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## Letter to the Editor

# Novel *WDR35* mutations in patients with cranioectodermal dysplasia (Sensenbrenner syndrome)

*To the Editor*:

Cranioectodermal dysplasia (CED, Sensenbrenner syndrome, OMIM 218330) is a rare autosomal recessive ciliopathy characterized by craniosynostosis, dolichocephaly, narrow chest, sparse hair, epicanthal folds, microdontia, brachydactyly, joint laxity, ophthalmological problems (nystagmus, myopia, and retinal dystrophy), nephronophthisis and cystic liver disease. CED is a genetically heterogeneous disorder, and mutations have been reported in *IFT122*, *WDR35*, *C14orf179* and *WDR19* (1–5). The products of all four genes are part of the intraflagellar transport complex A (IFT-A), a major complex for dynein-driven retrograde flagellar transport in cilia (6).

Here, we report on the detection of novel *WDR35* mutations in two unrelated CED patients.

The clinical features of both patients are listed in Table 1.

Patient 1 was born to remotely consanguineous Greek parents. She had short stature, short limbs, brachydactyly, dolichocephaly, frontal bossing, ptosis, micrognathia, high palate, low-set ears, fine sparse hair and dysplastic nails (Fig. 1a,b). Craniosynostosis was surgically corrected at the age of 2 months. Psychomotor development was retarded (walking at age 16 months and talking at age 2 years). X-ray examinations revealed narrow thorax with dysplastic ribs, bowed femora with abnormal epiphyses, short ulnae, brachydactyly, short metacarpals, short and bowed tibiae, short metatarsals and a triphalangeal hallux (Fig. 1c–e). Chronic renal failure was noticed in the first year of life. A brain magnetic resonance imaging (MRI) scan at the age of 2 years revealed a large cisterna magna and slight cortical atrophy.

Patient 2 was born to non-consanguineous parents. She had dolichocephaly, craniosynostosis, bilateral nystagmus, short limbs, brachydactyly, fine sparse hair, frontal bossing, micrognathia, low-set ears and widely spaced teeth (Fig. 1f,g). Renal dysfunction was noted at the age of 14 months. She received a kidney transplant at the age of 5 years. Hepatic cystic disease was detected at the age of 4 years. Psychomotor development was delayed (walking at the age of 3 years and no words at the age of 5 years). A brain MRI scan at the age of 4 years revealed no abnormalities.

In patient 1, analysis of the 28 coding exons and flanking intronic regions of *WDR35* revealed a homozygous missense mutation (c.A2912G; p.Tyr971Cys) in exon 25 (Fig. S1a). Tyrosine at position 971 is a highly conserved amino acid with a PhyloP score of 0.996. Both parents were heterozygous carriers of the mutation.

In patient 2, we detected a heterozygous missense mutation (c.T504A; p.Ser168Arg) in exon 6 which was inherited from the father and a heterozygous nonsense mutation in exon 18 (c.T1922G; p.Leu641X) which was inherited from the mother (Fig. S1b,c). Serine at position 168 is a highly conserved amino acid with a PhyloP score of 0.407. We excluded the presence of these mutations in 300 control chromosomes.

To date, *WDR35* mutations have only been reported in two other CED patients (2). Mutations in *WDR35* have recently also been identified in fetuses with short rib-polydactyly syndrome (SRP) (5, 7). SRP affects the same organs as CED, but with much greater severity (Table 1). The milder phenotype in CED might be due to some residual function of the CED-associated *WDR35* alleles. Functional studies will be needed to elucidate the biological consequences of different *WDR35* mutations.

Clinically, the two patients reported here share numerous features with those reported by Gilissen et al. (Table 1). Major clinical differences are developmental delay and the renal problems which were not reported in the Gilissen et al. patients. Additional patients with *WDR35* mutations need to be identified to get more insight into the clinical variability of *WDR35*-associated CED and to establish comprehensive genotype–phenotype correlations.

In conclusion, the patients reported here provide additional evidence that mutations in *WDR35* are associated with CED, and they broaden the spectrum of clinical features. This will eventually also contribute to a better understanding of the function of the *WDR35* gene product and its role in intraflagellar transport.

### Acknowledgements

We thank the parents of the patients for their support.

Table 1. Clinical details of patients and fetuses with *WDR35* mutations

| Patient | Gilissen et al., patient 1 | Gilissen et al., patient 2 | Present patient 1 | Present patient 2 | Mill et al., family of Kannu et al. therein, fetus 1 | Mill et al., family of Kannu et al. therein, fetus 2 | Mill et al., sporadic fetus |
|---|---|---|---|---|---|---|---|
| Clinical diagnosis | CED | CED | CED | CED | SRP | SRP | SRP |
| Sex | Male | Male | Female | Female | Male | Male | N.A. |
| Mutation (DNA) | c.1877A>G; c.25-2A>G | c.2891delT; c.2623G>A | c.A2912G | c.T504A; c.T1922G | Genomic deletion of 2847 bp | Genomic deletion of 2847 bp | c.1633C>T; c.781T>C |
| Mutation (Protein) | p.E626G; p.I9TfsX7 | p.P964LfsX15; p.A875T | p.Y971C | p.S168R; p.L641X | Deletion of exon 5 | Deletion of exon 5 | p.R545X; p.W261R |
| Age at examination | 7 years | 9 years | 8 years | 5 years | Pregnancy terminated at 15 weeks of gestation | Pregnancy terminated at 12 weeks of gestation | Pregnancy terminated at 13 weeks of gestation |
| Height | <3rd centile | <3rd centile | <3rd centile | <3rd centile | N.A. | N.A. | N.A. |
| Dolichocephaly | + | + | + | + | N.A. | N.A. | N.A. |
| Craniosynostosis | Surgically corrected at age 1 year | Surgically corrected at age 1 year | Surgically corrected at age 2 months | Surgically corrected at age 1 year | N.A. | N.A. | N.A. |
| Frontal bossing | + | + | + | + | N.A. | N.A. | N.A. |
| Fine, sparse hair | − | + | + | + | N.A. | N.A. | N.A. |
| Narrow palpebral fissure | + | + | − | + | N.A. | N.A. | N.A. |
| Hypermetropia | + | − | − | − | N.A. | N.A. | N.A. |
| Nystagmus | − | − | − | + | N.A. | N.A. | N.A. |
| Ptosis | Unilateral | − | + | − | N.A. | N.A. | N.A. |
| Hypertelorism | + | + | + | + | N.A. | N.A. | N.A. |
| Strabismus | + | − | − | + | N.A. | N.A. | N.A. |
| Low-set ears | + | + | + | + | N.A. | N.A. | N.A. |
| Simple ears | + | + | + | − | N.A. | N.A. | N.A. |
| Everted lower lip | + | + | + | − | N.A. | N.A. | N.A. |
| Micrognathia | + | − | + | + | N.A. | N.A. | N.A. |
| Widely spaced teeth | + | + | + | + | N.A. | N.A. | N.A. |
| Hypoplastic teeth | + | + | + | + | N.A. | N.A. | N.A. |
| Fused teeth | + | + | − | − | N.A. | N.A. | N.A. |
| Short neck | + | + | + | + | N.A. | N.A. | N.A. |
| Narrow thorax/short ribs | + | + | + | + | + | + | + |
| Pectus excavatum | + | + | + | + | N.A. | N.A. | N.A. |
| Short limbs | + | + | + | + | + | + | Extreme micromelia |
| Brachydactyly | + | + | + | + | N.A. | N.A. | N.A. |

Table 1. Continued

| Patient | Gilissen et al., patient 1 | Gilissen et al., patient 2 | Present patient 1 | Present patient 2 | Mill et al., family of Kannu et al. therein, fetus 1 | Mill et al., family of Kannu et al. therein, fetus 2 | Mill et al., sporadic fetus |
|---|---|---|---|---|---|---|---|
| Webbing of fingers | + | + | + | + | N.A. | N.A. | N.A. |
| Postaxial polydactyly | + | − | − | − | + | + | + |
| Triphalangeal hallux | − | − | + | − | N.A. | N.A. | N.A. |
| Restricted flexion of fingers | + | − | − | − | N.A. | N.A. | N.A. |
| Toe syndactyly | + | − | − | − | N.A. | N.A. | N.A. |
| Bilateral sandal gap | − | + | − | − | N.A. | N.A. | N.A. |
| Joint laxity | + | + | + | + | N.A. | N.A. | N.A. |
| Inguinal hernia | + | + | − | − | N.A. | N.A. | N.A. |
| Renal disease | − | − | + | + | + | N.A. | N.A. |
| Hepatic disease | − | − | − | + | N.A. | N.A. | N.A. |
| Recurrent lung infections | + | − | + | − | Fetus | Fetus | Fetus |
| Intelligence | Normal | Normal | Developmental delay | Developmental delay | Fetus | Fetus | Fetus |
| Brain malformation | − | − | Slight cerebral atrophy | − | N.A. | N.A. | N.A. |
| Behaviour | Happy, friendly | Happy, friendly | Happy, friendly | Happy, friendly | Fetus | Fetus | Fetus |
| Additional features | − | − | − | − | Hypospadias, bowing of limbs | Bowing of limbs, cleft palate, malrotation of the gut | 'Facial abnormalities' (not specified) |

CED, cranioectodermal dysplasia; N.A., not available; SRP, short rib-polydactyly syndrome.

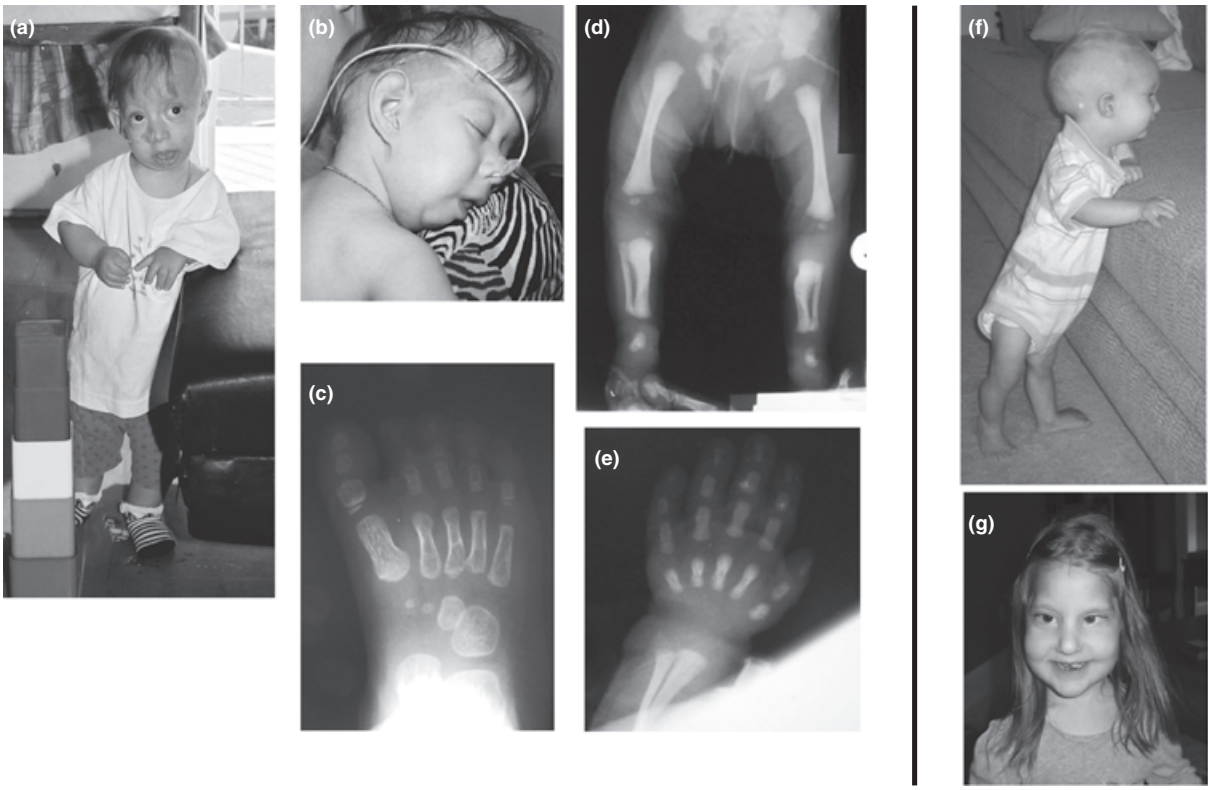


*Fig. 1.* Patient 1 at age 2 years. Note disproportionate short stature, frontal bossing, sparse hair, micrognathia and low-set ears (a, b). X-rays show triphalangeal hallux (**c**), bowed femora and tibiae (**d**), and brachydactyly (**e**). Patient 2 at age 13 months (**f**) and 5 years (**g**). Note dolichocephaly, short limbs, sparse hair and low-set ears.

## Supporting Information

The following Supporting information is available for this article:

Fig.SI.Chromatograms showing the *WDR35* missense mutation c.A2912G (p.Tyr971Cys) in the homozygous state in patient 1 and in the heterozygous state in the parents (**a**); the heterozygous missense mutation c.T504A (p.Ser168Arg) in patient 2 and her mother (**b**), and the heterozygous nonsense mutation c.T1922G (p.Leu641X) in patient 2 and her father (**c**).

Additional Supporting information may be found in the online version of this article.

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