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WDR35 Mutation in Siblings with Sensenbrenner Syndrome: A Ciliopathy With Variable Phenotype

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Abstract

Sensenbrenner syndrome and unclassified short rib-polydactyly conditions are ciliopathies with overlapping phenotypes and genetic heterogeneity. Mutations in WDR35 were identified recently in a sub-group of patients with Sensenbrenner syndrome and in a single family that presented with an unclassified form of short-rib polydactyly (SRP) syndrome. We report on siblings with an unusual combination of phenotypes: narrow thorax, short stature, minor anomalies, developmental delay, and severe hepatic fibrosis leading to liver failure and early death in two of the children. Both parents were unaffected suggesting autosomal recessive inheritance. The family and their affected children were followed over a decade. Exome sequencing was performed in one affected individual. It showed a homozygous missense mutation in a highly conserved position of the WDR35 gene. This family represents aWDR35-ciliopathy with a complex clinical presentation that includes significant overlap of the phenotypes described in Sensenbrenner syndrome and the unclassified SRPs. The accurate molecular diagnosis of this family exemplifies the power of exome sequencing in the diagnosis of Mendelian disorders and enabled us to broaden and refine our understanding of Sensenbrenner syndrome and SRP. Detailed genotype–phenotype information is provided as well as discussion of previously reported cases.

INTRODUCTION

Sensenbrenner syndrome, “cranioectodermal dysplasia,” is a rare recessive condition characterized by craniosynostosis, scaphocephaly, short stature, skeletal, and ectodermal anomalies (sparse hair and hypodontia/microdontia). Other skeletal findings include brachydactyly, single transverse palmar creases, terminal hyoplasia of the fingers, low bone density, and narrow rib cage [Sensenbrenner and Blizzard, 1975; Amar et al., 1997]. Renal

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abnormalities are frequent and often severe leading to failure due to chronic interstitial disease. Liver disease has been reported rarely, perhaps due to early mortality from to end-stage renal disease [Zaffanello et al., 2006; Konstantinidou et al., 2009]. Given the clinical manifestations in Sensenbrenner syndrome, a ciliopathy was suspected [Zaffanello et al., 2006]. Over the past 2 years, several gene mutations have been identified in Sensenbrenner syndrome patients including: intraflagellar transport 122 (IFT122) [Walczak-Sztulpa et al., 2010], the intraflagellar transport A gene WDR19 in a Norwegian family [Bredrup et al., 2011], C14ORF179 that encodes the intraflagellar transport 43 gene (IFT43) [Arts et al., 2011], and lastly WDR35, a homolog of TULP4 characterized as an intraflagellar transport gene [Gilissen et al., 2010].

Recently a non-consanguineous family from New Zealand was described with an unclassified formof short-rib polydactyly (SRP). The affected children in this family were found to have compound heterozygous mutations in WDR35 [Kannu et al., 2007; Mill et al., 2011]. The family had two affected pregnancies, both terminated early in the second trimester. These fetuses had hydrops, narrow chest, short limbs, postaxial polydactyly, syndactyly, posterior cleft palate, and intestinal malrotation. Autopsy showed renal involvement with multiple cysts scattered in the juxtamedullary zone, mostly glomerular but some tubular.

Here, we report on siblings with short rib polydactyly, short stature, minor anomalies, and severe liver fibrosis leading to early demise in several of their children. Exome sequencing in one of the affected individuals showed a homozygous missense mutation in WDR35.

MATERIALS AND METHODS

Sample DNA

In this family, informed consent was obtained for all subjects or their parents according to protocol approved by the BCM internal review board. Genomic DNA was extracted from peripheral leukocytes according to standard protocols.

Sequencing

The human exome was targeted for sequencing using the Roche NimbleGen SeqCap EZ Human Exome Library v2.0 liquid capture. Briefly, the total targeted region comprised _30,000 coding genes from RefSeq and CCDS comprising 36.5 Mb, as well as miRNAs from miRBase for a total of 44.1 Mb. Thesample was barcoded postcapture and loaded into one lane of Illumina HiSeq with three additional barcoded samples. The total number of mapped base pairs in the proband was 4.5 Gb and 65% of aligned reads were on target.

Targeted re-sequencing of HG19:chr2:20146297 in exon 16 of WDR35 was completed in the propositus and both parents. The region was PCR-amplified and sequenced by di-deoxy terminator sequencing on an ABI 3730XL. All chromatograms were inspected manually and genotype calls were based on bi-directional sequence reads with phred quality score >20.

Sequence Data Analysis and Bioinformatics

Sequence data were aligned using BWA [Li and Durbin, 2009] with the most recent version of the human reference sequence, HG19. Duplicate reads were removed using Picard. Recalibration and realignment of the data were accomplished using GATK [McKenna et al., 2010; DePristo et al., 2011]. Single-nucleotide variants (SNVs) were called using both Samtools [Li et al., 2009] and GATK. Small insertions and deletions (InDels) were determined using GATK. Quality control filtering of variants was based on coverage, strand bias, mapping quality, and base quality. Annotation of variants was conducted using internal perl scripts. Prediction for potential functional consequences of variants was conducted using SIFT [Ng and Henikoff, 2001].

The evolutionary conservation of this nucleotide position in the genome was determined by two methods. PhyloP predicts departures from neutral evolution as previously described [Siepel et al., 2006]. The phyloP score reported here results from analysis of an alignment of 46 different species. The absolute value of the phyloP score is the _log P-value under a null hypothesis of neutral evolution with 7 as the maximum conserved value. Genomic Evolutionary Rate Profiling (GERP) calculates estimates of evolutionary constraint using maximum likelihood estimation [Cooper et al., 2005; Davydov et al., 2010]. The GERPþþ score reported here is based on the alignment of 35 mammalian species and the maximum GERP score for this analysis is 6.18.

Clinical Information

This family of Mexican descent was referred for multiple congenital anomalies. This couple had four affected fetuses; one was terminated and three others resulted in living children (Fig. 1). This couple was non-consanguineous and born in different provinces in Mexico.

Patient 1

Prenatal ultrasonography at 18 weeks showed body wall and scalp edema, cystic hygroma, echogenic kidneys, hepatomegaly, and polyhydramnios. At 25 weeks of gestation there was hydrops and polyhydramnios suggesting non-immune hydrops. Results of analysis of chromosomes from amniocytes, rapid FISH and viral PCR were normal. Follow-up ultrasound study at 36 weeks showed resolution of hydrops. At birth this malewas noted to have multiple anomalies and growth restriction (II-I). He was born at 41 weeks of gestation, and had a birth weight of 2,579 g. He had a poor respiratory effort aggravated by a posteriorly placed tongue and microretrognathia. He was also noted to have a small chest. Apgar scores were 5 and 8 at 1 and 5 min, respectively. His OFC was 37 cm (75th centile), and length 47 cm (10th centile). He had a tall forehead, an occiput prominent superiorly and flattened inferiorly, overlapping sutures, low-set ears, micrognathia, high palate, multiple neck skin folds, narrow chest, brachydactyly, post-axial polydactyly in the left foot, and single transverse palmar creases. He required mechanical ventilation and any efforts to wean off or switch toCPAPwere unsuccessful (Fig. 2).Hehad a seizure possibly due to a hypoxic episode and metabolic decompensation. An eye examination showed congenital nystagmus. Placement of a G-button was required for feeding and growth purposes. At age 2 months he developed acute renal failure. He had persistent nonunion gap acidosis and was diagnosed with type 1 distal renal tubular acidosis (RTA), which was treated with a citric acid and

sodium citrate mix to alkalinize the urine. He had elevated liver enzymes. Limited X-ray studies showed shortened tibia and fibula on the left side, and a bell-shaped chest. Head CT scan at 2 months showed increased AP diameter, closed sagittal suture with patency of coronal and lambdoid sutures. Echocardiography showed mild thickening of mitral and tricuspid valves, a patent foramen ovale (PFO) and a small aortic isthmus.Aliver biopsy at 3months showed early biliary cirrhosis, severe cholestasis with extensive bile duct proliferation and acute cholangitis. The portal tracts were extensively widened by a complex proliferative pattern of bile ducts and an increase in fibrotic tissue and inflammatory infiltrates. The architectural pattern of the epithelium was described as markedly bizarre due to complex infolding and branching. Trichrome stain showed increased collagen in the portal tracts and around the bile ducts. At age 4 months a rib cartilage biopsy was performed that showed no architectural cartilage abnormalities and normal appearing chondrocytes. The only abnormalities seen included mild dilatation of the rough endoplasmic reticulum with mild to moderate accumulation of lipids in the chondrocytes. At age 5 months he underwent surgery to correct sagittal synostosis. He never left the hospital. At 9 months he developed severe desaturations and bradycardias that escalated into multiple asystoles and apneic episodes. He did not respond to resuscitation.

Patient 2

A second pregnancy was complicated by IUGR detected at around 26 weeks gestation. Ultrasonography at 351/2 weeks of gestation showed a small fetus with shortness of all limbs and a very narrow chest (radiograph in Fig. 3). Thickened skin was noted around the abdomen. This was a female baby (II-II) and born at 38 1/7 weeks of gestation. She was small for gestational age (SGA) with a birth weight of 2,315 g and had Apgar scores of 8 and 9 at 1 and 5 min, respectively. Echocardiogram showed a small patent ductus arteriosus (PDA) with left-to-right shunting and PFO with right to left shunting. She developed direct hyperbilirubinemia. A HIDA scan was consistent with cholestatic disease. She was treated with ursodiol and vitamin K. Renal ultrasound showed increased cortical echo density. A skeletal survey showed proximal thumbs, mesomelic shortness, and rib anomalies affecting 7th, 8th, and 9th ribs. At 2 weeks there was bitemporal narrowness, small eyes, upslanting palpebral fissures with epicanthal folds, cleft palate, microrethrognatia, midface hypoplasia, loose skin folds, posteriorly angulated ears, wide-spaced nipples, bridged palmar creases, left foot post-axial polydactyly, and fifth digit clinodactyly. The chest was narrow. Chromosomes were normal. Plasma amino acids were abnormal mostly related to liver dysfunction. Her liver disease remained stable with some improvement early on. She was discharged at 25 days. She was later on admitted to the hospital at 2 months with persistent conjugated hyperbilirubinemia and found to have a CMV infection. A liver biopsy and an intraoperative cholangiogram showed hypoplastic intrahepatic bile ducts, bridging portal fibrosis with bile duct proliferation, significant cholestasis, acute and chronic portal inflammation with cholangitis and patchy individual hepatocyte necrosis with mild lobular chronic inflammation. At 2 months her examination revealed a small OFC (33.5 cm <3rd centile; Fig. 4) and dysmorphic features as noted above. She had multiple hospital admissions subsequently due to failure to thrive, febrile illnesses and coagulopathy complications. She received a G-button at age 5 months. At 13 months she presented to the emergency room with bleeding from the G-tube and poor vital signs due to a generalized

coagulopathy. Attempts at resuscitation were unsuccessful. Her cause of death was a hypovolemic shock. Autopsy showed a brain weight of 765 g (expected 925 g) with cortical atrophy, a focal microdysgenesis in the parietal lobes, cortical atrophy of posterior frontal lobe, and ventriculomegaly. In addition she had two accessory spleens. Kidneys showed a chronic nephropathy with glomerulosclerosis and tubular atro-phy. The liver showed architectural distortion with loss of normal lobular configuration in many areas with expansion of the portal tracts by fibrosis and variable cholangiolar proliferation, focal bile stasis with plugging in more central sections, and mild portal inflammation with acute cholangitis. Cardiac examination showed left ventricular hypertrophy, and right atrial and ventricular dilatation.

Patient 3

This pregnancy was affected as well. An ultrasound study at approximately 21 weeks of gestation showed hydrops, hepatomegaly, and polyhydramnios. The ultrasound did not show any specific skeletal findings. The pregnancy was subsequently terminated (II–III). Postmortem skeletal examination showed clinodactyly of the 5th digits and a duplicated calcaneous (Table I).

Patient 4

He was evaluated at age 2 months (II–IV). Initially his development seemed to be age appropriate.He was diagnosed with atrial ectopic tachycardia treated by flecainide and propranolol, an atrial septal defect (ASD) and a PFO. He had liver dysfunction and cholestasis and treated with Ursodiol, and multivitamins(ADEK). At 2months he had an OFC of 40.1 cm (slightly above the 50th centile), length 56 cm (10–25 centile), weight 4.365 kg (>95 centile). His head shape was dolichocephalic with prominent occiput, upward slanting palpebral fissures, normal ears, narrow and small chest with short ribs (X-ray image shown in Fig. 5). There was post-axial polydactyly of his feet, and an extra digit on the right fifth fingerwas attached to the middle phalanx, with normal palmar creases. He was evaluated again at 10 months and still not able to sit independently and had not yet started to crawl. He could transfer objects from hand to hand. He was able to coo and babble. Physical therapy had been initiated at age 5 months because of mild delays. Growth parameters at 10 months showed a length of 64.4 cm (<5th centile), weight 7.155 kg (<5th centile), and OFC 45 cm (25–50 centile). At age 2 years he was still taking Ursodiol, propranolol, tocopherol, multivitamins, and thiazides.He had global developmental delay by then and was receiving occupational, physical and speech therapy. On examination he had striking dolichocephaly with bitemporal narrowing, upslanting palpebral fissures, narrow nose with hypoplasia of alae nasi, borderline low set ears with simple helices, mild midface hypoplasia, narrow chest, hepatomegaly (4–5 cm below the costal margin). The hands showed post-axial polydactyly on the right hand consistent of a small digit hanging from a skin tag. There was generalized brachydactyly and syndactyly. The lower limbs showed bilateral post-axial polydactyly, brachydactyly, and partial syndactyly of all toes. At 3 years ASD and PFO as well as his atrial ectopic tachycardia resolved. AST was 89 U/L with ALT of 41 U/L, alkaline phosphatase 442 U/L and GGT 227 U/L. He was still delayed able to walk, speak up to 40 words and put up to 5 words together. He could follow 2 and 3 step commands. At 3 years physical examination showed OFC of 50.2 cm (50–75th centile), height 89.8 cm

(<3rd centile, 50th centile for 21/2 years), and weight 16.5 kg (_50th centile). At 4 years of age he had short stature, narrow chest, polydactyly, liver dysfunction, and global developmental delay. He had difficulties gaining weight right around the time he was switched from Peptamen Junior to regular meal so he was started on PediaSure two cans per day in addition to regular food. A liver biopsy at 4 years showed several broad scars with established collagen in which somewhat enlarged, dilated, and irregularly shaped bile ducts were present without bile retention or inflammation. The bile ducts appeared larger and often irregularly configured whereas small oneswere irregularly distributed and relatively sparse. Portal veins were not evident and arteries and arterioles had swollen endothelium. On comparison review of the prior biopsy, the portal veins were also missing or obscured. These changes were compatible with a malformation of the ductal plate. These changes in liver architecture have been described previously in Sensenbrenner syndrome [Zaffanello et al., 2006; Walczak-Sztulpa et al., 2010]. Subsequently the couple had a normal boy and girl.

RESULTS

DNAof the propositus (II–IV) was sequenced using exome capture which yielded an average target coverage of 55_. SNVs and small insertions and deletions (InDels) were scored. 16,970 SNVs and 283 InDels were identified in gene coding regions. There were 50 nonsynonymous, homozygous, non-reference variants not present in dbSNP132. Of these 17 were predicted to be damaging to the protein function by SIFT. WDR35 which was recently reported to be pathogenic in SRP caseswas in this short list of candidate genes [Mill et al., 2011].

A homozygous missense mutation in WDR35 HG19:chr2: 20146297,A/G was identified. This mutation is in exon 16 (of 28 exons total for the longestWDR35isoform) and results in the amino acid change L520P. Predicted to be highly damaging by SIFT which gives this mutation the lowest (most damaging) possible score of 0. This mutation lies outside the WD40 super family domain which is the only functional domain predicted for the WDR35 protein. However, this domain spans just 25% of the protein. The mutation is in a nucleotide position that is highly conserved across species. Two separate methods for determining evolutionary conservation both yielded highly significant results in support of site-specific conservation. PhyloP analysis based on the alignment of 46 species yielded a score of 4.9. GERPþþ analysis based on an alignment of 35 mammals scored 5.9. Generally speaking base positions with GERP and PhyloP scores >2 are considered conserved. Additional support for the pathogenicity of this variant is that it has not been observed in the large-scale sequencing efforts of the 1000 Genome Project, NHLBI ESP, and NIEHS EGP. Collectively these data represent sequencing of over 7,000 humans; the majority of whom are European or African derived, however, there are 207 Hispanic individuals in this dataset.

Confirmational sequencing of the proband by Sanger sequencing validated the next-generation sequencing results. In addition, the parents and unaffected siblings of the propositus were sequenced for the region of WDR35 spanning this mutation and all were heterozygous for the mutation site (Fig. 1).

DISCUSSION

This family exemplifies the complexity seen in most of the ciliopathies. The children described in this family have a number of features characteristic of Sensenbrenner syndrome, and overlap with the short rib polydactyly syndromes. Until the results of the exome sequencing analysis, the diagnosis of Sensenbrenner was not fully entertained. This was mainly due to a number of issues: (1) polydactyly is infrequent in Sensenbrenner syndrome, (2) liver involvement has also been rarely reported although only recently described, (3) cognitive problems have not been commonly described in Sensenbrenner while the three affected children in this family were developmentally delayed. In the first two cases, the chronic diseases and multiple hospitalizations could have been considered an associated factor; but the oldest surviving child of this family, Patient 3, has been rather stable and did not require many hospitalizations, yet he is clearly delayed. Our cases were thought to represent an unclassified form of short rib polydactyly and liver fibrosis.

The liver disease in these affected sibs is quite severe and compromised their lifespan before the renal disease manifested. Two of the three affected children died around age 1 year. There is one affected child who is still alive at almost age 5 years. His liver disease was stable until recently but his biopsies have clearly shown worsening over time. He has now developed renal function abnormalities consistent with a RTA. The renal disease in patients with Sensenbrenner syndrome receives the most attention but perhaps liver function should be thoroughly investigated and followed.

In this study, exome sequencing of a single proband yielded a molecular diagnosis for sibs with a complex clinical presentation and significantly overlapping differential diagnoses. Utilizing a model of recessive pattern of inheritance and expectation of amino acid change of damaging effect to protein function enabled us to quickly focus attention onto 17 candidate genes. Within this short list of genes, the homozygous damaging missense mutation in a highly conserved nucleotide position in WDR35 was clearly pathogenic. The accurate molecular diagnosis of this family exemplifies the utility and benefit ofexome sequencing as a very powerful tool in the diagnosis of Mendelian disorders and enabled us to broaden and refine our understanding of Sensenbrenner and short rib polydactylies.

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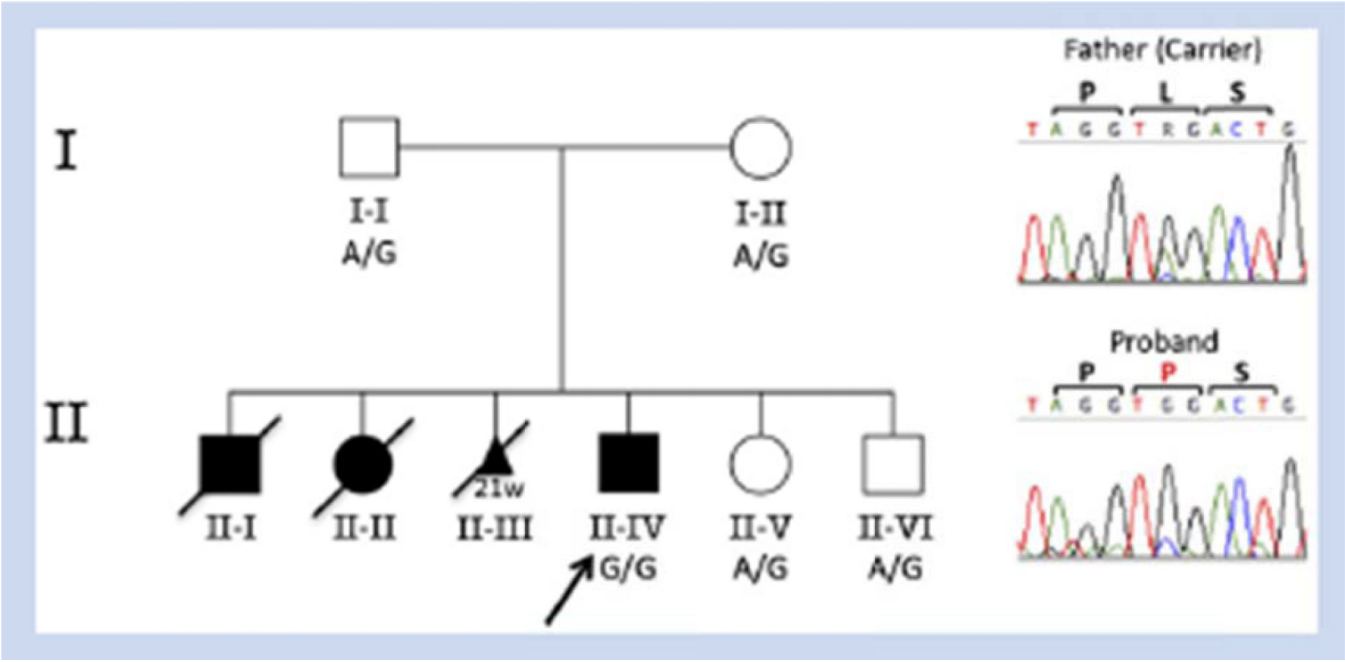

Figure 1.

Pedigree of family with SRP and liver dysplasia. Proband is noted by black arrow. Sequence chromatograms for each genotype in the family are shown. The DNA sequence is displayed along with the corresponding amino acid sequence.

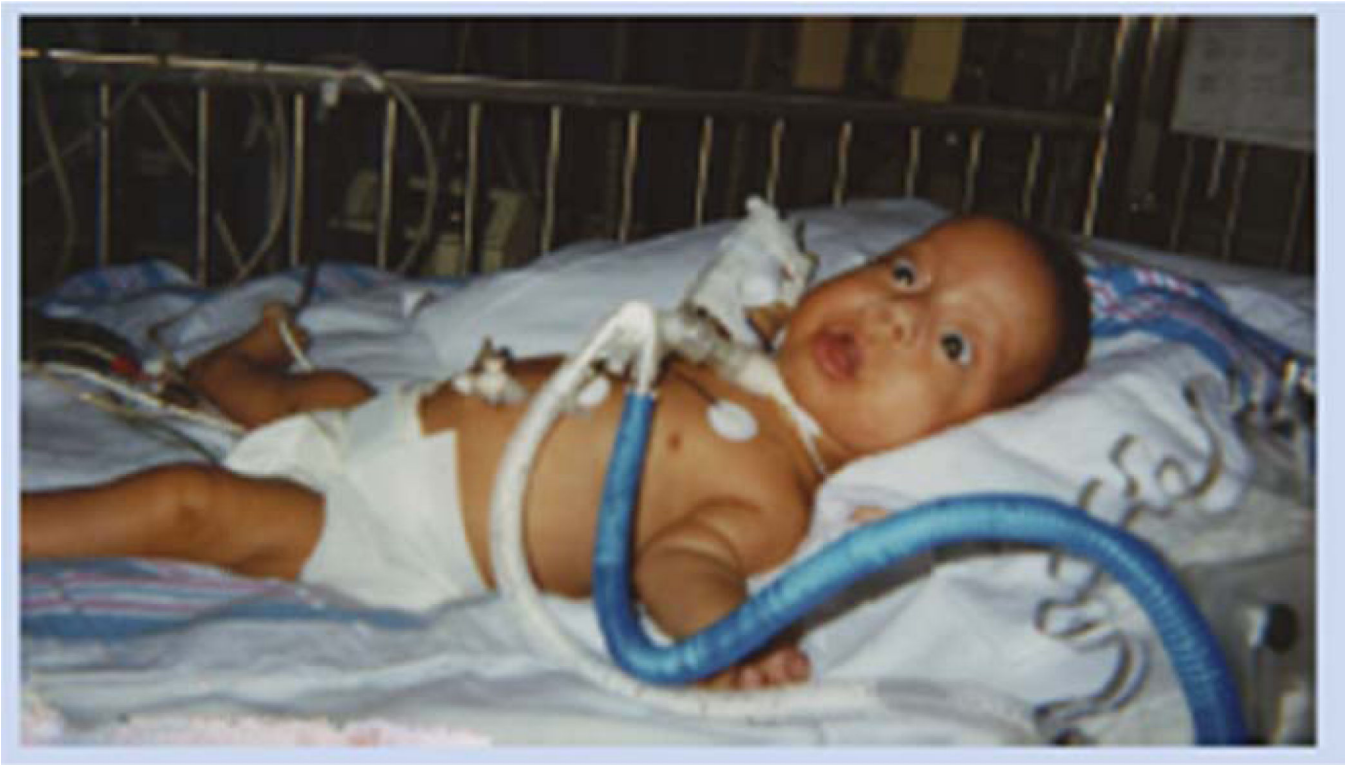

Figure 2.

Picture of first affected deceased male (Patient 1/II-I) during infancy. Note dysmorphic features with shallow orbits, tall forehead, and prominence of metopic region.

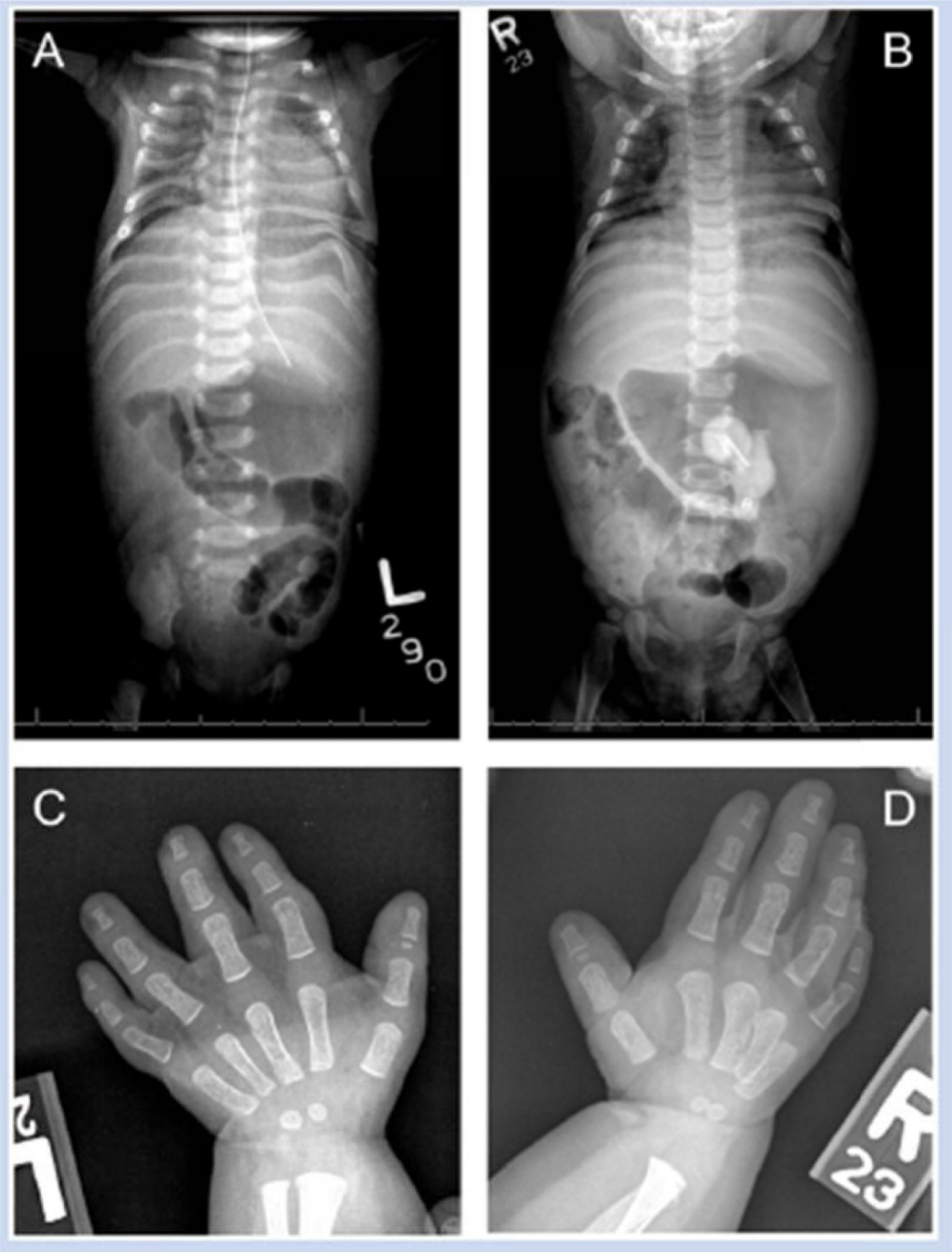

Figure 3.

A: AP view of the chest from Patient 2 (II-II). A: Note AP view of the chest with narrowing and rib deformities, in some cases displaying coat hanger appearance. B: AP view of the chest from II–IV at approximately 1 year of age. The chest narrowing is still present, broad ribs and some improvement of the rib deformities. C,D: AP view of both hands of II-IV at approximately 1 year of age. Note shortening and terminal blunting of the distal phalanges.

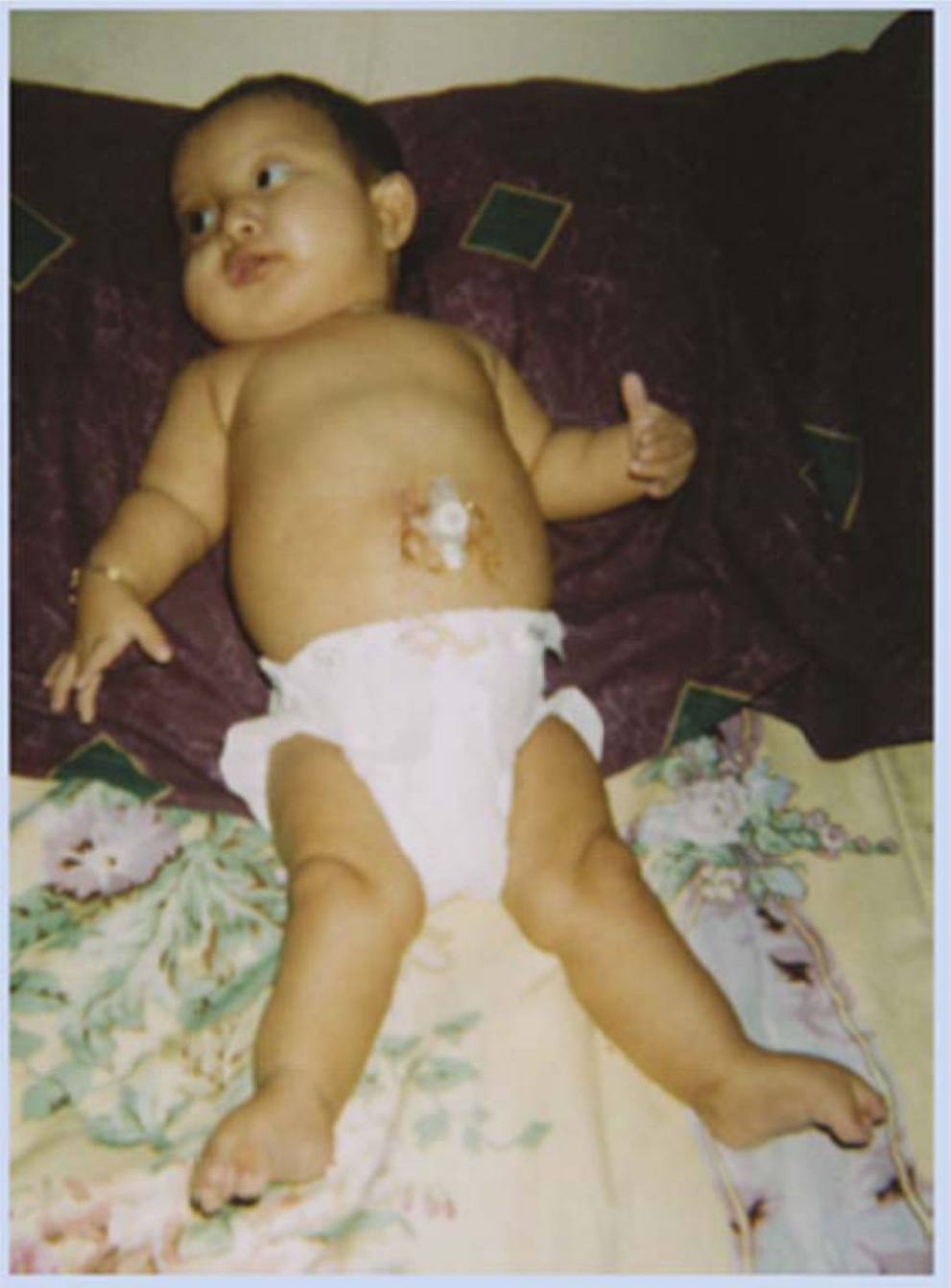

Figure 4.

Picture of affected deceased female (Patient 2/II-II) at around 6 months of age. She has very similar features to her deceased brother. Observe the narrow chest, tall forehead, unfolded and low-set ears, midface hypoplasia, micrognathia, and a short neck.

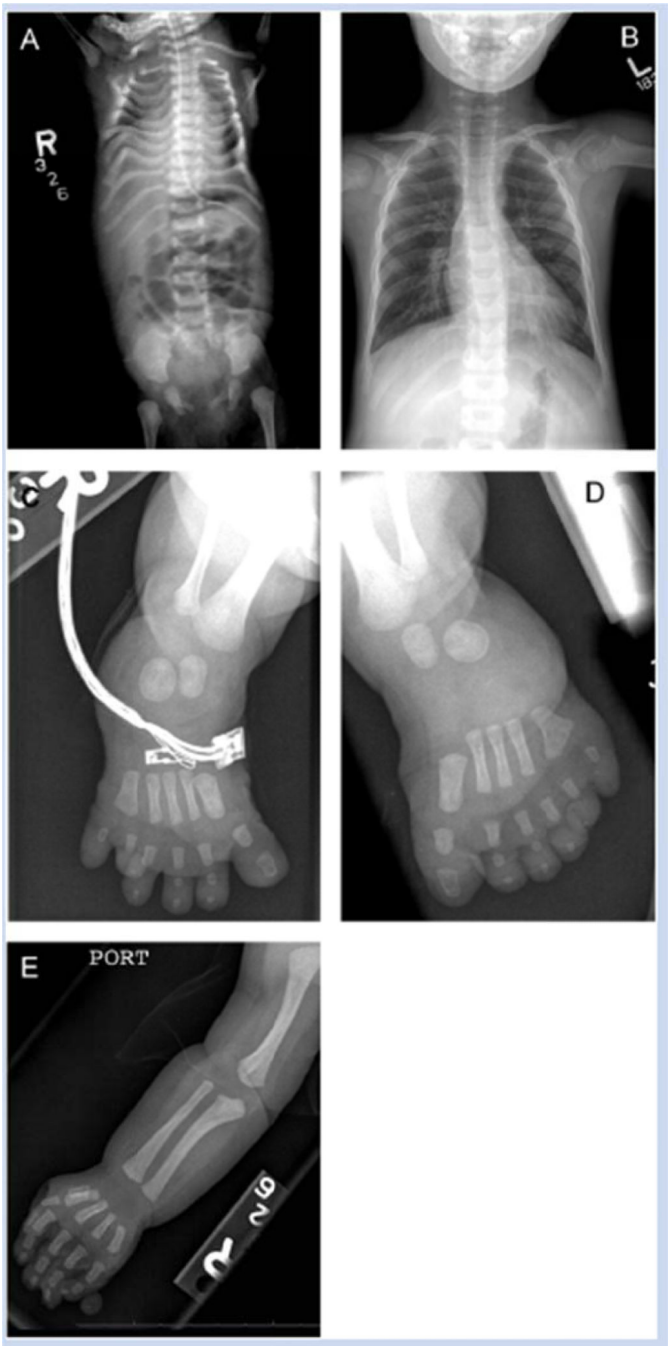

Figure 5.

A: Limited babygram AP view of Patient 4 (II–IV). The thorax is narrow and the ribs are malformed with some displaying a coat hanger shape appearance. Hips, spine, and proximal femurs are normal. B: Chest AP view at 41/2 years of age. The thorax remains narrow. The ribs have normalized compared to early images. C: Right foot showing post-axial polydactyly and broadened Y-shaped 5th metatarsal. D: Left foot with post-axial polydactyly and broadened Y-shaped 5th metatarsal. E: Right arm shows mild mesomelic shortening and a post-axial polydactyly with a very small digit barely attached to the ulnar aspect of the hand.

Table 1

This Table Highlights the Most Salient Clinical Features Seen in Our Family in Comparison to Previously Reported Patients with WDR35 Mutations

	This issue, Patient 1	This issue, Patient 2	This issue, Patient 3	Thin issue, Patient 4	Kannu et al. [2007], Patient 1	Kannu et al. [2007], Patient 2	Gilissen et al. [2010], Patient 1	Gilissen et al. [2010], Patient 2
Hydrops	+	+	+	–	+	+	–	–
Polyhydramnios	+	–	+	–	–	–	–	–
Cystic hygroma	+	–	+	–	+	+	–	–
Dolicocephaly	+	+	–	+	–	–	+	+
Prominent/tall forehead	+	+	–	+	–	–	+	+
Craniosynostosis	+	–	–	–	–	–	+	+
Low-set simple ears	+	+	–	–	–	–	+	+
Palate	Arched	Cleft	–	Arched	Cleft	Cleft	–	–
Midface hypoplasia	–	+	–	+	–	–	–	–
Short stature	+	+	–	+	+	+	+	+
Polydactyly	+	+	–	+	+	+	+	–
Brachydactyly	+	+	–	+	+	–	+	+
Syndactyly	–	–	–	+	+	–	+	–
Clinodactyly	–	–	+	+	–	–	–	+
Narrow thorax	+	+	–	+	+	+	+	+
Short or abnormal ribs	+	+	–	+	+	+	–	–
Pulmonary hypoplasia	+	–	–	–	+	–	–	–
Shortened limbs	+	+	–	+	+	+	+	+
Hepatomegaly	+	+	+	+	–	–	–	–
Abnormal liver Function tests	+	+	–	+	–	–	–	–
Abnormal liver biopsy	+	+	–	+	–	–	–	–
Spleen abnormalities	–	+	–	–	?	–	–	–
Penal abnormalities	+	+	–	+	+	–	–	–
Heart defects	+	+	–	+	–	–	–	–
Developmental delay	+	+	N/A	+	N/A	N/A	–	–
Other		Brain abn.	Dup calc		Hyp	Int Malr		

Hyp, hypos padlas; int mair, intestinal malrotation; dup cal, duplicated calculations.