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CASE REPORT

No, it is not mutually exclusive! A case report of a girl with two genetic diagnoses: Craniofrontonasal dysplasia and pontocerebellar hypoplasia type 1B

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Key Clinical Message

Multiple genetic disorders can coexist in one patient. When the phenotype is not fully explained with one diagnosis, it is recommended to perform further genetic investigations in search for coexisting second diagnosis.

Abstract

Craniofrontonasal dysplasia (CFND) (MIM: 304110) is an X-linked dominant disorder that shows paradoxically greater severity in heterozygous females than in hemizygous males. It is caused by a pathogenic variant in *EFNB1*. Pontocerebellar hypoplasia type 1B (PCH1B) (MIM: 614678) is an extremely rare condition with over 100 individuals reported to date. It is caused by biallelic pathogenic variants in *EXOSC3*. This report presents the case of a girl who was diagnosed prenatally with CFND based on the findings on the prenatal imaging and the known diagnosis of CFND in her mother. She has severe global development delay that cannot be explained solely by the CFND diagnosis. Around the age of 2 years, she was diagnosed with PCH1B following whole exome sequencing (WES) testing. The objective of this study is to highlight the importance of pursuing genetic investigation if the available genetic diagnosis cannot fully explain the clinical picture. This is a case report of one patient and review of the literature. Informed consent was obtained from the parents. WES was performed by a private lab using next-generation sequencing (NGS), DNA was sequenced on the NovaSeq 6000 using 2 × 150 bp paired-end read. WES identified the following: homozygous pathogenic variant in *EXOSC3*: C.395A>C, p.ASp132Ala, maternally inherited, likely pathogenic duplication at Xq13.1 (includes *EFNB1*) and paternally inherited 16p11.2 duplication that is classified as a variant of uncertain significance. Perusing more extensive genetic testing like: WES is indicated if the current genetic diagnosis cannot fully explain the phenotype in a patient.

KEYWORDS

CFND, PCH1B, rare genetic disease, single gene mutation, X-linked inheritance

1 | INTRODUCTION

Craniofrontonasal dysplasia (CFND) (MIM: 304110) is an X-linked dominant disorder that shows paradoxically greater severity in heterozygous females compared to hemizygous males.[1,2]

Although X-linked disorders typically affect males only or are present in a more severe form in males than females, CFND exclusively affects females. CFNS is identified as a subgroup of frontonasal dysplasia.[3] Affected females typically exhibit hypertelorism, coronal craniosynostosis, downslanting palpebral fissures, clefting of the nasal tip, craniofacial asymmetry, frontal bossing, longitudinally grooved fingernails, wiry hair, and abnormalities of the thoracic skeleton, and other digital anomalies. Affected males, on the other hand, show only hypertelorism.[1,2,4]

Craniofrontonasal dysplasia is diagnosed through clinical evaluation following observing characteristic physical findings. To confirm diagnosis, molecular genetic testing for pathogenic and likely pathogenic variants in the *EFNB1* gene is available. CFND can also be detected prenatally by ultrasound.[5]

The second disorder we are discussing is pontocerebellar hypoplasia type 1B (PCH1B) (MIM: 614678). It is a rare condition caused by biallelic pathogenic variants in *EXOSC3*. The term pontocerebellar hypoplasias (PCH) describes a group of rare heterogeneous conditions, in which an abnormally small cerebellum and brain stem develop in the prenatal period. This is commonly associated with profound psychomotor delay.[6-8]

The clinical picture varies widely; however, commonly there is a profound intellectual disability and delayed or absent psychomotor milestones. PCH has a poor prognosis and is usually fatal early in life. At least six types of pontocerebellar hypoplasia type 1 is characterized by central and peripheral motor dysfunction from birth.[9,10]

Pontocerebellar hypoplasia can present prenatally with reduced fetal movement due to polyhydramnios. The newborn appears floppy and usually exhibits respiratory insufficiency. Multiple congenital contractures of large joints (arthrogryposis multiplex congenita) may be observed at birth. The hallmark of PCH type 1 is severe muscle weakness and hypotonia. Intellectual disability, as well as cerebellar symptoms such as nystagmus and ataxia, are observed later.[11]

Pontocerebellar hypoplasia is inherited in an autosomal recessive pattern. Males and females are equally affected, with more than 100 PCH type 1B cases have been reported. Cerebellar, brainstem, and spinal motor neuron degeneration start at birth. Microcephaly, muscle weakness, seizures, and progressive global developmental delay are also present. Symptoms vary according to type. Case-to-case variability is also present. Feeding difficulties and aspirations are common early in life.[6–8] Herein, we present a case of a female patient who was originally diagnosed with a genetic disorder (CFND) (MIM: 304110). However, because this diagnosis did not fully explain the phenotype, further investigations were pursued and revealed the presence of a second genetic disorder pontocerebellar hypoplasia type 1B (PCH1B) (MIM: 614678).

2 | CASE PRESENTATION

2.1 | The proband

The proband was diagnosed prenatally by CFND based on the prenatal ultrasound, brain MRI and the positive family history of CFND in the mother. The brain MRI at the age of 30 weeks gestational age confirmed absent cavum septi pellucidi, widely parallel lateral ventricles and absent corpus callosum and hypertelorism.

The proband was born term at 39 weeks and 4 days by emergency cesarean section due to intrapartum breech presentation. The birth weight was 3.17 kg (50th %ile), the birth length was 51 cm (just above 50th %ile) and the head circumference was 33 cm (50th %ile). The Apgar's score was 9 and 9 at 1 and 5 min, respectively. She had breathing difficulty shortly after birth that requires resuscitation, respiratory support, and neonatal intensive care admission (NICU). The Skull X-ray was done and revealed craniosynostosis predominantly of the sagittal sutures (Figures 1 and 2). MRI was performed and revealed corpus callosal agenesis and cerebellar hypoplasia and loss of the cortical gray-white differentiation (Figures 3 and 4). The paired midline intercostal structures remained central.

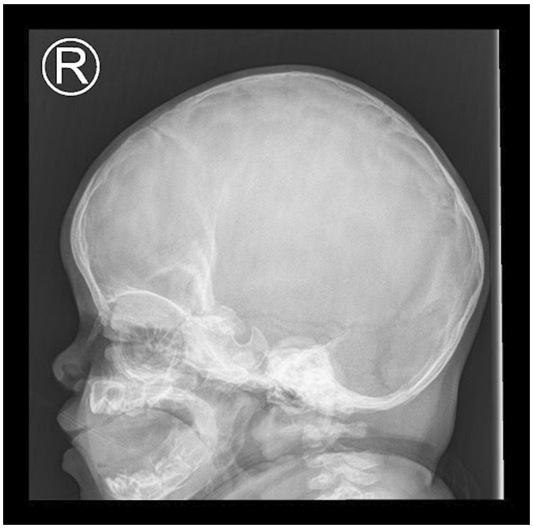

FIGURE 1 Skull X-ray was done and revealed craniosynostosis predominantly of the sagittal sutures.

Our patient had feeding difficulties, failure to thrive and aspiration and episodes of apneas and desaturations. She required NJ tube feeding and eventually G-tube requiring multiple hospital admissions. During one of the admissions around the age of 2 years for aspiration pneumonia and desaturations, medical genetics was consulted again for severe global developmental delay. At the age of 2 years, she was not able to walk without help, had severely delayed fine motor skills and cannot say proper words.

The physical exam at the time of genetics evaluation showed weight of 7.4 kg which corresponds to a *z*-score of −3.7, head circumference of 42 cm which corresponds to a *z*-score of −3.7. The dysmorphology exam showed the typical features of CFND of ocular hypertelorism, broad nasal tip and bifid nose, and upturned ear lobes. The right hand has fourth and fifth clinodactyly, the left hand shows scar from previously operated polysyndactyly. She has significant hypotonia both centrally and peripherally (Figures 5 and 6).

She has significant skeletal involvement including craniosynostosis, polysyndactyly, left hip dislocation, and scoliosis. She underwent multiple surgical interventions including, coronal suturectomy for the craniosynostosis, polydactyly, and syndactyly repair. Whole based on the complex clinical presentation and the severe developmental delay, whole exome sequencing (WES) was requested.

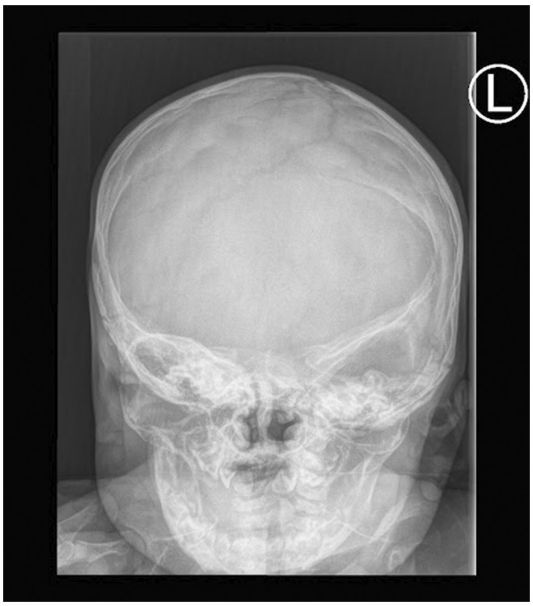

FIGURE 2 Skull X-ray was done and revealed craniosynostosis predominantly of the sagittal sutures.

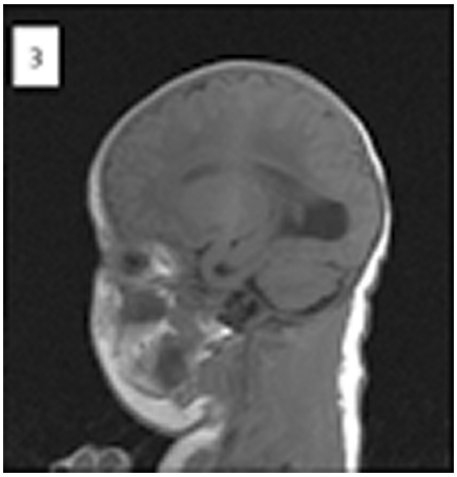

FIGURE 3 Brain MRI images: Brain MRI without contrast, sagittal TI/performed at the first week of life. This figure and Figure 4 show corpus callosal agenesis, and cerebellar hypoplasia.

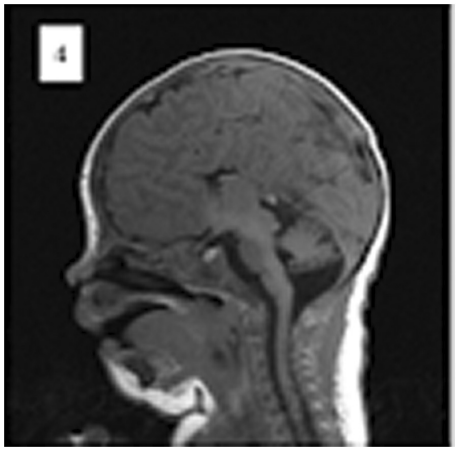

FIGURE 4 Brain MRI images: Brain MRI without contrast, sagittal TI/performed at the first week of life. Figure 3 and this figure show corpus callosal agenesis, and cerebellar hypoplasia.

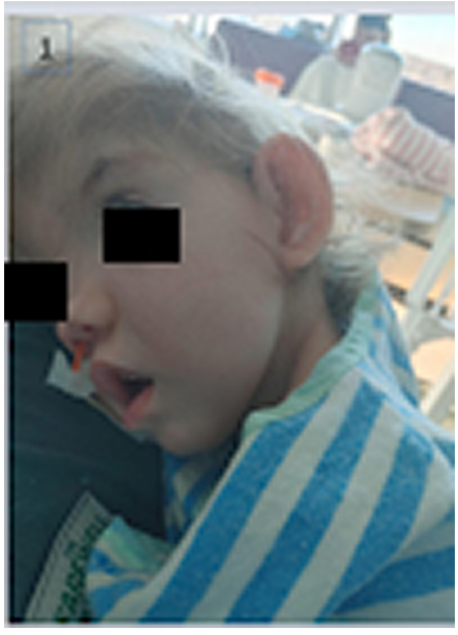

FIGURE 5 Clinical features of our CFND patient.

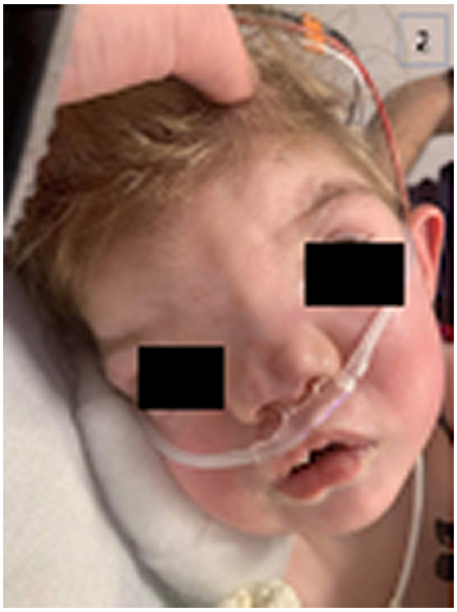

FIGURE 6 Clinical features of our CFND patient.

She passed away at the age of 30 months from respiratory complications.

Regarding the family history, proband's mother is of Polish/Ukrainian descent on her maternal side and Irish/Scottish/English descent on her paternal side. The proband's father is of German descent on his paternal side and German/English descent on his maternal side. The proband's mother has a confirmed diagnosis of CFND, which was inherited from her father.

The proband was followed by a multidisciplinary team of a developmental pediatrician, physiotherapist, occupational therapist, and dietician. In addition, she was seen by orthopedic surgeons for the evaluation and management of scoliosis and hip dislocation. She had multiple hospital admissions to both the pediatric wards and the pediatric intensive care unit (PICU).

Regarding surgical management, she underwent coronal suturectomy and left unicoronal synostosis at the age of 5 months. She underwent surgical correction of the complex polysyndactyly at about 1.5 years of age.

The proband was started on NGT feeds at the age of 22 months and had a laparoscopic insertion of a gastrostomy tube at age of 2 years.

2.2 | The proband's mother

The proband's mother was brought to medical attention since birth. The distinctive facial features were described as "resembling Crouzon syndrome". At the age of 3 months she had a clinical diagnosis of CFND based on the clinical finding of craniosynostosis predominantly of the sagittal suture, hypertelorism, absent corpus callosum, and mild hydrocephalus. She underwent the first surgery of craniorbital reshaping around the age of 6 months. She has subsequent surgeries around the age of 6 and 15 years. She was thriving and developing well. She works as an early childhood educator. She presented again to medical genetics around the age of 28 years for preconception counseling. By the time genetic testing was offered to her she was already pregnant. She has a chromosomal microarray and craniosynostosis panel.

3 | RESULTS

3.1 | Array comparative genomic hybridization—microarray analysis

The microarray identified a duplication of approximately 883 kb mapping to the region Xql3.l. in the proband and her mother and the proband. The duplication was first classified as "uncertain significance". And this was reclassified to likely pathogenic given as it segregates in both clinically affected family members. The Genome build was NCBI Build 37/UCSC Human genome—Feb. 2009 (GRCh37/hg19) Assembly.

3.2 | Whole exome sequencing

Captured DNA is sequenced on the NovaSeq 6000 using 2×150 bp paired-end reads (Illumina). It identified the following results:

Homozygous pathogenic variant in the EXOSC3 (NM_016042.3); c.395A>C, which is predicted to result in the amino acid substitution p.Asp132AIa. This variant has been reported as causative for pontocerebellar hypoplasia in both the homozygous and compound heterozygous states. Copy number variation (CNV) detection by next-generation sequencing (NGS) analysis also identified the maternally inherited Xq13.1 duplication, which has been previously reported in this patient by the chromosomal microarray. The private lab classified this variant as a variant of uncertain significance based on the available literature of a similar duplication involving EFNB1 was reported to be associated with familial hypertelorism,[12] and another duplication involving EFNB1 was observed in 9 of 2026 healthy individuals.[13] However, we know that this duplication is likely pathogenic. The WES also identified 206.3 kb duplication at band 16p11.2. and was classified as variant of uncertain significance. This duplication interval contains many genes, including *ATXN2L, TUFM,*

SH2B1, ATP2A1, RABEP2, CD19, NFATC2IP, SPNS1, LAT, MIR4721, ATP2A1-AS1, and *MIR4517*. Interestingly, this variant was not identified before by the chromosomal microarray.

3.3 | Quantitative polymerase chain reaction test

Quantitative polymerase chain reaction (qPCR) was performed to confirm the duplications of 16p11.2. The DNA copy number was examined by qPCR with primers targeted to the *SH2B1* gene (cytoband 16p11.2, genomic coordinates chr16 28883586_28883660 [GRCh37]). qPCR analysis showed three copies of the locus examined which is consistent with a microduplication of this chromosomal region. rsa [GRCh37]16p11.2 (28883586_28883660) X3. Parental qPCR studies using the same primers showed that is paternally inherited.

4 | DISCUSSION

Craniofrontonasal dysplasia is a unique condition in terms of inheritance. It is an X Linked condition that almost exclusively affects women. This is the opposite of most X-linked disorders; typically X-linked disorders affect men only or are more severe in men than women. One of the theories that explain this is a concept known as "cellular interference". *EFNB1* gene is thought to be a redundant gene, men have been found that have zero copies of *EFNB1*; they have no clinical symptoms or health concerns. This indicates that this gene is "unnecessary" or "extraneous". There have however been a small number of men who are a "mosaic" for a mutation in *EFNB1*. This refers to a mutation that occurs following embryo development; this means that a portion of their body tissues will have the mutation, while other tissues will not. One recent publication was able to demonstrate that men's mosaic for an *EFNB1* mutation presents more similarly to affected women. It is thought that clinical symptoms of CFND are due to having more than one gene expression level in different body tissues. Mosaic men and affected women can both be explained by having two different copies of the EFNB1 gene. Women have two X chromosomes and hence will have two copies of *EFNB1* with a mutation in one copy and a "normal" EFNB1. The differing tissue expression levels for women occur as one of their X chromosomes is inactivated in each cell.[12]

Although our proband had received an established diagnosis of CFND, she presented with a severe global developmental delay that could not be fully explained by CFND. Posey et al.,[13] reported that if a patient already has one rare genetic disease, there is a 5% chance that they have a second one, and in a recent report,[14] the proportion of finding multiple disorders in one patient was found to be approximately 2%–7.5% of diagnosed cases. Hence, further clinical and genetic investigations were sought and revealed the presence of another genetic disorder, PCH type 1B. The new diagnosis explained the complicated phenotype of the proband such as multiple feeding and respiratory complications, hospitalization, and procedures. Those complications eventually ended with the proband's death at the age of 2 years and 6 months.

Donkervoort et al.[15] similarly identified three cases where two genetically confirmed conditions were identified. They referred to these patients using the term "double trouble" patient population. We agree with Donkervoort et al.; clinicians should be aware that the possibility of having two unrelated genetic conditions is not low. The presence of a clinical sign or symptom that is not fully explained by an already established genetic diagnosis warrants further investigation.

Rosina et al.,[14] reported eight cases, each with two different genetic diagnosis; similarly, Cianci et al.[16] and Pezzani et al.[17] Cianci et al.[16] reported two cases of dual diagnosis of neurofibromatosis, type 1 OMIM #162200 and KBG syndrome OMIM #148050, one was 2 years and 6 months old, the other was 4 years and 7 months old. Pezzani et al.[17] reported a 4 months old with dual diagnosis of mosaic variegated aneuploidy syndrome 2 OMIM #614114, as well as short-rib thoracic dysplasia 3 with or without polydactyly OMIM #613091.

The findings of Posey et al.[13] as well as Rosina et al.[14] alert clinical geneticists that identifying a single genetic diagnosis does not mean that their diagnostic investigation is complete.

In this specific patient population, where two or more genetic disorders are diagnosed, symptoms and signs of the diseases are usually blended, where each sign or symptom can either represent one disease or could be attributed to two or more diseases. When the feature is a result of an overlap between two genetic disorders, the phenotype could be expected to be more severe.[18] In our case, it was the degree of developmental delay and intellectual disability that cannot be explained solely by CFND.

Whole exome sequencing can be useful in cases where a second genetic diagnosis is considered. Stavropoulos et al.[19] found that WES provided a potential molecular diagnosis for 25% of patients referred for evaluation of suspected genetic conditions.

5 | CONCLUSION

It is not uncommon for patients with one established diagnosis of a genetic disorder to be diagnosed with a second genetic disorder. Studies reported 2%–7.5% chance of diagnosing a second genetic disorder. pursuing more extensive genetic testing like WES is indicated if the current gene diagnosis cannot fully explain the phenotype or the severity of the disorder in a patient.

AUTHOR CONTRIBUTIONS

Iman Ibrahim: Data curation; formal analysis; resources; writing – original draft; writing – review and editing. **Tara Scriver:** Data curation; investigation. **Shuaa A. Basalom:** Conceptualization; funding acquisition; methodology; project administration; supervision; writing – review and editing.

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No funding was received for this case report.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Consent was obtained in compliance with the University of Saskatchewan ethics department. No special ethics approval is required for single case report.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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