De novo 14q24.2q24.3 microdeletion including IFT43 is associated with intellectual disability, skeletal anomalies, cardiac anomalies, and myopia

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We report an 11-year-old girl with mild intellectual disability, skeletal anomalies, congenital heart defect, myopia, and facial dysmorphisms including an extra incisor, cup-shaped ears, and a preauricular skin tag. Array comparative genomic hybridization analysis identified a de novo 4.5-Mb microdeletion on chromosome 14q24.2q24.3. The deleted region and phenotype partially overlap with previously reported patients. Here, we provide an overview of the literature on 14q24 microdeletions and further delineate the associated phenotype. We performed exome sequencing to examine other causes for the phenotype and queried genes present in the 14q24.2q24.3 microdeletion that are associated with recessive disease for variants in the non-deleted allele. The deleted region contains 65 protein-coding genes, including the ciliary gene IFT43. Although Sanger and exome sequencing did not identify variants in the second IFT43 allele or in other IFT complex A-protein-encoding genes, immunocytochemistry showed increased accumulation of IFT-B proteins at the ciliary tip in patient-derived fibroblasts compared to control cells, demonstrating defective retrograde ciliary transport. This could suggest a ciliary defect in the pathogenesis of this disorder.

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Key words: congenital heart defect; intellectual disability; 14q24 microdeletion; skeletal anomalies; IFT43; cilia

INTRODUCTION

Interstitial deletions encompassing the 14q24.2q24.3 region are rare and associated with intellectual deficit in the majority of patients. Defining a consistent clinical phenotype and determining the causal genes within the deletion remains a challenge. Recently, two patients with overlapping 14q24 deletion were reported: one with a 5.4-Mb deletion and mild intellectual disability (ID), atrial septal defect (ASD), small thumbs, and facial dysmorphisms [Oehl-Jaschkowitz et al., 2014]; and one with a 5.3-Mb deletion and mild psychomotor delay, ASD, short digits, facial dysmorphisms, and focal epilepsy [Tassano et al., 2014]. The DECIPHER database reports 13 patients with overlapping copy number loss in the 14q24 region, and clinical features that include ID in seven patients. Thereafter, we provide an overview of the literature on 14q24 microdeletions and further delineate the associated phenotype. We performed exome sequencing to examine other causes for the phenotype and queried genes present in the 14q24.2q24.3 microdeletion that are associated with recessive disease for variants in the non-deleted allele. The deleted region contains 65 protein-coding genes, including the ciliary gene IFT43. Although Sanger and exome sequencing did not identify variants in the second IFT43 allele or in other IFT complex A-protein-encoding genes, immunocytochemistry showed increased accumulation of IFT-B proteins at the ciliary tip in patient-derived fibroblasts compared to control cells, demonstrating defective retrograde ciliary transport. This could suggest a ciliary defect in the pathogenesis of this disorder.
patients, heart defect in one patient, and preauricular skin tag in one patient [Firth et al., 2009] (Online Supplemental Table S1).

Here, we report a patient with a de novo 4.5-Mb 14q24.2q24.3 microdeletion with clinical features as previously reported in patients with overlapping 14q24 deletions: mild ID, skeletal anomalies including small thumb, ASD, and facial dysmorphisms including cup-shaped ears and preauricular skin tag. We explored genetic and environmental factors that could have contributed to the phenotype and further characterized the phenotypic spectrum associated with 14q24 microdeletions. Finally, we investigated whether the distinctive skeletal, ocular, and ectodermal abnormalities in the index patient could reflect a ciliary defect associated with deletion of the gene encoding intraflagellar transport protein 43 (IFT43) (MIM# 614068), one of the 65 protein-coding genes located within the 14q24.2q24.3 microdeletion.

CLINICAL REPORT

The index patient is the second child of non-consanguineous Caucasian parents; she has a healthy older brother. Mother of the patient has a history of insulin-dependent diabetes type I. The patient was born after a full-term pregnancy, with birth length: 51 cm (0 SD), weight: 3,505 g (0 SD), and OFC: 32.5 cm (−1.2 SD). At 11 years of age, she presented at the genetics clinic with mild ID (TIQ 66 measured with WISC-III, VIQ 71, PIQ 66) and multiple congenital malformations. Her height was 141.5 cm (−0.4 SD), weight: 35.6 kg (+0.5 SD), and OFC: 52 cm (−0.4 SD). She had a wide nasal bridge, cup-shaped ears, long limbs (sitting-height/length ratio 0.49 [−1.8 SD], arm span 157.2 cm [+2 SD]) and digits, and a short, broad thorax (Fig. 1). Previous medical history mentioned hip dysplasia, deviation of the sacrum with dysplastic corpora and lipomas around the conus and proximal filum terminale. On the right hand she had a small thumb for which she underwent pollicization of the index finger, contracture of the proximal interphalangeal joint of the third finger, and flexion contracture of the wrist. Her preauricular skin tag and extra central incisor had been surgically removed. In addition, she had a ventricular septal defect that had closed without intervention and a large ASD that required surgical closure. Ultrasound of the abdomen showed normal kidneys. She had astigmatism and a large ASD that required surgical closure. Ultrasound of ventricular septal defect that had closed without intervention. In addition, she had a contracture of the wrist. Her preauricular skin tag and extra central proximal interphalangeal joint of the third finger, and flexion minale. On the right hand she had a small thumb for which she had been surgically removed. In addition, she had a ventricular septal defect that had closed without intervention and a large ASD that required surgical closure. Ultrasound of the abdomen showed normal kidneys. She had astigmatism and a large ASD that required surgical closure.
shows a whole-field image of the cells. Patient-derived fibroblasts showed a statistically significant increase in cells with substantial accumulation of IFT88 in the ciliary tip compared to control fibroblasts ($P = 0.0002$). There was no statistically significant difference in primary cilia length or number between patient- and control cells (data not shown).

**DISCUSSION**

We describe a patient with mild ID, ASD, skeletal anomalies, and facial dysmorphisms who has a de novo 14q24.2q24.3 microdeletion encompassing 65 protein-coding genes. Mild ID and congenital heart defect have been reported in all four previously reported patients with a 14q24 deletion [Oehl-Jaschkowitz et al., 2014; Tassano et al., 2014] and small or proximally-set thumb in two. However, the deletion in the index patient does not overlap with the smallest region of overlap of the previously reported patients (Online Supplemental Fig. S5), suggesting the effect of multiple loci on 14q24 or elsewhere in the genome associated with these features. Haploinsufficiency of genes located within the deletion could contribute to the phenotype. Heterozygous mutation in TGFB3 (MIM# 190230) has been reported in patient with arachnodactyly and marked contractures of the proximal interphalangeal joints that were also observed in the index patient [Rienhoff et al., 2013] and in four other patients with Marfan and Loeys–Dietz-like phenotypes [Matyas et al., 2014; Kuechler et al., 2015], suggesting that this gene could be involved in skeletal features. The mouse homologue of VSX2 (MIM# 142993) was demonstrated to be a regulator of formation of the lumbosacral region, possibly accounting for sacral hypoplasia [Wellik and Capecchi, 2003]. Previously, C14orf169 (MIM# 611919), NUMB (MIM# 603728), and PSEN1 (MIM# 104311) have been proposed
to contribute to skeletal, cardiac, and neurological anomalies [Tassano et al., 2014]. Maternal diabetes mellitus, a risk factor for sacral hypoplasia and congenital heart defect, could also have contributed to the phenotype [Al Kaissi et al., 2008; Liu et al., 2013].

Because of the combination of skeletal, ectodermal, and ocular features in the index patient, we investigated a ciliary defect on the cellular level and found excess accumulation of IFT88 in ciliary tips of patient-derived fibroblasts. Accumulation of IFT-B proteins (marked by IFT88) in ciliary tips indicates impaired retrograde ciliary transport [Cole, 2003; Arts et al., 2011], characteristic of cranioectodermal dysplasia (CED) (MIM# 614099) [Arts et al., 2011; Lin et al., 2013]. Biallelic mutations in IFT43 have been identified in a family with CED [Arts et al., 2011]. Deletion of IFT43 could therefore be a modifier of the 14q24 microdeletion syndrome phenotype. However, there are differences between the phenotype of the index patient and CED (long fingers and limbs instead of short fingers and limbs, a short, broad thorax instead of a narrow thorax, and an extra central incisor instead of hypodontia), and we did not detect mutations in or imprinting of the non-deleted IFT43 allele. Exome sequencing was used to examine oligogenic inheritance and modifier genes, which have been reported in ciliopathies [Katsanis et al., 2001]. Although we did not identify variants in other ciliopathy-associated genes, we cannot exclude variants in genes encoding unknown regulators of IFT-A or regulatory elements of ciliopathy-associated genes.

In conclusion, we report a patient with mild ID, skeletal anomalies, congenital heart defect, myopia, and facial dysmorphism caused by a de novo 14q24.2q4.3 microdeletion. The deletion encompasses 65 genes and shows partial overlap with previously reported 14q24 microdeletions. Patient cells showed defective retrograde ciliary transport. This could be associated with haploinsufficiency of IFT43; however, additional variants in ciliary genes or gene regulatory elements are required to support the role of a ciliary defect in the pathogenesis of skeletal, ocular, and ectodermal features. Further patients with overlapping deletions are needed to confirm the pathophysiological mechanisms underlying this phenotype.

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REFERENCES


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