

Culler-Jones Syndrome Across Three Generations: Variable Expressivity of a Pathogenic GLI2 Variant—a Case Report

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Case Report

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Abstract

Background

Culler-Jones syndrome is a rare developmental disorder associated with pathogenic variants in *GLI2* gene. The phenotype is highly variable and may include hypopituitarism, growth hormone deficiency, postaxial polydactyly, craniofacial abnormalities, and other developmental abnormalities involving midline structures. Variable expressivity and incomplete penetrance can complicate diagnosis and genetic counseling, particularly when relatives carrying the same pathogenic variant have few or no apparent manifestations.

Case presentation

A 24-year-old woman of Native American ancestry on both the maternal and paternal sides of her family was referred to the Adult Genetics Clinic for evaluation of congenital craniofacial abnormalities, hypopituitarism, growth hormone deficiency, short stature, and hypogonadotropic hypogonadism. Her history included bilateral cleft lip, anterior cleft palate, midline upper lip and gingival tissue masses, severe growth delay, and abnormal pubertal development. Brain magnetic resonance imaging performed in early childhood demonstrated a Chiari I malformation and absence of most or all of the pituitary gland. Genetic testing identified a heterozygous pathogenic variant in *GLI2*, NM_005270.4:c.1421G>A (p.Trp474*). Targeted familial testing subsequently identified the same variant in her mother, sister, and maternal grandmother, all of whom were reportedly without significant manifestations of *GLI2*-related disease. Her brother tested negative for the familial variant.

The maternal family history was notable for postaxial polydactyly in multiple relatives. Two maternal uncles reportedly had both postaxial polydactyly and multiple supernumerary nipples, with up to five additional nipples reported in affected individuals. These relatives were not available to undergo genetic testing.

Conclusions

This family demonstrates marked variable expressivity associated with a pathogenic *GLI2* variant across three generations. The proband had a severe multisystem phenotype, whereas three relatives carrying the same variant were reportedly without significant manifestations. Multiple supernumerary nipples in two maternal relatives who have not had molecular confirmation of the *GLI2* familial variant represent a potentially new phenotype finding that has not been established as part of the recognized phenotype of Culler-Jones syndrome. This case highlights the importance of detailed family history assessment, cascade testing, and careful genetic counseling in families with *GLI2*-related disease.

Background

Culler-Jones syndrome is a rare developmental disorder associated with pathogenic variants in *GLI2* gene. It was originally described in individuals with hypopituitarism and postaxial polydactyly [1]. Since

that initial description, the recognized phenotype has expanded to include variable combinations of hypopituitarism, growth hormone deficiency, short stature, postaxial polydactyly, craniofacial anomalies, and abnormalities involving the pituitary and other midline structures [2, 4–6].

The clinical expression of *GLI2*-related disease can vary substantially, even among individuals within the same family. Variable expressivity and incomplete penetrance have been reported, creating challenges for diagnosis and genetic counseling [3, 5, 6]. Genotype–phenotype studies have further demonstrated that truncating *GLI2* variants are strongly associated with hypopituitarism and that postaxial polydactyly may occur within the broader spectrum of *GLI2*-related disease [5].

We describe a family in which the truncating pathogenic variant *GLI2* NM_005270.4:c.1421G > A (p.Trp474*) was identified across three generations. The proband had a severe phenotype involving craniofacial development, pituitary function, growth, and pubertal development. In contrast, her mother, sister, and maternal grandmother carried the same variant but were reportedly without significant manifestations of *GLI2*-related disease.

The maternal family history was also notable for postaxial polydactyly in multiple relatives. Two maternal uncles reportedly had multiple supernumerary nipples in addition to postaxial polydactyly, with up to five additional nipples reported in affected individuals. Because these relatives were not genetically tested, it is not possible to determine whether these findings were related to the familial *GLI2* variant. Their presence is nevertheless noteworthy as a potentially new phenotype finding for *GLI2*-related disease.

This case report was prepared in accordance with the CARE reporting guidelines.

Case presentation

The patient was a 24-year-old woman of Native American ancestry on both the maternal and paternal sides of her family who was referred to the Adult Genetics Clinic at the University of North Carolina at Chapel Hill for evaluation of congenital craniofacial abnormalities, hypopituitarism, growth hormone deficiency, short stature, and hypogonadotropic hypogonadism.

She was born with bilateral cleft lip, complete on the right and incomplete on the left, as well as an anterior cleft palate. She also had two midline tissue masses, one involving the upper lip and another involving the central gingiva. The gingival mass contained eight teeth, all of which required removal before definitive repair of her cleft lip and palate. Her craniofacial and dental abnormalities were subsequently surgically repaired, and included in the referral was the concern for possible central incisor.

At approximately 2 years of age, brain magnetic resonance imaging (MRI) demonstrated protrusion of the cerebellar tonsils through the foramen magnum, consistent with a Chiari I malformation. The same imaging study demonstrated absence of most or all of the pituitary gland. She also had a history of migraines, which had improved from approximately weekly episodes to approximately monthly episodes with medication.

Endocrine testing performed in 2003 supported significant pituitary dysfunction. Available laboratory results included a total T4 of 7.9, thyroid-stimulating hormone of 1.28, cortisol of 7.2 mcg/dL, somatomedin C of less than 6 ng/mL, insulin-like growth factor I of less than 25, and insulin-like growth factor-binding protein 3 of 0.6 mg/dL.

She experienced severe growth delay and was evaluated for short stature in 2005. Growth hormone replacement therapy was initiated and continued for approximately 9 months. Her mother discontinued treatment because of reported tiredness and fatigue associated with therapy. Growth hormone was later restarted at half dose but was again discontinued. At the time of her genetics evaluation, her height was 142.4 cm (< 1st percentile).

Her endocrine abnormalities also affected pubertal development and reproductive function. According to her mother, she did not undergo typical pubertal development and had no axillary or pubic hair and minimal breast development. She had a history of markedly irregular or absent menstrual periods.

A transvaginal pelvic ultrasound performed on February 17, 2022, reportedly documented absence of the uterus and both ovaries. A subsequent pelvic MRI performed in 2023, however, demonstrated a small uterus measuring approximately 4.1 × 1.2 × 1.8 cm. The MRI report stated that neither the right nor left ovary was identified, and no masses were seen.

According to her mother, the patient experienced a menstrual period in 2023. A subsequent ultrasound performed by an outside obstetrician-gynecologist reportedly demonstrated very small ovaries, although those records were not available for review. At the time of her genetics evaluation, she had not experienced a menstrual period for approximately 6 months. Taken together with her known pituitary dysfunction, her abnormal pubertal development and menstrual irregularity were consistent with hypogonadotropic hypogonadism.

Chromosomal microarray analysis performed the year prior identified a single interstitial 11.6-Mb stretch of homozygosity on chromosome 1. This finding was considered clinically insignificant and did not include genes known to explain her phenotype. Although the finding raised consideration of a recessive disorder or other mechanisms, it did not provide a unifying diagnosis.

A detailed multigenerational family history was obtained with assistance from the patient's mother. Two maternal uncles and four maternal great-uncles reportedly had postaxial polydactyly. The two maternal uncles also reportedly had multiple supernumerary nipples, with up to five additional nipples reported in affected individuals. None of these relatives underwent genetic testing.

Her physical exam revealed a very pleasant 24-year-old female of significant short stature (< 1st percentile). She was generally normocephalic although her eyes did appear mildly hypoteloric and scarring from repaired cleft lip and palate were apparent. The remainder of her physical exam was generally unremarkable including a non-focal neurologic exam.

The combination of midline congenital anomalies suggestive of holoprosencephaly including craniofacial abnormalities (including concern for possible central incisor), severe pituitary dysfunction, growth hormone deficiency, hypogonadotropic hypogonadism, and a family history of postaxial polydactyly raised suspicion specifically for a *GLI2*-related disorder. Molecular testing with a Holoprosencephaly Panel, which included the *GLI2* gene, was performed.

Results of this testing identified a heterozygous truncating pathogenic variant in *GLI2*, NM_005270.4:c.1421G > A (p.Trp474*). This finding was consistent with *GLI2*-related Culler-Jones syndrome and provided a unifying explanation for many of her clinical findings, including her craniofacial abnormalities, pituitary dysfunction, growth hormone deficiency, short stature, and hypogonadotropic hypogonadism.

Targeted familial testing was subsequently performed. The patient's mother, sister, and maternal grandmother were each found to carry the same pathogenic variant. Her brother tested negative for the familial variant. Despite carrying the variant, the mother, sister, and maternal grandmother were reportedly without significant craniofacial, endocrine, growth, or reproductive abnormalities. The three-generation pedigree demonstrating segregation of the familial *GLI2* variant and variable clinical expression is shown in Fig. 1. A timeline of the proband's major clinical and diagnostic events is summarized in Table 1.

Table 1
Timeline of major clinical and diagnostic events

Age/year	Clinical event
Birth/infancy	Bilateral cleft lip and anterior cleft palate identified; midline upper lip and gingival tissue masses noted
Early childhood	Surgical management of craniofacial abnormalities and removal of eight teeth associated with the gingival mass
Approximately age 2 years	Brain MRI demonstrated Chiari I malformation and absence of most or all of the pituitary gland
2003	Endocrine evaluation supported significant hypopituitarism and growth hormone deficiency
2005	Evaluated for severe short stature; growth hormone replacement initiated and subsequently discontinued
February 2022	Pelvic ultrasound reportedly demonstrated absence of the uterus and both ovaries
2023	Pelvic MRI demonstrated a small uterus; neither ovary was identified
2023	Menstrual period reportedly occurred; outside ultrasound reportedly demonstrated very small ovaries, although records were unavailable
Age 24 years	Evaluated in the UNC Chapel Hill Adult Genetics Clinic
Following genetics evaluation	<i>GLI2</i> NM_005270.4:c.1421G > A (p.Trp474*) identified
Subsequent familial testing	Mother, sister, and maternal grandmother tested positive; brother tested negative

Discussion

This case demonstrates the striking clinical variability that can occur within families carrying pathogenic *GLI2* variants. The proband had a severe phenotype involving craniofacial development, pituitary function, growth, and pubertal development. In contrast, her mother, sister, and maternal grandmother carried the same pathogenic variant but were reportedly without significant manifestations of *GLI2*-related disease.

Culler-Jones syndrome was originally described in individuals with hypopituitarism and postaxial polydactyly [1]. Since then, the recognized phenotype has broadened substantially. Pathogenic *GLI2* variants have been associated with growth hormone deficiency, short stature, hypogonadotropic hypogonadism, craniofacial anomalies, and structural abnormalities of the pituitary and other midline structures [2, 4–6].

Pituitary dysfunction was one of the most prominent aspects of the proband's presentation. MRI performed during early childhood showed absence of most or all of the pituitary gland, and subsequent

endocrine testing supported significant hypopituitarism. She had severe growth delay and growth hormone deficiency, followed by abnormal pubertal development and menstrual irregularity consistent with hypogonadotropic hypogonadism.

The patient's reproductive phenotype was complicated by conflicting imaging findings. A 2022 ultrasound reportedly showed absence of the uterus and both ovaries, whereas MRI in 2023 identified a small uterus but did not identify either ovary. The patient's mother later reported that the patient experienced a menstrual period, and an outside ultrasound reportedly showed very small ovaries, although those records were unavailable for review. The precise reproductive anatomy therefore remains uncertain. Nevertheless, her history of abnormal pubertal development and menstrual irregularity in the setting of significant pituitary dysfunction supports hypogonadotropic hypogonadism.

Previous reports have demonstrated that heterozygous nonsense and other truncating *GLI2* variants can be associated with congenital hypopituitarism and structural pituitary abnormalities without holoprosencephaly [4, 5]. More recent cohort data similarly support an association between pathogenic *GLI2* variants, hypopituitarism, and pituitary morphological abnormalities [6].

The proband also had significant craniofacial abnormalities, including bilateral cleft lip, anterior cleft palate, and two midline tissue masses involving the upper lip and central gingiva. The combination of these findings with severe pituitary abnormalities was consistent with a developmental disorder affecting midline structures. Orofacial clefting has also been documented within the broader phenotypic spectrum associated with pathogenic *GLI2* variants [5].

Her Chiari I malformation was another notable finding. It is unclear whether this was directly related to the familial *GLI2* variant or represented an unrelated developmental abnormality. Its relationship to Culler-Jones syndrome should therefore be interpreted cautiously.

The family history of postaxial polydactyly was an important clue to the diagnosis. Two maternal uncles and four maternal great-uncles reportedly had postaxial polydactyly. This feature is well recognized in *GLI2*-related disease and was part of the original description of Culler-Jones syndrome [1]. Larger genotype–phenotype studies have also identified postaxial polydactyly within the spectrum of pathogenic *GLI2* variants [5].

However, because these relatives did not undergo genetic testing, their reported findings cannot be definitively attributed to the familial *GLI2* variant. This limitation is important when interpreting the apparent segregation of clinical features within the family.

An additional finding of interest was the presence of multiple supernumerary nipples in two maternal uncles who also reportedly had postaxial polydactyly. According to the family history, affected individuals had up to five additional nipples.

Supernumerary nipples, also known as polythelia, are congenital developmental anomalies. Familial occurrence has been documented, including pedigrees demonstrating polythelia across multiple

generations [7–9].

Based on the literature reviewed for this report, supernumerary nipples have not been established as part of the recognized phenotypic spectrum of Culler-Jones syndrome or *GLI2*-related disease. The significance of this finding in the present family therefore remains uncertain.

Because the two maternal uncles with postaxial polydactyly and multiple supernumerary nipples did not undergo genetic testing, it is not possible to determine whether either finding segregated with the familial *GLI2* variant. Familial polythelia can occur independently of other syndromic findings, and the supernumerary nipples in this family may represent a separate familial developmental trait [8, 9].

Nevertheless, the presence of multiple supernumerary nipples, including up to five additional nipples, in relatives who also reportedly had postaxial polydactyly is noteworthy. At present, this observation should not be interpreted as establishing an expanded *GLI2*-related phenotype. Genetic testing and detailed phenotypic evaluation of these relatives would be necessary to determine whether these findings segregate with the familial pathogenic variant.

The most striking aspect of this family is the difference in clinical presentation among confirmed carriers of the same pathogenic variant. The proband had a severe and clinically apparent phenotype, whereas her mother, sister, and maternal grandmother were reportedly without significant manifestations. This observation is consistent with previous reports describing substantial variable expressivity among individuals with *GLI2* alterations [3, 5].

Reduced penetrance is also possible in *GLI2*-related disease, but it cannot be definitively established in this family. Although the mother, sister, and maternal grandmother were reportedly asymptomatic, the available information does not indicate that all three underwent comprehensive endocrine testing, brain imaging, or detailed phenotypic evaluation. Mild or subclinical manifestations may therefore have gone undetected. This family most clearly demonstrates **marked variable expressivity**.

This variability has important implications for genetic counseling. An apparently unaffected individual carrying a pathogenic *GLI2* variant may transmit that variant to a child with a substantially more severe phenotype. Clinical findings in one family member cannot reliably predict the severity of disease in another. Cascade testing and appropriate clinical evaluation of at-risk relatives are therefore important, even when those relatives do not report obvious symptoms.

The case also illustrates the value of a detailed multigenerational family history. The history of postaxial polydactyly among multiple maternal relatives provided an important diagnostic clue when considered alongside the proband's congenital craniofacial abnormalities and severe hypopituitarism. Identification of the pathogenic *GLI2* variant subsequently allowed targeted testing of relatives and demonstrated transmission across three generations.

Limitations

This report has several limitations. Detailed medical records and comprehensive clinical evaluations were not available for all family members. The maternal relatives with postaxial polydactyly and multiple supernumerary nipples did not undergo genetic testing; therefore, these findings cannot be definitively linked to the familial *GLI2* variant. In addition, the reproductive phenotype of the proband was difficult to characterize because of conflicting imaging findings and the unavailability of outside medical records. Finally, the reportedly asymptomatic carriers did not all undergo comprehensive endocrine evaluation or neuroimaging, and subtle manifestations of *GLI2*-related disease may therefore have been unrecognized.

Conclusions

This report describes a family with *GLI2* NM_005270.4:c.1421G > A (p.Trp474*) transmitted across three generations and associated with marked variable expressivity.

The proband had severe congenital craniofacial abnormalities, profound pituitary dysfunction, growth hormone deficiency, short stature, and hypogonadotropic hypogonadism. In contrast, her mother, sister, and maternal grandmother carried the same pathogenic variant but were reportedly without significant manifestations of *GLI2*-related disease.

The family history of postaxial polydactyly provided an important diagnostic clue. Multiple supernumerary nipples, including up to five additional nipples, were also reported in two maternal uncles with postaxial polydactyly. Because these relatives were not genetically tested, the relationship of these findings to the familial *GLI2* variant remains uncertain and, although compelling, cannot definitively be described as an expanded phenotype for *GLI2*-related disease at this time.

This family adds to the evidence that pathogenic *GLI2* variants can produce markedly different clinical presentations within the same family and identifies an additional familial phenotypic observation warranting further investigation. Recognition of this variability is important for diagnosis, family evaluation, and genetic counseling.

Abbreviations

GH

Growth hormone

IGF-I

Insulin-like growth factor I

IGF-BP3

Insulin-like growth factor-binding protein 3

MRI

Magnetic resonance imaging

Declarations

Availability of data and materials

Data sharing is not applicable to this article because no datasets were generated or analyzed during the current study.

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Authors' contributions

AM and RO evaluated the patient, coordinated and interpreted familial genetic testing, collected and interpreted the clinical and genetic information, and contributed to the development and writing of the case report. **FA** contributed to the writing and preparation of the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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Figures

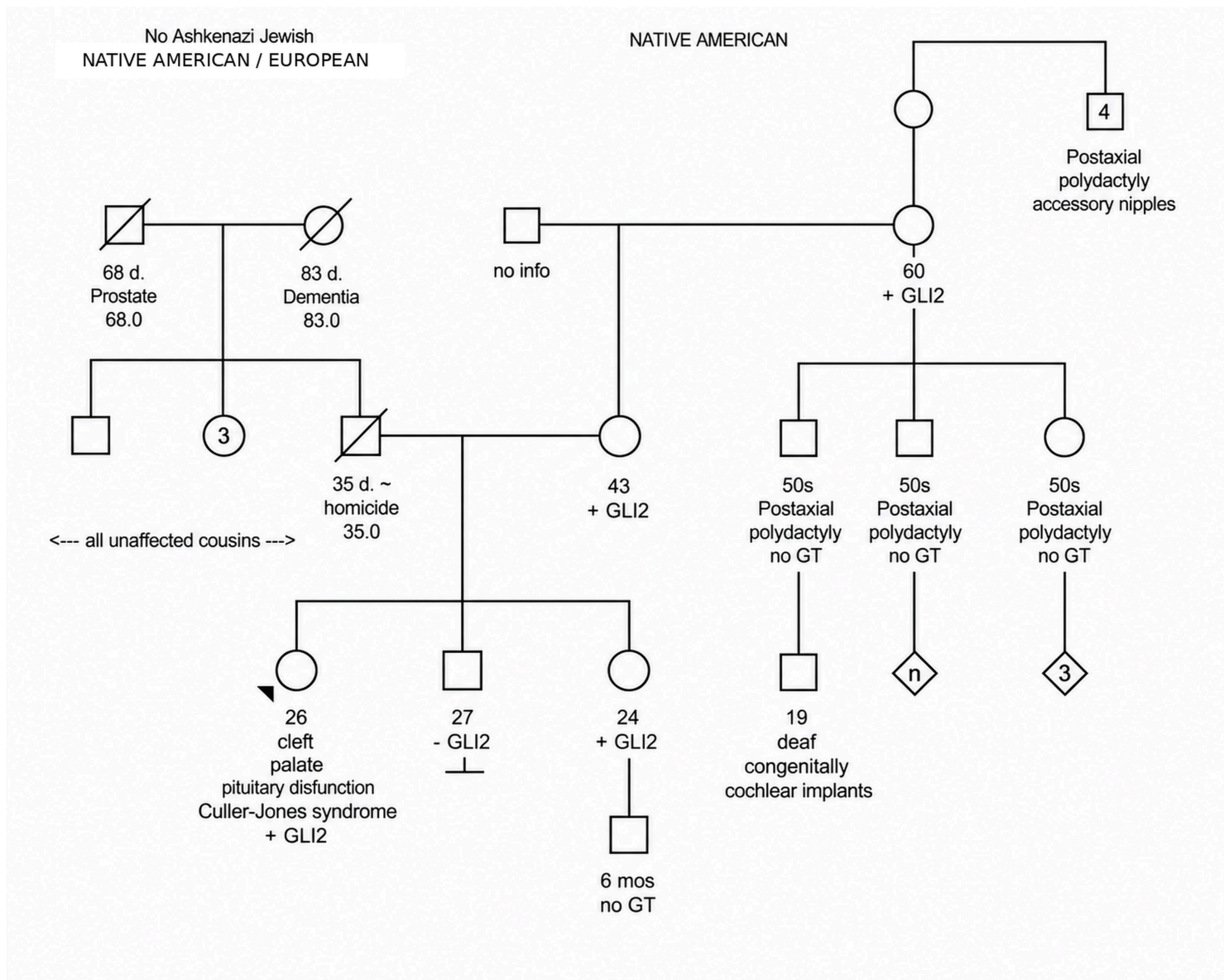


Figure 1

Three-generation pedigree demonstrating familial segregation of the pathogenic *GLI2* variant and marked variable clinical expression

The pedigree demonstrates transmission of *GLI2* NM_005270.4:c.1421G>A (p.Trp474*) across three generations. The proband had a severe multisystem phenotype including bilateral cleft lip and palate, midline craniofacial abnormalities, severe pituitary dysfunction, growth hormone deficiency, short stature, and hypogonadotropic hypogonadism. Targeted familial testing identified the variant in her mother, sister, and maternal grandmother. Her brother tested negative for the familial variant. Multiple maternal relatives reportedly had postaxial polydactyly. Two maternal uncles reportedly had both postaxial polydactyly and multiple supernumerary nipples, with up to five additional nipples reported in affected individuals. These relatives did not undergo genetic testing, and their reported findings therefore cannot be definitively attributed to the familial *GLI2* variant.