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CRIPT exonic deletion and a novel missense mutation in a female with short stature, dysmorphic features, microcephaly and pigmentary abnormalities

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Abstract

Mutations in *CRIPT* encoding cysteine-rich PDZ domain-binding protein are rare, and to date have been reported in only two patients with autosomal recessive primordial dwarfism and distinctive facies. Here, we describe a female with biallelic mutations in *CRIPT* presenting with postnatal growth retardation, global developmental delay, and dysmorphic features including frontal bossing, high forehead, and sparse hair and eyebrows. Additional clinical features included high myopia, admixed hyper- and hypopigmented macules primarily on the face, arms, and legs, and syndactyly of 4–5 toes bilaterally. Using whole exome sequencing (WES) and chromosomal microarray analysis (CMA), we detected a c.8G>A (p.C3Y) missense variant in exon 1 of the *CRIPT* gene inherited from the mother and a 1,331 bp deletion encompassing exon 1, inherited from the father. The c.8G>A (p.C3Y) missense variant in *CRIPT* was apparently homozygous in the proband due to the exon 1 deletion. Our findings illustrate the clinical utility of combining WES with copy number variant (CNV) analysis to provide a molecular diagnosis to patients with rare Mendelian disorders. Our findings also illustrate the clinical spectrum of *CRIPT* related mutations.

Keywords

Postnatal growth retardation; microcephaly; *CRIPT* mutation; whole exome sequencing; genome wide microarray

ACCESSION NUMBERS

The ClinVar accession numbers for the DNA variants reported in this paper are SCV000262606 and SCV000262607.

INTRODUCTION

Clinical whole exome sequencing (WES) has become a powerful and practical tool to diagnose individuals with rare genetic disorders [Yang et al., 2014; Yang et al., 2013]. While whole exome sequencing has allowed the identification of novel Mendelian disease genes, this diagnostic approach has also provided expansion of the phenotypic spectrum of known disorders [Yang et al., 2014; Yang et al., 2013; Prada et al., 2014; Pena et al., 2016; Bekheirnia et al., 2012]. For instance, through the use of whole exome sequencing, previously undiagnosed individuals with atypical course have been reported to harbor pathogenic variants in genes causing known disorders such as galactosialidosis and methionyl-tRNA formyltransferase (MTFMT) deficiency [Prada et al., 2014; Pena et al., 2016]. These patients were not diagnosed clinically because of the rarity of the disorder and our limited knowledge regarding the phenotypic spectrum of the disease [Prada et al., 2014; Pena et al., 2016]. This can be particularly challenging for newly discovered Mendelian disorders where the continuum range of clinical features is yet to be determined. Unless specific set of features support a diagnosis at the clinical level, genome wide approaches using WES with copy number variant (CNV) analyses are the best tools to capture the genetic heterogeneity of phenotypes such as short stature and microcephaly, thus providing a definitive diagnosis to these patients.

In 2014, Shaheen *et al.* reported two unrelated individuals with severe growth restriction of prenatal onset characteristic of primordial dwarfism [MIM: 615789][Shaheen et al., 2014]. One patient was found to be homozygous for a loss of function variant in *CRIPT.* The other patient was presumed homozygous for a loss of function variant based on the heterozygous status of the parents and the overlapping clinical presentation. To our knowledge, these two individuals are the only patients publically reported with a defect in the *CRIPT* gene. Here, we describe the clinical findings of an additional patient presenting with postnatal growth restriction, microcephaly, ophthalmological abnormalities, intellectual disability, and cutaneous findings who was found to be compound heterozygous for a c.8G>A (p.C3Y) missense variant and a deletion of exon 1 in the *CRIPT* gene.

CLINICAL REPORT

The study was performed in accordance with the ethical guidelines for human subject research and was approved by the Institutional Review Board at Baylor College of Medicine. Informed consent was obtained from the family for publication of photographs.

The patient was a 4-year old African-American female, born at 34 weeks gestation to a 21-year old mother via c-section. Clinical characteristics and parameters are provided in Table I. Birth weight was 2.01 kg (31st centile), and birth length was 45 cm (65th centile). She was diagnosed with failure to thrive by early infancy, with all growth parameters falling below the 5th centile. At chronological age of 7 months, she was diagnosed with high myopia (−9.00 OU), intermittent exotropia, and latent nystagmus. She had normal optic discs with no evidence of retinopathy. She sat independently at 13 months and walked unassisted at 2 years of age. When re-evaluated at 4 years, she had significant language delay and had started developing complex partial seizures. Her weight was 11.3 kg (Z=−3.74), length was

90.5 cm (Z=−3.11), and head circumference was 47 cm (Z=−2.7). Her dysmorphic features included microcephaly, frontal bossing, high forehead, sparse hair and eyebrows, telecanthus with normal interpupillary distance, long and flat philtrum and retromicrognathia (Fig. 1A and B). She also had proximally placed thumbs, and syndactyly of 4–5 toes bilaterally (Fig. 1C and 1D and supplementary Fig. S1). Her skin abnormalities consisted of an admixture of hyper and hypopigmented macules which started on the face at approximately 2 years of age with subsequent development on the arms and legs including the dorsal hands and feet, reminiscent of dyschromia symmetrica hereditaria or other entities with mottled or reticulate dyspigmentation. (Fig. 1E and Supplementary Fig. S1). In addition, she had a keratosis-pilaris like eruption on the cheeks and arms with hyperkeratotic follicular papules. (Fig. 1B). By report, hair on the scalp was of normal density in infancy and childhood with gradual thinning starting from age 3; while eyebrows were sparse from birth. A representative skin biopsy of an area of dyspigmentation on the arm showed only basilar hyperpigmentation. Electron microscopy of a hair sample showed no structural abnormalities. Brain magnetic resonance imaging (MRI) study was unremarkable. Auditory brainstem response (ABR) audiometry showed normal hearing sensitivity bilaterally. Her skeletal survey revealed eleven pairs of ribs with mild hypoplasia of femoral head and neck bilaterally (Supplementary Fig. S2). Metacarpals and phalanges were slender and elongated. Phalangeal hypoplasia was not observed (Supplementary Fig. S3). X-rays of the feet showed bilateral hindfoot valgus and forefoot abduction, with lateral subluxation of the tarsal navicular bones (Supplementary Fig. S3).

Chromosomal microarray (CMA) and WES were requested for her evaluation. DNA was extracted from blood samples from the patient, and her biological parents. The patient underwent a “proband WES” testing approach, for which the proband’s DNA was sequenced and analyzed. Parental genotyping was performed using Sanger sequencing to assess the inheritance of variants related to the phenotype of the patient. The results were interpreted following the WES standard operating procedures at the Baylor Miraca Genetics Laboratories (BMGL) [Yang et al., 2014; Yang et al., 2013]. The study revealed an apparently homozygous novel missense variant (NM_014171.5, c.8G>A, p.C3Y) in *CRIPT*, confirmed by Sanger sequencing (Fig. 2A). Parental studies showed that the mother was heterozygous for the change but the father was negative (Fig. 2A). Subsequent genetic testing confirmed paternity (data not shown). Additional WES variants were detected but none of these variants presented a more plausible explanation for the patient’s phenotype. These variants are listed in Supplementary Table SI and include: 1) heterozygous variants of unknown significance (VUS) in genes causing an autosomal dominant disorder, inherited from an asymptomatic parent; 2) single heterozygous VUS in genes causing an autosomal recessive disorder without a second hit; 3) heterozygous loss of function variants and biallelic variants in genes not known to be causing-disease or causing a disorder unrelated to our patient’s phenotype. CMA revealed a small heterozygous deletion between 281 bp and 1.6 kb in size on chromosome 2 (Fig. 2D). The minimum interval spanned between genomic positions 46,844,284 and 46,844,565 bp (hg19) and the maximum interval spanned between 46,844,135 and 46,845,755 bp. (Fig. 2D). Custom primers were designed surrounding this locus to confirm the deletion (Fig. 2D and 2E). Sanger sequencing was also performed on the PCR product harboring of the deletion to capture the breakpoint. This deletion was

delineated to a 1,331 bp segment from 46,844,000 to 46,845,330 bp (Fig. 2D and 2E) and was found to be inherited from the father (Fig. 2C and 2E). The 1.3 kb interval encompassed exon 1 of the *CRIPT* gene (cDNA level: NM_014171.4:c.−422_17-582del) and the non-translated exon 1 of the *PIGF* gene (Supplementary Fig. S4). Deletion of exon 1 of *CRIPT* was also observed in the read depth from the next-generation sequencing data from WES in this patient (Supplementary Fig. S5). Defects in *PIGF* are not known to cause human disease at this time. No other rare variant was found in the *PIGF* gene and the gene was fully covered at 20× by WES.

Taken as a whole, our patient was found to be compound heterozygous for the c.8G>A (p.C3Y) variant in exon 1 of the *CRIPT* gene, inherited from the mother, and an exon 1 deletion, inherited from the father (Fig. 2C). The cysteine at position 3 of the amino acid chain is highly conserved in evolution as far as *C. elegans* (Figure 2B). The change from cysteine to tyrosine is also predicted to be deleterious using SIFT, Polyphen-2 and Combined Annotation Dependent Depletion (CADD) [Adzhubei et al., 2010; Kumar et al., 2009; Kircher et al., 2014]. The SIFT algorithm predicted the change to affect the protein function with a score of 0; Polyphen-2 predicted the change to be possibly damaging with a score of 0.962; CADD provided a PHRED-like scaled C-score of 29.5, indicating that the change is predicted to be approximately in the 0.1% most deleterious substitutions possible in the human genome. The c.8G>A (p.C3Y) variant has been reported in the ExAC database (http://exac.broadinstitute.org) and subsequently in the NCBI (rs757078301, http://www.ncbi.nlm.nih.gov/snp) based on the ExAC database. However because of the low quality of the variant, neither frequency nor allele count was reported in ExAC. Further investigation of the ExAC database revealed seven heterozygous loss of function variants over 10 individuals in *CRIPT* with minor allele frequency of less than 0.0001. At the time of this submission, only one South Asian individual has been reported with a homozygous missense variant (NM_014171.5, c.262A>G, p.K88E) and no homozygous loss of function variants have been reported in the same database. In addition, in our cohort of over 6,000 clinical WES samples, no other individual has been identified with a homozygous or compound heterozygous variants in *CRIPT*. The most conserved domain of the CRIPT protein is located in the N- and C-terminal region, which contains the CXXC repeats. The change identified in our patient affects the first cysteine of the first CXXC repeat, which may be involved in disulfide bonds and likely to affect the function. Considering the genetic data in our patient and the phenotypic overlap with the two previously reported patients, we conclude that the c.8G>A (p.C3Y) variant is likely pathogenic and the compound heterozygous changes in the *CRIPT* gene are most likely responsible for the clinical presentation in this patient.

DISCUSSION

Here, we report a third patient with biallelic *CRIPT* mutations presenting with postnatal growth retardation and microcephaly. The diagnosis was established using both CNV and single nucleotide variation (SNV) analyses in our patient. The two individuals previously reported with homozygous *CRIPT* mutations had primordial dwarfism with prenatal growth restriction, developmental delay, distinctive facial features including frontal bossing, sparse hair, upturned nares, and skeletal abnormalities including hypoplastic terminal phalanges

with talipes deformity in one patient (Table I). Vision was impaired in both patients with retinal changes highlighted in one. Similarly to our patient, skin pigmentary abnormalities described as mottled pigmentation was also reported in one of these patients, notably on the face and dorsal feet. Of the two reported individuals, one passed away at 70 days of life [Shaheen et al., 2014]. Both unrelated patients carried a confirmed or presumed homozygous frameshift pathogenic variants predicted to lead to a loss of function of the protein (NM_014171.5, c.133_134insGG, p.Ala45Glyfs*87 and c.141delT, p.Phe47Leufs*84). While our patient carried a heterozygous deletion of exon 1, the second change located in trans-configuration was a rare missense variant. The change was novel, highly conserved and predicted to affect the protein. While this change was categorized as a likely pathogenic variant, the deleterious effect of this missense change on the protein may be less severe than a loss of function variant and possibly represents a hypomorphic mutation.

It is notable that prior to the first description of two patients with *CRIPT* mutations in 2014, at least two individuals with overlapping features of growth retardation, microcephaly, distinctive facies, and cutaneous pigmentary abnormalities have been described without a molecular diagnosis [Belligni et al., 2011]. The phenotypic overlap including the mottled pigmentation between our patient and, in particular, patient 2 of this previous report cannot be discounted despite the variance in localization of pigmentary lesions in comparison to the photodistributed areas in our patient. It is plausible that the generalized hyper- and hypopigmented macules may be a distinguishing feature of this rare Mendelian disorder affecting skeletal growth and intellectual function. Future studies of additional patients will be important to underscore the comprehensive phenotype related to *CRIPT* mutations.

CRIPT is expressed ubiquitously, including in the brain. The protein binds specifically onto the third PDZ domain (PDZ3) of the post synaptic density-95 (PSD95) protein (also named DLG4) and may play a role in the relocation of the PSD95 protein to microtubules at the synaptic junction [Niethammer et al., 1998]. However its precise functional significance is currently unknown. A $Cript^{tm1.1(KOMP)Vlcg}$ null allele mouse model has previously been generated (https://www.jax.org/strain/024332). Homozygous embryos are lethal at E9.5 and display severe developmental abnormalities including reduced size, failure of axial rotation, asynchronous development of numerous structures and enlarged heart, indicating that the gene is essential in development (Supplementary Fig. S6).

Primordial dwarfism is a genetically heterogeneous condition and multiple genes have been associated with this phenotype [Klingseisen and Jackson, 2011]. This report expands the phenotypic spectrum associated with *CRIPT* mutations, including postnatal growth deceleration as a notable presentation. Our findings also highlight the importance of including exon-specific CNV analysis with exome sequencing in evaluating patients with undiagnosed diseases. This has also been underscored in prior studies [Bayer et al., 2014; Parri et al., 2010]: Bayer et al. previously reported a pathogenic SNV and a small deletion in *IL7R* in a patient with severe combined immunodeficiency (MIM: 608971) [Bayer et al., 2014]. A combined genome wide approach, using both WES and CMA is frequently indispensable in the determination of rare molecular diagnoses in patients.

In conclusion, we describe a third patient with defects in the *CRIPT* gene responsible for short stature, microcephaly, and distinctive facies [MIM:615789]. The clinical presentation of our patient expands the phenotype of *CRIPT* mutations to include postnatal growth delay, distinct from primordial dwarfism. As the use of clinical whole exome sequencing becomes ubiquitous, more patients will be ascertained, further delineating the phenotypic spectrum of this disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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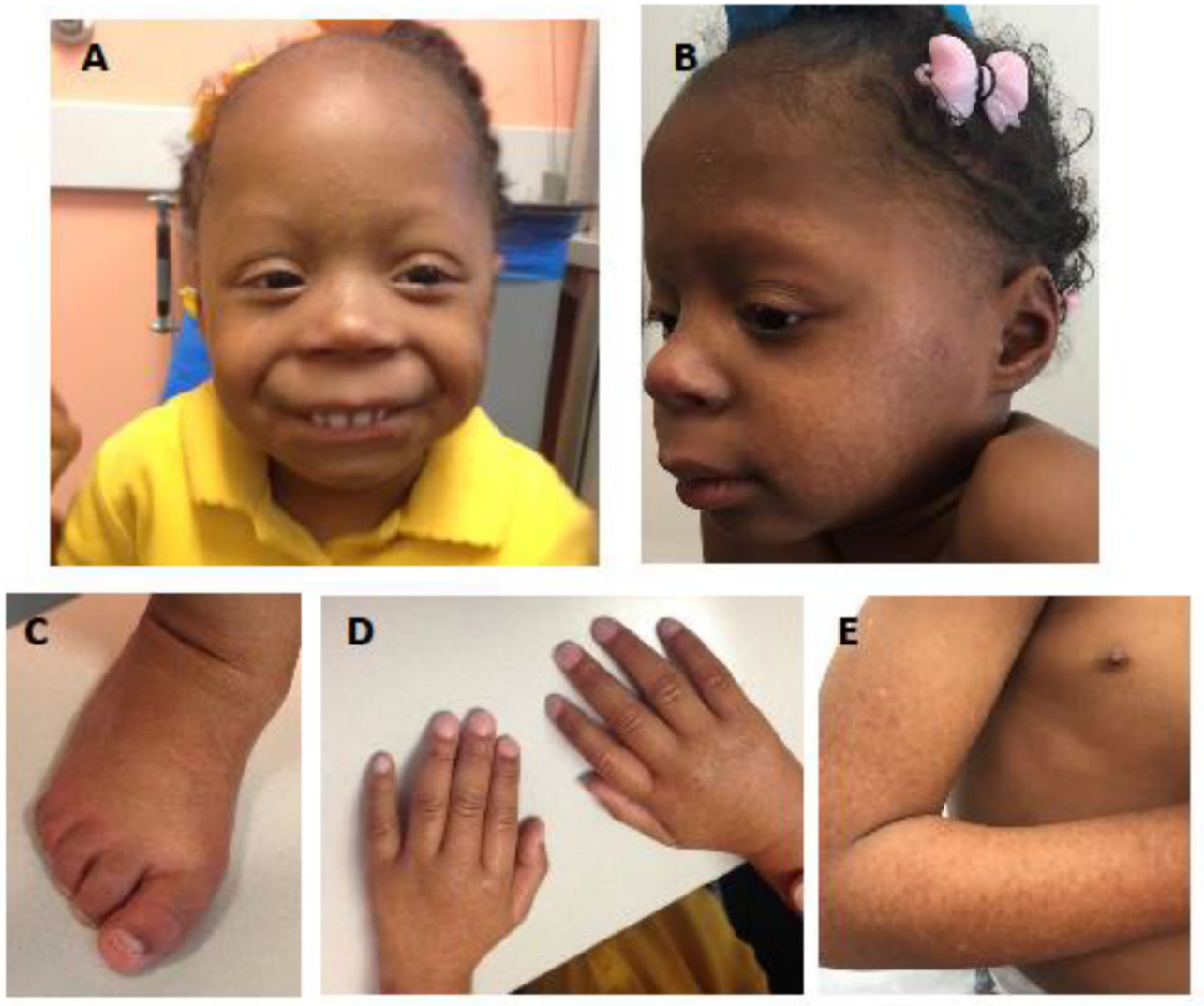

FIGURE 1.

Clinical features of the patient in this report. (A, B) Craniofacial features showing frontal bossing, high forehead, sparse hair and eyebrows, telecanthus, long philtrum and retromicrognathia; (C) Syndactyly of 4–5 toes involving the right foot, and (D) Hands showing proximal displacement of thumbs bilaterally ; (E) Pigmentary abnormality of the skin is highlighted. Pictures A, C and D were taken at 3 years of age; pictures B and E, at 4 years of age. Additional clinical features are highlighted in supplementary Fig. S1, S2 and S3.

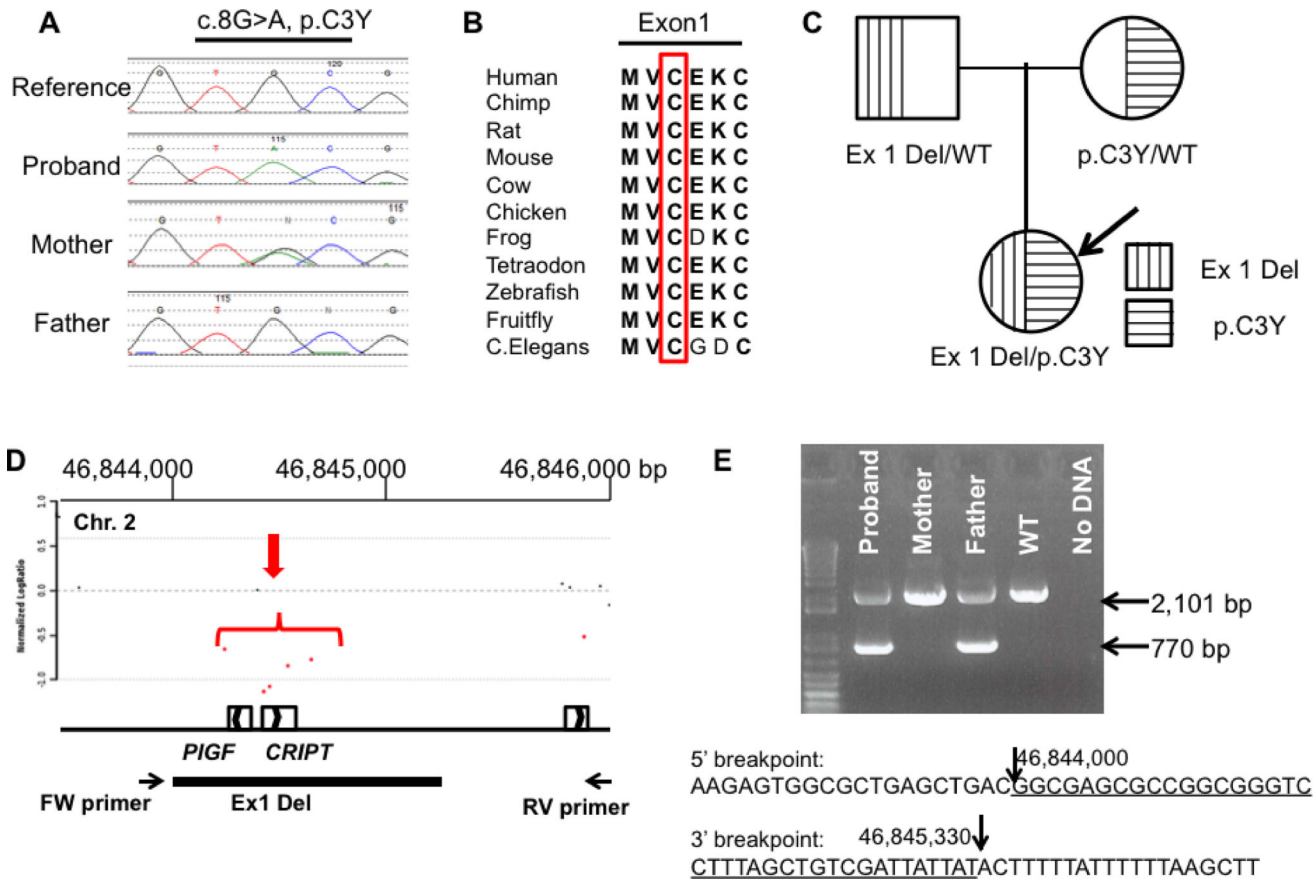

FIGURE 2.

Whole exome sequencing and chromosomal microarray molecular findings in the family. (A) Sanger sequencing results in the patient and her parents are shown; (B) Amino acid conservation among species of the *CRIPT* exon 1; (C) Pedigree of the family showing the segregation of the missense variant and the deletion of exon1 in the *CRIPT* gene; (D) Microarray results of chromosome 2 showing the deletion in patient (probes in red) highlighted in red arrow. The primer locations used for the PCR confirmation are also shown. One probe within the deletion showed no copy number change. This probe had high GC content and high dye density and was therefore not considered in the interval estimation; (E) PCR confirmation of the deletion. Forward and reverse primers were designed surrounding the deletion (FW: AGAGGCAGGATCAAAGAGCA; RV: CCTGTGGTATTCCTAGCACCA). A 2,101 bp PCR product was detected in all members of the family. A smaller PCR product at 770 bp, harboring the deletion, was detected in the proband and father. Sanger sequencing was performed on the deleted band and the deletion breakpoints are indicated below; the deleted sequence is underlined.

Table I

Clinical presentation of patients with defects in the *CRIPT* gene

	Patient PD_F4 Shaheen *et al*	**Patient PD_F5 Shaheen *et al.***	**Our patient**
Gender/Age	Male	Male	Female
***CRIPT* mutations**	NM_014171.4, c.133_134insGG, p.Ala45Glyfs*87 Homozygous	NM_014171.4, c.141delT p.Phe47Leufs*84 Homozygous	NM_014171.4, c.8G>A p. Cys3Tyr, heterozygous + exon 1 deletion
Current age	3 years, 2 months	Deceased (70 days)	4 years
General growth			
At birth			
FOC (cm)	ND	ND	ND
Weight (Kg)	1.2	1.59	2.01 (31st centile)
Length (cm)	ND	ND	45 (65th centile)
At present			
FOC (cm)	45 (−2.5 SD)	35 (−2.7 SD)	47 (Z=−2.7)
Weight (Kg)	8.3 (−4.5 SD)	2.850 (−5 SD)	11.3 (Z=−3.74)
Length (cm)	77 (−5.3 SD)	50 (−4.3 SD)	90.5 (Z=−3.11)
Developmental delay	Yes	ND	Yes
Speech/language delay	Yes	ND	Yes
Hearing	ND	ND	Normal
Vision	Visually blind	Markedly impaired retinal function, albinoid fundus	High myopia
Facial features	High forehead, mild proptosis, sparse hair and eyebrows, telecanthus anteverted nares, flat nasal bridge	High forehead, mild proptosis, sparse hair and eyebrows, telecanthus anteverted nares, flat nasal bridge	Microcephaly, frontal bossing, high forehead, telecanthus, sparse hair and eyebrows, long and flat philtrum, retromicrognathia
Skeletal	Hypoplastic digits with hypoplastic terminal phalanges on x-rays, osteopenia, talipes deformity	Hypoplastic digits with hypoplastic terminal phalanges	Proximally placed thumbs, syndactyly of 4–5 toes, bilateral hindfoot valgus and forefoot abduction, with lateral subluxation of the tarsal navicular bones, eleven pairs of ribs with mild hypoplasia of femoral head and neck bilaterally
Skin findings	“Mottled” pigmentation (face and dorsal feet in figure)	ND	Admixture of hyper/hypopigmented macules on face, arms, legs including dorsal hands and feet Keratosis pilaris (cheeks and arms)
Other clinical findings	ND	Recurrent infections, PDA, persistent anemia (Hb 8.3 g/dl) with anisopoikilocytosis.	Complex partial seizures
Brain MRI	Bifrontal subdural hygroma	Increase white matter signal and hypogenesis of corpus callosum	Normal Study

ND-Not determined