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.

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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, genitourinary 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 To our knowledge, the latter mutation has never been reported previously. 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.

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.5,6 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.5,6
The BBS10 protein has three chaperonin functional domains: the equatorial domain, the intermediate domain and the apical domain. One mutation (NM_024685.3:c.1677C->A) causes the termination of the BBS10 protein in the intermediate domain, 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.

Approximately 16 percent of BBS cases result from mutations in the BBS10 gene. 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, 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. Additionally, severe renal disease has been reported in French patients with mutations in the BBS6, BBS10 and BBS12 genes.

We compared the clinical symptoms in our patient with those of patients who were reported on in a review article (Table 1). 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 patients with BBS exhibit retinal degeneration, a serial ophthalmologic examination is needed. 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. Behavioral problems might not be a main feature of patients with BBS10 gene mutations. 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.

HGV DATABASE
The relevant data from this Data Report are hosted at the Human Genome Variation Database at http://dx.doi.org/10.6084/m9.figshare.hgv.1387 and http://dx.doi.org/10.6084/m9.figshare.hgv.1390.

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COMPETING INTERESTS
The authors declare no conflict of interest.

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