The Application of Clinical Genetics

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CASE REPORT

A Novel EBP c.452A>G Mutation Identified in a Girl with Conradi–Hünermann–Happle Syndrome Presenting with Hydronephrosis

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Background: Conradi–Hünermann–Happle syndrome (CDPX2, OMIM 302960) is an X-linked dominant inherited disorder caused by variants in the *EBP* gene, which primarily affects the skin, bones, and eyes.

Objective: To describe the clinical manifestations and genetic mutation in a 7-year-old girl presenting with severe scoliosis, hydronephrosis, and other skeletal abnormalities.

Methods: The patient's medical history was collected from birth. Exome sequencing was performed to identify candidate genes, and the detected variant was confirmed by Sanger sequencing.

Results: Exome sequencing revealed a de novo *EBP* mutation (c.452A>G, p.Gln151Arg) in the patient.

Conclusion: The patient was diagnosed with X-linked chondrodysplasia punctata type 2 (CDPX2). This novel missense mutation expands the mutation spectrum of CDPX2 and underscores the clinical utility of exome sequencing in diagnosing this condition.

Keywords: EBP, c.452A>G, p.Gln151Arg, exome sequencing, CDPX2

Introduction

Chondrodysplasia punctata (CDP) is a clinically and genetically heterogeneous disorder characterized by punctiform calcification of the bones with a prevalence of 1–9/1000 000. X-linked dominant CDP (CDPX2, MIM 302960), also referred to as Conradi–Hünermann–Happle(CHH) syndrome,[1] is the most well-characterized form of CDP. CDPX2 arises almost exclusively in females and has been presumed lethal in males, although a few affected males have been reported. There are several characteristics with this syndrome. Firstly, CDPX2 is typically skeletal dysplasia characterized by asymmetrical bone defects including punctiform calcification of the long bones, radiographic epiphyseal stippling, shorten of limbs, scoliosis, short stature, craniofacial abnormalities. Secondly, it manifests with transient severe congenital ichthyosis following linear hypopigmented patches with follicular atrophoderma as well as patches of scarring alopecia. Thirdly, it may show ocular changes including cataracts, microphthalmia or microcornea.[2–4]

CDPX2 is caused by mutations in the emopamil-binding protein (*EBP*) gene, which encodes an integral membrane protein primarily located in the endoplasmic reticulum. This protein functions as a key enzyme in the final steps of the sterol biosynthesis pathway.[5] Recently, next-generation sequencing applied in family-based and case–control studies has extensively identified specific genes contributing to the risk of complicated hereditary diseases, including dysosteogenesis disorders caused by *EBP* gene variations.

Herein, we report a 7-year-old girl with short stature, craniofacial defects, extremely severe scoliosis, digital abnormality, malformations with centrums, sectorial cataract in the right eye, ichthyosis and alopecia, and hydronephrosis. Whole exome sequencing (WES) revealed a missense mutation (c.452G>A) in the *EBP* gene, leading to

Received: 16 January 2025
Accepted: 28 April 2025
Published: 14 May 2025

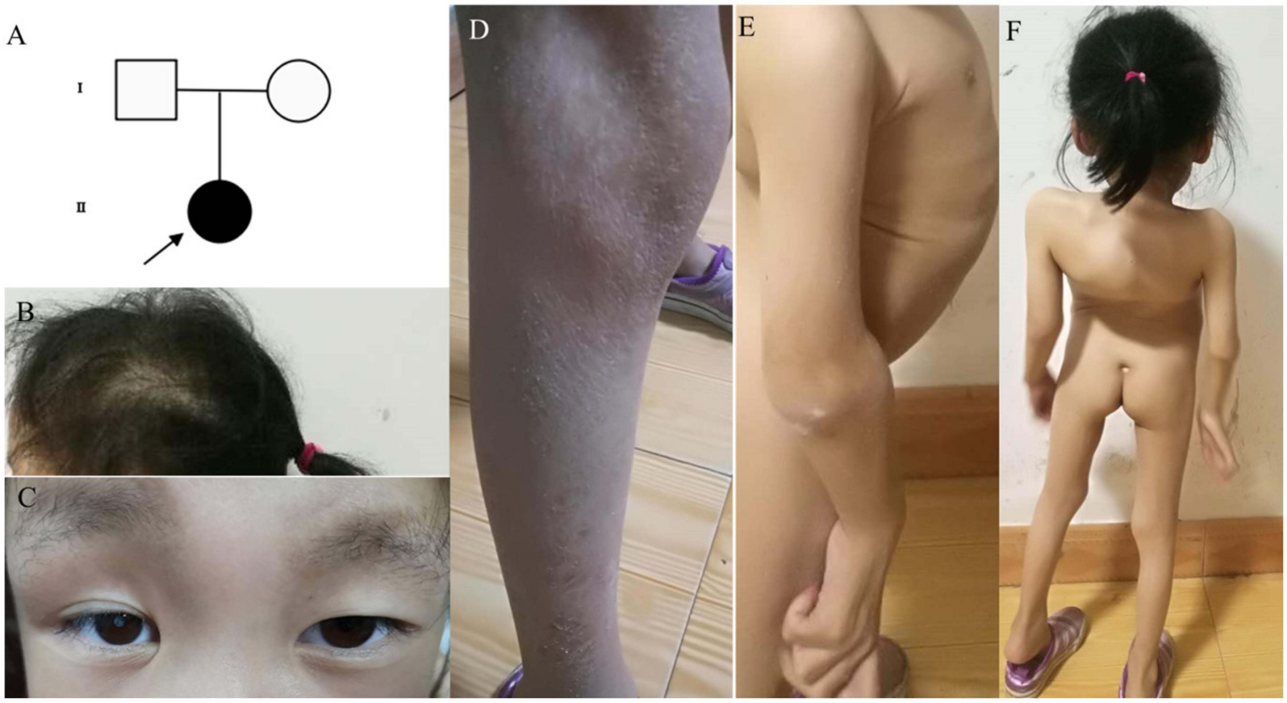

Figure 1 Clinical features of the 7-year-old proband. (**A**) Family diagram. (**B**) Cicatricial alopecia. (**C**) Sectorial cataract of right eye, sparse eyebrows. (**D**) Ichthyosis of the leg. (**E**) Camptodactylia of right hand. (**F**) Scoliosis and asymmetric shortening of limbs.

a genetic diagnosis of CDPX2. Hydronephrosis is not a common feature of CDPX2, and this case represents the first report of the characteristic in China, thereby expanding the phenotype spectrum of the syndrome. Additionally, we reviewed 43 publications, including cases from several *EBP* reviews, and identified 97 *EBP* mutations in patients with skin abnormalities, bone defects or cataracts.[1,6–46]

Clinical Description

The 7-year-old girl was born via cesarean delivery at 38 weeks of gestation, measuring 45 centimeters in length (−2.7 SD) with short legs, and weighed 3.85 kilograms. Her mother and father are of normal height, 169 cm and 173cm, respectively. Both parents are healthy except that the mother has a history of irregular menstruation and amenorrhea for ten years without pregnancy, and she conceived the baby through ovulation induction therapy. The father has poor sperm motility and hypoplastic lumbar vertebrae. No abnormalities were found during prenatal testing.

She was first referred to our genetics department for evaluation at the age of 4 years. A detailed medical history was collected from birth. There's no genetic disease history in the family (Figure 1A). Significant developmental delay was observed during her infancy. Ichthyosis persisted from birth to childhood, and hair abnormality included scarring alopecia in patches, sparse eyelashes and coarse, lusterless hair (Figure 1B–D). Cataracts in the right eye, low-set ears and downslanting palpebral fissures were presented in the proband (Figure 1C). She also presented with elbows valgus, flexion of the fingers, and bowleg (Figure 1E and F). Radiographic findings revealed stippling (chondrodysplasia punctata) involving the epiphyses of the long bones and vertebrae (Figure 2A and B). She also had asymmetric shortening of the limbs, primarily affecting the femur and humerus, and severe spinal deformity (Figure 2C and D). Hydronephrosis of the right kidney was onset since her birth (Figure 3A and B).

Materials and Methods

Whole exome sequence analysis To identify the gene mutation responsible for the patient's typical phenotype, genomic DNA was extracted from peripheral blood samples from the family after informed consent was obtained. Whole exome

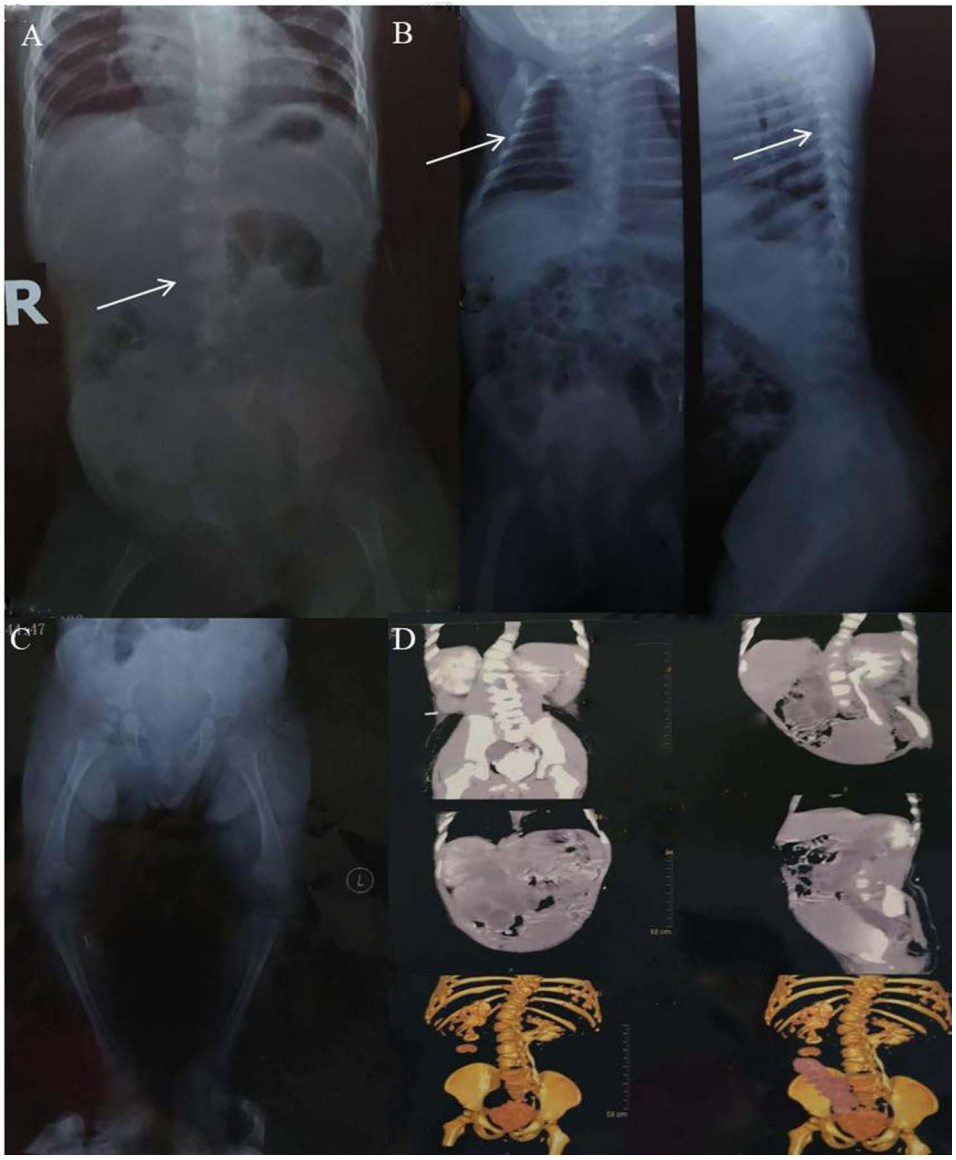

Figure 2 Radiological features of spine and limbs of the girl at 2.5 years old. (**A**) Multiple butterfly like vertebrae and scoliosis. (**B**) Punctate calcific stippling sternum, ribs. (**C**) Scoliosis and deformities of ischium and pubis. (**D**) CT shows neurogenic bladder, and hydronephrosis of right kidney and right ureter.

sequence analysis was performed. DNA libraries were prepared from the proband and her parents and pooled using a standard protocol. Quantitative PCR was performed to test the quality of the enriched nucleotides. An Agilent Bioanalyzer 2100 was used to determine the fragment size distribution and DNA concentration. Exome capture libraries were prepared using the SureSelect Human All Exon V6 kit (Agilent Technologies, USA). All samples were sequenced on the Illumina HiSeq2500 platform.

After the removal of adapter sequences and the elimination of low-quality reads (where the quality score threshold for raw data was set at Q30 < 85%, and for clean data at Q30 < 90%), the remaining high-quality sequencing reads were mapped to the reference genome (GRCh37/hg19) utilizing the Burrows-Wheeler Aligner (v 0.7). PCR duplicates were subsequently removed using samtools (version 0.1.18). Variant identification and annotation were conducted using the Broad Institute's GATK (version 4.0) and Annovar software, respectively. The median sequencing depth achieved was 100×, with 98% of the target regions covered at a depth of at least 10×. Variant calls were required to have a minimum of four supporting reads, accounting for over 20% of the total reads at each position; calls failing to meet this threshold were

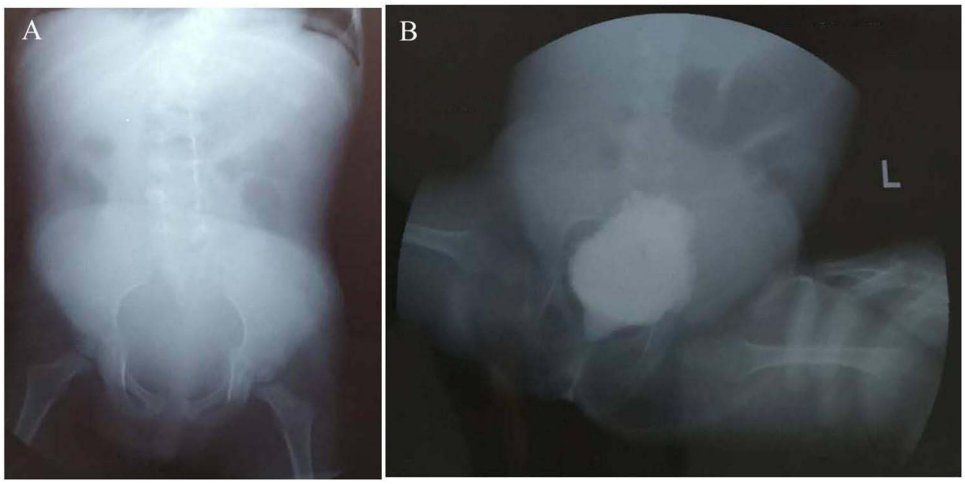

Figure 3 Voiding cystourethrogram of the girl at 2.5 years old. (**A**) Hydronephrosis of right kidney and right ureteral dilatation; bladder wall showed a "room beam-like" change. (**B**) Poor bladder emptying, more contrast agent residue.

excluded. Variants with a minor allele frequency exceeding 0.5% in public databases (including 1000 Genomes, dbSNP, ExAC, and gnomAD) were filtered out. Prioritization of variants was based on their potential to disrupt protein function, as predicted by tools such as SIFT, Polyphen2, Mutation Taster, Provean, Revel and Human Splicing Finder (version 3.0). Additionally, amino acid conservation across species was evaluated using PhyloP and PhastCons. The correlation between genotype and phenotype played a crucial role in identifying candidate variants, which were further inspected using the Integrative Genomics Viewer for visual validation and confirmed through Sanger sequencing.All the selected variants were then classified as pathogenic, likely pathogenic, VOUS, likely benign or benign according to the American College of Medical Genetics and Genomics (ACMG) guidelines.[47]

Sanger sequencing validation Sanger sequencing was used to validate the variant. Exon 4 of the *EBP* gene (NM006579.3): c.452A>G(p.Gln151Arg) was amplified using primers F: 5′-GAGCACTAATGGGCTAACCTGTAG-3′ and R: 5'-AGGGATACATCTGTGTCTGTGGAT-3 with an annealing temperature of 60°C. The amplified product length was 275 bp.

Results

WES identified a mutation, c.452A>G (p.Q151R), in the *EBP* gene, which was confirmed by Sanger sequencing (Figure 4). The mutation was *de novo*, and the phenotype of the patient was consistent with the disease (ACMG variant evidence: PS2). The mutation was not found in ExAC, gnomAD or 1000G database (ACMG variant evidence: PM2_P); Computational prediction tools unanimously supported a deleterious effect on the gene. Glutamine at position 151 is located in endoplasmic reticulum 2 (ER2) lumen and is conserved across species, including Homo sapiens (human), Macaca Mulatta, Fcatus, Mus musculus (mouse), Takifugu rubripes, and Danio rerio (ACMG variant evidence: PP3); A previously reported amino acid change at position 151, a stop-gain mutation (c.451C>T), has been described in the literature.[9,27] Therefore, the variant c.452A>G (p.Q151R) in the *EBP* gene was classified as likely pathogenic (PS2, PM2_P, PP3) according to the ACMG guidelines.

Discussion

All *EBP* mutation reports included in this study encompass 141 cases: 86 female, 25 male, 15 female fetuses, and 15 cases with unknown gender (Table 1). The three main malformations associated with CDPX2 are skeletal changes, skin scaling ichthyosis, and ocular abnormalities. Among these cases, epiphyseal stippling was observed in 41.8% (59/141), skin deformities in 78.7% (111/141), and cataracts in 36.9% (52/141). In some cases, skin lesions may not be noticed unless the female has a child with asymmetrical shortening of long bones or ichthyosis-like skin. Digital abnormalities,

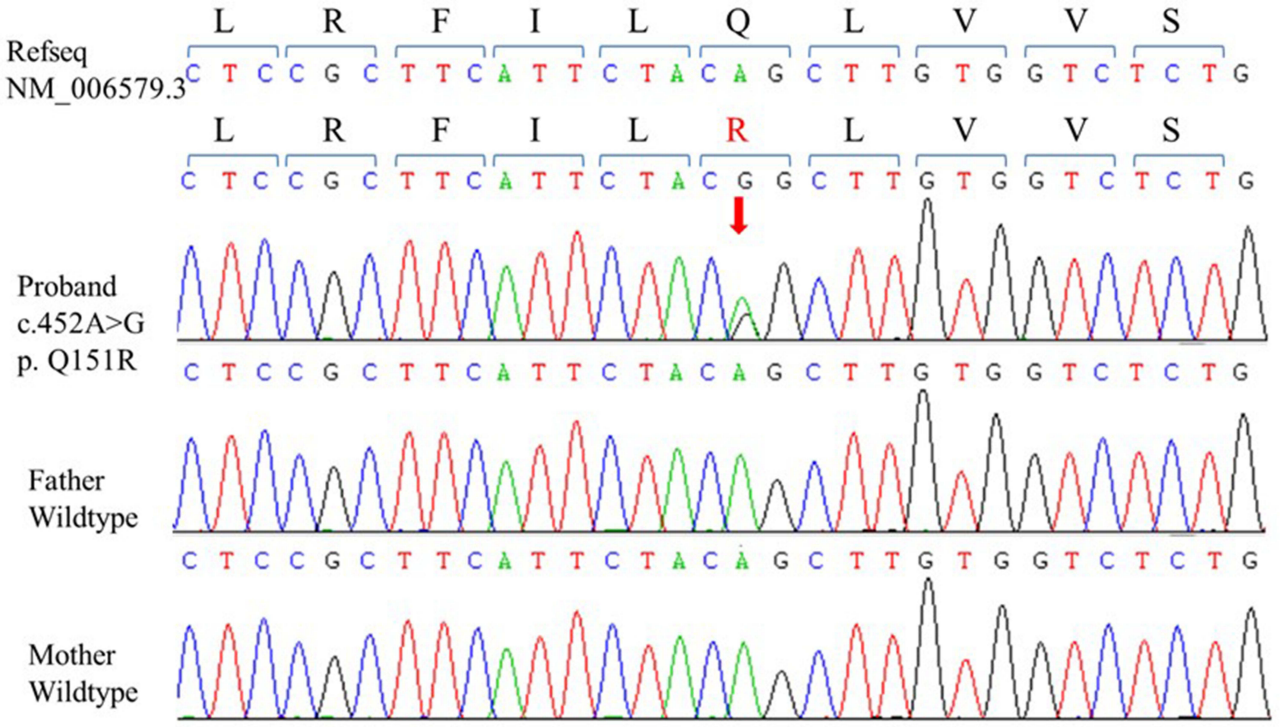

Figure 4 DNA analysis of the *EBP* gene in the proband and her parents by Sanger sequencing.

sparse and lusterless hair, or alopecia are also common features in some patients. In contrast, intra-familial reports show a higher proportion of these manifestations. More than 95% of patients diagnosed with CDPX2 exhibit ichthyosis, while chondrodysplasia punctata, alopecia, and asymmetric shortening of long bones along with short stature are present in

Table 1 Summary of Major Manifestations in Reported CDPX2

Literature No. (Author Year)	Case Affected	S.S	E.S.	S.A.	Scoliosis	D.A.	Skin	Hair/ Alopecia	Cataracts	Renal	F.H.
Happle R. et al 1979[1]	1 female	N.A.	N.A.	1	1	0	1	1	0	Absence	0
Sutphen R. et al 1995[6]	1 male + 3 female	4	N.A.	3	2	2	3	4	4	0	3
Becker K. et al 2001[7]	1 female	0	0	0	1	0	1	1	1	0	0
Herman GE. et al 2002[8]	22 female	N.A.	17	N.A.	N.A.	Postaxial polydactyly2	18	N.A.	10	1	
Has C. et al 2002[9]	14	6	N.A.	6	N.A.	2–3 toe syndactyly1	12	11	6	2	3
Aughton DJ. et al 2003[10]	1 male	0	1	1	1	0	1	1	0	0	0
Shirahama S. et al 2003[11]	4 female	4	4	3	4	0	4	Sparse hair2	4	0	0
Whittock NV. et al 2003[12]	1 female	0	0	0	0	0	1	1	0	0	0
Milunsky JM. et al 2003[13]	1 male	0	0	0	0	1	1	0	1	1	1
Shotelersuk V. et al 2005[14]	2 female	1	1	1	1	1	2	1	1	0	0
Kelley RI. et al 2005[15]	4 male	N.A.	N.A.	N.A.	N.A.	Polydactyly 1	N.A.	N.A.	1	3	N.A.

(*Continued*)

https://doi.org/10.2147/TACG.S513953

Table 1 (Continued).

Literature No. (Author Year)	Case Affected	S.S	E.S.	S.A.	Scoliosis	D.A.	Skin	Hair/ Alopecia	Cataracts	Renal	F.H.
Umranikar S. et al 2006[16]	1 female + 3 female fetuses	1	3	3	1	0	0	1	1	0	2
Feldmeyer L. et al 2006[17]	3 female	1	3	0	1	0	3	3	3	0	1
Hellenbroich Y. et al 2007[18]	1 female + 1 female fetus	N.A.	1	1	0	Postaxial polydactyly1	1	0	0	1	1
Steijlen PM. et al 2007[19]	3 female	1	1	1	1	0	3	1	N.A.	N.A.	N.A.
Tysoe C. et al 2008[20]	3 female	N.A.	N.A.	2	2	0	2	2	1	0	2
Umekoji A. et al 2008[21]	1 female	0	1	0	0	0	1	1	0	0	N.A.
Furtado LV. et al 2010[22]	7 male	0	1	0	0	2–3 toe syndactyly6	7		6	7	7
Tan C. et al 2010[23]	1 male	0	0	0	0	2–3 toe syndactyly1	0	0	0	0	0
Hello M. et al 2010[24]	1 female	0	1	0	0	0	1	1	0	0	1
Morice-Picard F. et al 2011[25]	2 female	1	N.A.	1	1	0	2	1	0	0	1
Arnold AW. et al 2012[26]	1 male	0	0	0	0	0	1	1	0	0	0
Canueto J. et al 2012[27]	13 female	8	10	7	5	Polydactyly2	11	5	5	0	5
Arnold AW. et al 2012[26]	1	0	0	0	0	0	0	0	0	0	0
Bode H. et al 2013[28]	1 male	0	N.A.	0	0	1	1	Sparse hair1	1	1	0
Lambrecht C. et al 2014[29]	2 female	0	0	1	1	0	1	2	0	0	1
Barboza-Cerda MC. et al 2014[30]	1 male	1	0	0	1	1	1	0	0	1	1
Hartill VL. et al 2014[31]	4 male	0	0	0	3	2–3 toe syndactyly3	0	0	0	0	4
Lefebvre M. et al 2015[32]	9 female fetuses	8	9	7	N.A.	1	8	1	0	0	3
Ozyurt K. et al 2015[33]	1 female	1	0	1	1	0	1	1	1	0	
Leclerc-Mercier S. et al 2015[34]	8 female	N.A.	N.A.	N.A.	N.A.	N.A.	8	1	N.A.	N.A.	0
Posey JE. et al 2015[35]	1female	1	0	1	1	0	1	0	1	0	1
Pacault M. et al 2018[36]	1 male + 1female + 1 female fetuse	3	1	2	0	0	2	2	0	0	2
Chang G. et al 2018[37]	2 female	2	0	1	1	1	1	1	1	0	1
Liu Y. et al 2019[38]	1 female fetus	1	0	1	0	0	1	0	0	0	0
Honigman A. et al 2019[39]	1 male	1	1	0	0	0	1	1	0	0	0
Satake M. et al 2019[40]	1 female	1	1	1	0	0	1	1	0	0	0
Horinouchi T. et al 2019[41]	1 male	1	1	1	1	0	1	0	0	0	0
Agud-Dios M. et al 2021[42]	1 female	1	0	0	0	0	1	1	0	0	0
Hong JK. et al 2021[43]	3 female	3	1	2	1	Polydactyly1	3	0	2	0	1
Rajabi F. et al 2021[44]	1 female	1	0	1	0	4–5 fingers fused1	1	0	0	0	0
Hiraide T. et al 2022[45]	2 female	2	1	2	1	0	2	0	1	0	1

(*Continued*)

Table 1 (Continued).

Literature No. (Author Year)	Case Affected	S.S	E.S.	S.A.	Scoliosis	D.A.	Skin	Hair/ Alopecia	Cataracts	Renal	F.H.
Del Rio-Martinez CJ. et al 2023[46]	1 female	1	0	1	0	0	1	1	1	0	0
Total	86f + 15f.f + 25m + 15 = 141	55	59	52	32	27	111	51	52	17	42

Abbreviations: N.A., not available; S.S., short stature; E.S., Epiphyseal stippling; S.A., skeleton asymmetrical; D.A., digital abnormality; Skin, ichthyosis or erythrodermic; F.H., family history; f, female; f.f, female fetus; m, male.

80% of patients. Unilateral or bilateral cataracts are observed in 60% of cases.[8,48] Asymmetrical skeletal deformities and cutaneous lesions are the two primary manifestations of CDPX2. Skeletal changes, including vertebral malformations, epiphyseal stippling, or flocculent calcifications, are notable findings on X-ray.[11,27,29,35,49]

Our proband is a girl affected by a *de novo* missense variant. Her clinical features are consistent with those of individuals carrying previously reported *EBP* variants, including multiple butterfly-like vertebrae, severe scoliosis, punctata calcific stippling of the sternum and ribs, deformities of the ischium and pubis on radiographs, cataract in the right eye, sparse eyebrows and eyelashes, and patchy alopecia. Pigmented scales were also observed on her lower legs. Additionally, asymmetric lower limb length and genu varum (bowlegs) were identified in this case.

However, atypical hydronephrosis of the right kidney and right ureter, along with a neurogenic bladder, were observed in this case. This is a rare clinical feature. Among the previous reports, only one female with hydronephrosis has been reported by Herman GE had.[8] Additionally, thirteen males with *EBP* mutations have been reported to exhibit renal deformities or abnormalities of the genitourinary system, including urinary incontinence, hypospadias, renal anomalies, cryptorchidism.[9,13,22]

In addition, digital abnormalities were reported in 27out of 141 cases in previous studies. The most common features of digital abnormalities include 2–3 toe syndactyly (11/27) and polydactyly or postaxial polydactyly (7/27). However, camptodactyly was observed in this case, a feature not previously reported.

The *EBP* gene, also known as emopamil binding protein, is localized to the endoplasmic reticulum and functions as a molecular acceptor of emopamil. It was the only gene identified as responsible for CDPX2, as reported by Braverman et al in 1999.[3] To date, over 90 mutations in the *EBP* gene have been reported as causes of CDPX2. Among these, eight mutations were identified in males, four of which were reclassified as male *EBP* disorder with neurological defects (MEND) syndrome. In the literatures, 37 missense mutations, 24 nonsense mutations, 21 frameshift mutations, and 8 splice variants in the *EBP* gene were reported (Figure 5).

Previous studies suggested that *EBP* frameshift or nonsense mutations, which cause truncated proteins, result in typical CDPX2 with complete clinical features involving skeleton, dermatologic, and ocular manifestations, whereas the clinical severity of missense mutations is variable.[2] However, in our case, the missense mutation exhibited all typical manifestations, as well as neurogenic bladder, hydronephrosis and camptodactylia. Therefore, the clinical phenotype cannot be predicted solely based on the genotype. WES is particularly useful for diagnosing rare genetic disorders with heterogeneous presentations due to differences in severity or expressivity, as well as the involvement of multiple genes causing similar phenotypes.

To date, the treatment of CDPX2 remains symptom-based. However, it is crucial for the parents to undergo prenatal diagnosis during subsequent pregnancies following a genetic diagnosis.

In conclusion, we identified a novel missense mutation in the *EBP* gene in a Chinese family, expanding the mutation spectrum of CDPX2. Meanwhile, we reviewed previously reported cases to summarize variations in the *EBP* gene, which may facilitate clinical applications. Furthermore, we highlight the value of WES in providing genetic diagnoses for rare diseases.

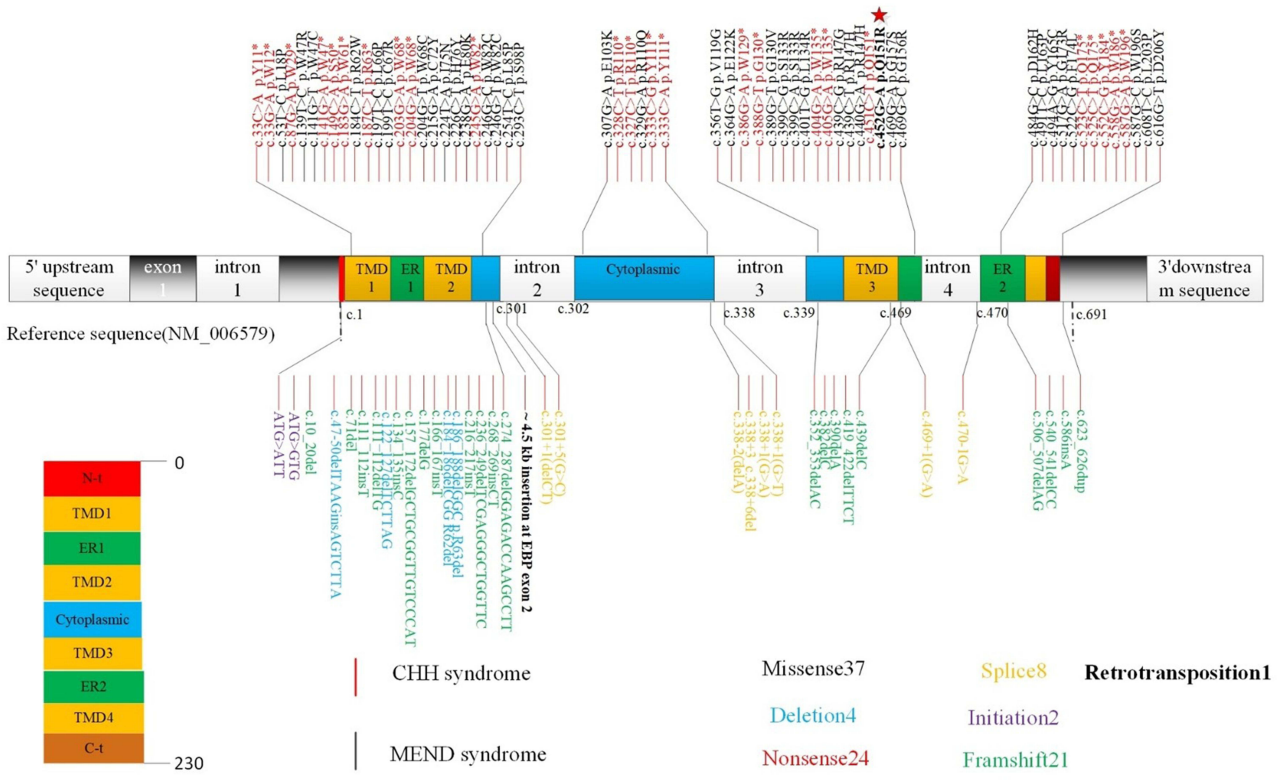

Figure 5 Mutations in CHH syndrome and MEND syndrome in reports of *EBP* gene. Ninety-one mutations are concluded. Missense and nonsense mutations are represented using amino acid sequence while deletions, insertions, splicing and initiation mutations showed only with cDNA sequence. *EBP* mutation of this case was shown with red five-pointed star. *stop codon position in a protein sequence.

Abbreviations: N-t, N terminal; TMD, transmembrane domain; ER, endoplasmic reticulum; C-t, C terminal.

Editorial Policy and Ethical Considerations

This study ([2019]KY-080) was approved by the Ethics Committee of the Nanjing Maternity and Child Health Care Hospital and adhered to the Declaration of Helsinki. Samples and information were collected from the parents after written informed consent was obtained. The written informed consent included consent for publication of case details and any accompanying images.

Funding

This work was supported by the National Key R&D Program of China (2022YFC2703400), Scientific Research Project of Jiangsu Maternal and Children Health Care Association (FYX202118); Maternal and Children Health Project of Jiangsu Province (F202158).

Disclosure

All authors declared no conflicts of interest in this work.

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