DATA REPORT

A novel *BBS10* mutation identified in a patient with Bardet–Biedl syndrome with a violent emotional outbreak

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We report a 10-year-old girl with Bardet–Biedl syndrome caused by a novel mutation in the *Bardet–Biedl syndrome 10* (*BBS10*) gene. She had multiple malformations, including a dysmorphic face, postaxial polydactyly, polycystic kidney and amblyopia. She presented with typical BBS features, including intellectual disability with emotional outbursts and mild obesity. Whole-exome sequencing identified compound heterozygous mutations with NM_024685.3:c.1677C>A [p.(Tyr559*)] and c.1974T>G [p.(Tyr658*)]. To our knowledge, the latter mutation has never been reported previously.

Bardet–Biedl syndrome (BBS; MIM 209900) is a rare autosomal recessive ciliopathy that is clinically characterized by obesity, pigmentary degeneration of the retina, postaxial polydactyly, genito-urinary abnormalities and intellectual disability with autistic spectrum disorder.[1] To date, 21 mutations in *BBS* genes have been reported in patients with BBS.[2,3] The cellular basis of BBS is closely linked to the dysfunction of the primary cilium.[4] Here, we present a 10-year-old girl with BBS caused by a novel mutation of the *BBS10* gene as confirmed by whole-exome sequencing.

The 10-year-old patient was the first child born to non-consanguineous Japanese healthy parents. The family history was unremarkable. The girl was born at 40-weeks of gestation with vacuum extraction but did not suffer any asphyxia. The birth weight was 3226 g. She exhibited dysmorphic features, including an upslanted palpebral fissure, hypertelorism, pointed chin and high arched palate as well as postaxial polydactyly of the right hand and left foot, polycystic kidneys and an atrial septum defect that was closed at 3 months of age. Her motor and intellectual developments were delayed since early childhood; she could not walk or speak a meaningful word at presentation. Brain MRI and electroencephalogram revealed no abnormalities. Various blood tests, including amino acid analysis, lactate and pyruvate, were within the normal limits. Karyotype analysis revealed a normal female karyotype of 46,XX.

Rumination was present at the age of two but disappeared spontaneously a few years later. This condition recurred at the age of nine, but faded out again at a later stage. An ophthalmologic examination revealed severe myopia with optic disk excavation but no pigmentary degeneration of the retina. She exhibited daily emotional outbreaks and sleep disturbances that required some sedative drugs, such as carbamazepine, cyproheptadine and risperidone, since early childhood. Mild obesity was evident, although neither type 2 diabetes nor hypertension was recognized. An echogram of the kidneys at the age of 10 years identified a few cysts around the renal pelvis and a high echoic area in the medulla of the bilateral well-developed kidneys.

The estimated GFR was normal for her age, which suggests stable kidney function.

During the course of a whole-exome analysis, informed consent from the parents and approval from the University of Tsukuba Hospital review board were obtained for the molecular studies. DNA was extracted from peripheral blood samples obtained from the patient and her parents. A whole-exome analysis was performed using a HiSeq 2500 platform (Illumina, San Diego, CA, USA) and a SureSelectXT Human All Exon Kit V6 (Agilent Technologies, Santa Clara, CA, USA). The sequencing reads were aligned to the reference human genome sequence (hs37d5) using Burrows-Wheeler Transform 3 and local realignment around the indels, and base quality score recalibration was performed using the Genome Analysis Toolkit 4. Duplicate reads were removed using Picard (http://picard.sourceforge.net). Nonsynonymous coding variants, splice acceptor and donor site variants, and frameshift-coding indels were filtered against dbSNP137, the 1000 Genomes Project (http://www.1000genomes.org/), ESP6500, Japanese Genome Variation Database (https://ijgvd.megabank.tohoku.ac.jp/) or the Japanese SNP dataset of 1208 normal individuals (Human Genetic Variation Browser: http://www.genome.med-kyoto-u.ac.jp/SnpDB). The mean coverage was more than 60 reads.

Whole-exome sequencing revealed compound heterozygous mutations with NM_024685.3:c.1677C>A [p.(Tyr559*)] and c.1974T>G [p.(Tyr658*)] in *BBS10* (OMIM #615987), which were inherited from each of the parents (Figure 1). To our knowledge, the latter mutation has never been reported previously.

Mutations in at least 21 *BBS* genes have been identified thus far in BBS.[2,3] These *BBS* genes play a crucial role in the formation and function of the cilium, which is required for Hedgehog and Wnt signal transduction.[4,5] Eight BBS proteins (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9 and BBIP10/BBS18) physically interact to form a complex 'BBSome,' which functions as a coat for vesicles destined to the cilium, whereas BBS10 forms a CCT/TRiC/BBS chaperonin complex with BBS6 and BBS12 to mediate the assembly of the BBSome.[4,6]

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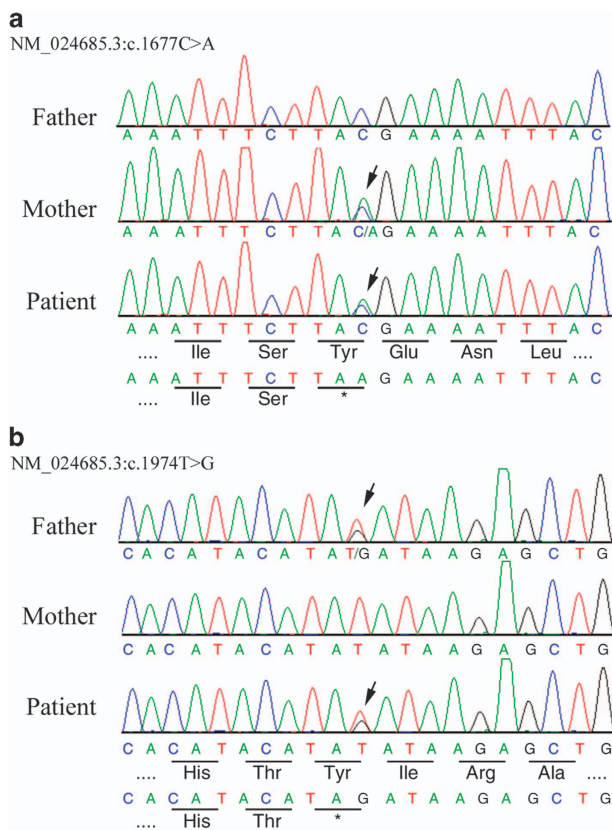
Figure 1. Sanger sequences of the patient and parents in *BBS10* and predicted amino acid sequences. (**a**) The patient and mother have NM_024685.3:c.1677C>A mutation (arrow), which causes the termination of the BBS10 protein. (**b**) The patient and father have NM_024685.3:c.1974T>G mutation (arrow), which causes the termination of the protein. Thus, the patient has compound heterozygous mutations in the *BBS10* gene.

The BBS10 protein has three chaperonin functional domains: the equatorial domain, the intermediate domain and the apical domain.[7] One mutation (NM_024685.3:c.1677C>A) causes the termination of the BBS10 protein in the intermediate domain,[8] and another (c.1974T>G) causes termination in the equatorial domain, which is responsible for ATP binding and hydrolysis, to act on non-native polypeptides and facilitate their folding or unfolding.[7]

Approximately 16 percent of BBS cases result from mutations in the *BBS10* gene.[9] Although there are no apparent phenotypic differences between patients with mutations in genes associated with the BBSome and those with mutations associated with the chaperonin complex,[1] previous reports of patients with mutations in the *BBS10* gene and of *BBS10* null mutant mice suggest that there could be some tendency for differences in clinical symptoms. The *BBS10*^{−/−} mouse exhibits obesity, retinal degeneration, structural defects in the glomeruli, polyuria associated with high circulating arginine vasopressin concentrations, and vacuolated, yet ciliated, renal epithelial cells.[10] Additionally, severe renal disease has been reported in French patients with mutations in the *BBS6*, *BBS10* and *BBS12* genes.[11]

We compared the clinical symptoms in our patient with those of patients who were reported on in a review article (Table 1).[2] Our patient lacked pigmentary degeneration of the retina and hypogonadism, which are the primary features of BBS. Although our patient developed severe myopia with optic disk excavation since early childhood, a detailed fundus examination did not show retinal degeneration so far at the age of 10 years. An electroretinogram has yet to be performed. Because 93% of

Table 1. Comparison of phenotypes of reported patients with *BBS10* gene mutations and our patient

	Reported cases	Our case
Primary features		
Pigmentary degeneration of the retina	+	−
Polydactyly	+	+
Obesity	+	+
Learning problems	+	+
Hypogonadism	+	−
Renal dysfunction	+	+
Secondary features		
Liver fibrosis	+	−
Diabetes mellitus	+	−
Neuro-motor problem	NA	−
Speech deficits	NA	+
Behavioral problem	NA	+
Facial dysmorphism	+	+
Dental irregularities	NA	+
Developmental delay	+	+
Hypertension	NA	−
Cardiac problem	NA	−
Hearing loss	+	−
Anosmia/hyposmia	+	−
Respiratory problem	+	−
Hypothyroidism	NA	−
Atopy	NA	−
Syndactyly	NA	−

Abbreviation: NA, not available (based on data by Khan *et al*[2]).

patients with BBS exhibit retinal degeneration, a serial ophthalmologic examination is needed.[1] Because the patient is at the pre-pubertal age, tests for hypogonadism were not performed. With regard to the secondary features, the facial dysmorphism observed in our patient was compatible with that reported previously.[1] Behavioral problems might not be a main feature of patients with *BBS10* gene mutations.[2] Our patient has displayed violent emotional outbreaks and sleep disturbances since the age of 2 years; various medications were used to treat these symptoms. Furthermore, rumination, which has not been reported previously in BBS, was observed during early and later childhood, but the patient did not vomit during rumination, and the latter did not affect body growth. Further studies are needed to determine the relationship between *BBS10* gene mutations and rumination.

In conclusion, we identified a novel *BBS10* mutation (NM_024685.3:c.1974T>G, [p.(Tyr658*)]) in a Japanese girl who presented with relatively typical symptoms of BBS.

COMPETING INTERESTS

The authors declare no conflict of interest.

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