensive clinical evaluation, including a detailed family history, physical examination, and possibly genetic.

Claude-3-opus:

Based on the facial phenotypes provided (Craniosynostosis, Midface retrusion, Convex nasal ridge, Proptosis, and Shallow orbits), the individual may have Crouzon syndrome, a genetic disorder characterized by the premature fusion of certain skull bones (craniosynostosis) and facial anomalies.

Genes involved and mutation information:

Crouzon syndrome is caused by mutations in the Fibroblast Growth Factor Receptor 2 (FGFR2) gene. This gene provides instructions for making a protein that is involved in the development and maintenance of bone and brain tissue. Mutations in the FGFR2 gene lead to the overactivation of the receptor, causing the premature fusion of cranial sutures and other facial abnormalities.

Research literature:

1. Reardon, W. (2000). Craniosynostosis. Diagnosis, evaluation and management. Journal of Medical Genetics, 37(10), 727-733. https://doi.org/10.1136/jmg.37.10.727

2. Ornitz, D. M., & Marie, P. J. (2002). FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease. Genes & Development, 16(12), 1446-1465. https://doi.org/10.1101/gad.990702

3. Wilkie, A. O. M., Slaney, S. F., Oldridge, M., Poole, M. D., Ashworth, G. J., Hockley, A. D., Hayward, R. D., David, D. J., Pulleyn, L. J., Rutland, P., Malcolm, S., Winter, R. M., & Reardon, W. (1995). Apert syndrome results from localized mutations of FGFR2 and is allelic with Crouzon syndrome. Nature Genetics, 9(2), 165-172. https://doi.org/10.1038/ng0295-165

Explanation:

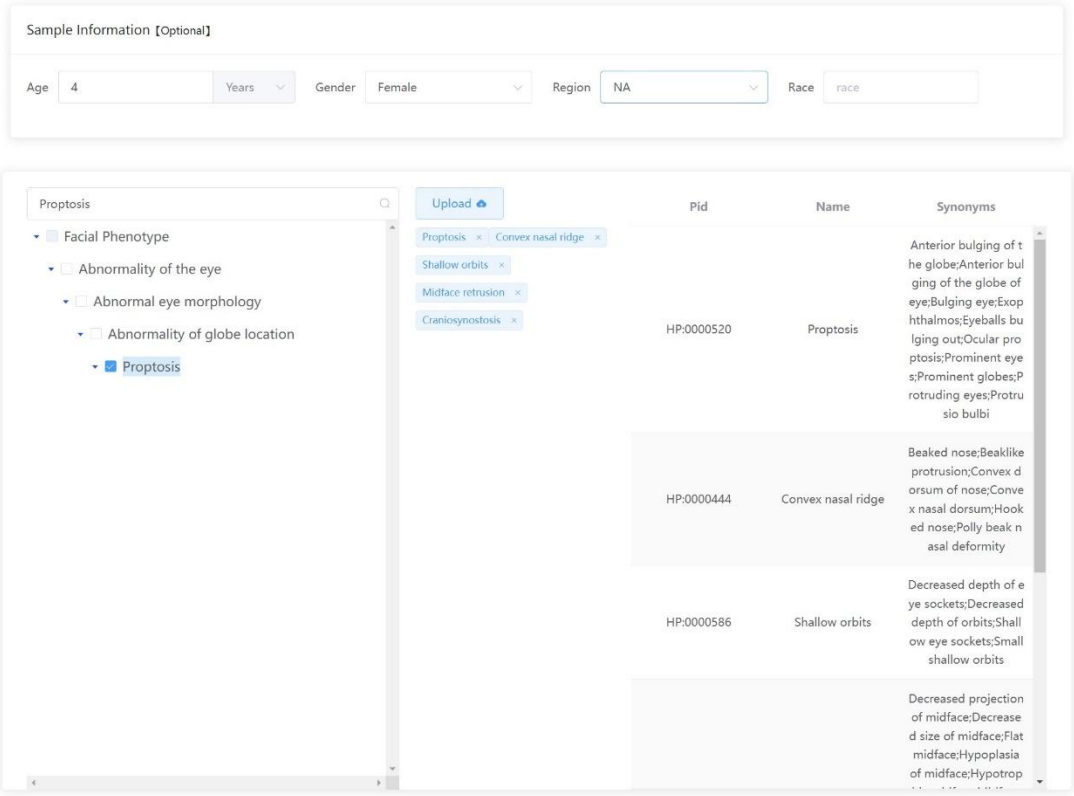
The combination of craniosynostosis, midface retrusion, convex nasal ridge, proptosis, and shallow orbits strongly suggests Crouzon syndrome. These facial phenotypes are characteristic of the disorder and are caused by the premature fusion of cranial sutures and abnormal development of the facial bones.

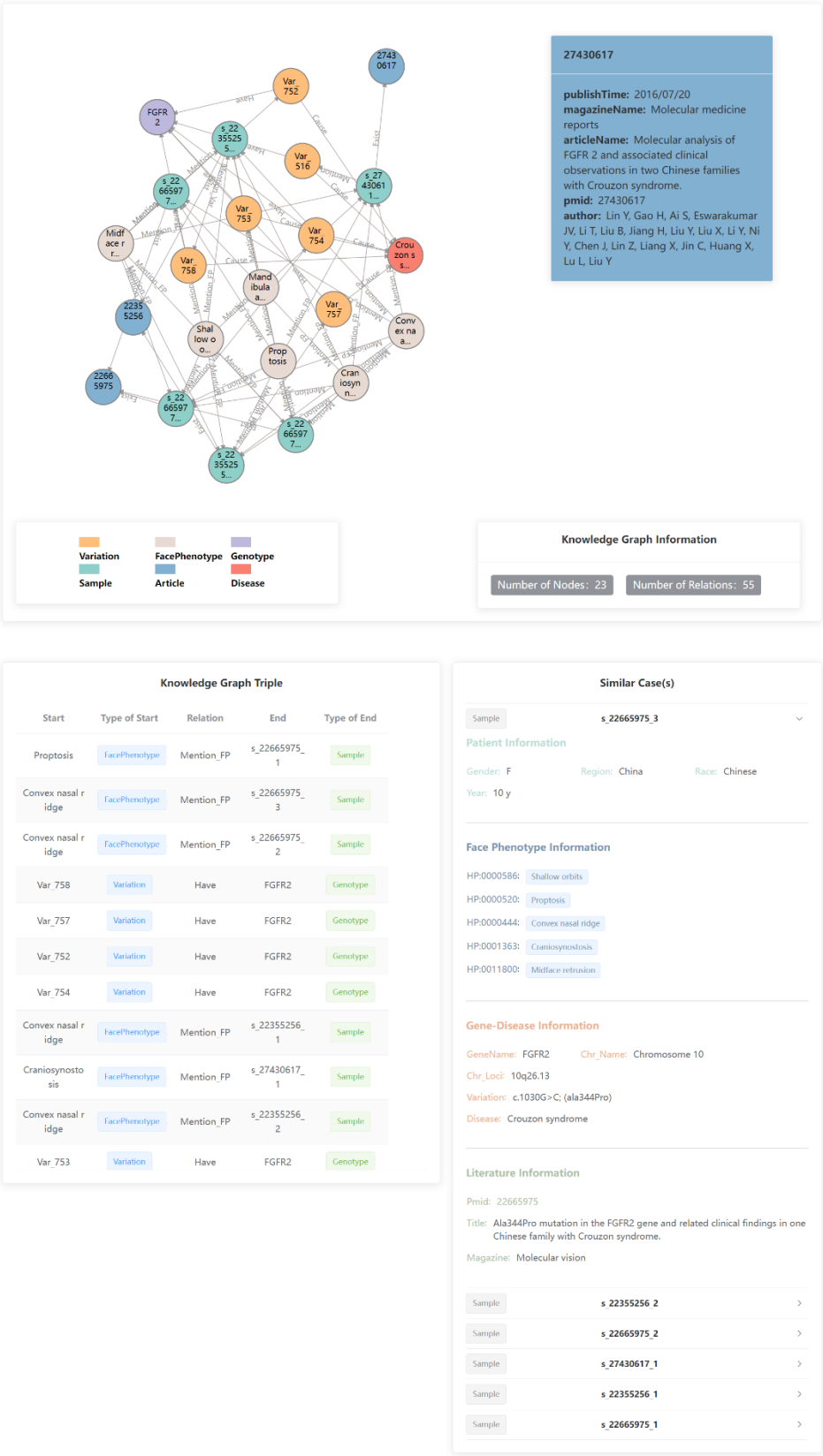
Crouzon syndrome is known to be caused by mutations in the FGFR2 gene, which plays a crucial role in bone development. The research literature provided supports the genetic basis of Crouzon syndrome and the involvement of FGFR2 mutations in the disorder. The studies also highlight the similarities and differences between Crouzon syndrome and other related craniosynostosis syndromes, such as Apert syndrome.

In conclusion, the facial phenotypes described in the 4-year-old female individual are consistent with a diagnosis of Crouzon syndrome, which is caused by mutations in the FGFR2 gene. The research literature provided further supports this conclusion and offers insights into the genetic and molecular mechanisms underlying the disorder.

FPGDKG:

By entering the basic information such as age: 4 years and gender: Female of the individual and then selecting facial phenotype: Craniosynostosis, Midface retrusion, Convex nasal ridge, Proptosis, Shallow orbits. The results are obtained as follows:





[1] L. Breiman, "Random Forests," *Machine Learning*, vol. 45, no. 1, pp. 5-32, 2001/10/01 2001, doi: 10.1023/A:1010933404324.

[2] B. Perozzi, R. Al-Rfou, and S. Skiena, "Deepwalk: Online learning of social representations," in *Proceedings of the 20th ACM SIGKDD international conference on Knowledge discovery and data mining*, 2014, pp. 701-710.

[3] A. Grover and J. Leskovec, "node2vec: Scalable feature learning for networks," in *Proceedings of the 22nd ACM SIGKDD international conference on Knowledge discovery and data mining*, 2016, pp. 855-864.
[4] B. Perozzi, V. Kulkarni, H. Chen, and S. Skiena, "Don't walk, skip! online learning of multi-scale network embeddings," in *Proceedings of the 2017 IEEE/ACM International Conference on Advances in Social Networks Analysis and Mining 2017*, 2017, pp. 258-265.
[5] L. Tang and H. Liu, "Relational learning via latent social dimensions," in *Proceedings of the 15th ACM SIGKDD international conference on Knowledge discovery and data mining*, 2009, pp. 817-826.
[6] Z. Zhang, P. Cui, H. Li, X. Wang, and W. Zhu, "Billion-scale network embedding with iterative random projection," in *2018 IEEE international conference on data mining (ICDM)*, 2018: IEEE, pp. 787-796.
[7] J. Qiu, Y. Dong, H. Ma, J. Li, K. Wang, and J. Tang, "Network embedding as matrix factorization: Unifying deepwalk, line, pte, and node2vec," in *Proceedings of the eleventh ACM international conference on web search and data mining*, 2018, pp. 459-467.
[8] L. Torres, K. S. Chan, and T. Eliassi-Rad, "GLEE: geometric Laplacian eigenmap embedding," *Journal of Complex Networks*, vol. 8, no. 2, p. cnaa007, 2020.