DATA REPORT

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A novel compound heterozygous mutation in *TTC8* identified in a Japanese patient

Shigeru Sato¹, Takeshi Morimoto^{1,2}, Kikuko Hotta³, Takashi Fujikado^{1,2} and Kohji Nishida¹

Abstract

Bardet–Biedl syndrome (BBS), characterized by rod-cone dystrophy, postaxial polydactyly, central obesity, hypogonadism, renal abnormalities, and mental retardation, is a rare autosomal recessive disorder. To date, 21 causative genes have been reported. Here we describe a Japanese BBS patient with a novel compound heterozygous mutation in *TTC8*. To the best of our knowledge, this is the first description of a BBS patient with a mutation in the *TTC8* gene in Japan.

Bardet–Biedl syndrome (BBS) is a rare autosomal recessive disorder characterized by rod-cone dystrophy, postaxial polydactyly, central obesity, hypogonadism, renal abnormalities, and mental retardation. BBS is often complicated by strabismus/cataracts/astigmatism, diabetes mellitus, Hirschsprung disease, heart disease, and/or liver fibrosis. To date, 21 causative genes have been reported, comprising ~80% of BBS genetic abnormalities among BBS patients are not yet known. In the present study, we performed whole-exome sequencing (WES) of a classical BBS patient.

The patient was diagnosed with BBS at 8 years of age, in accordance with criteria reported previously³. Primary and secondary signs of BBS in this patient are listed in Table 1. When the patient first visited Osaka University Hospital at 17 years of age, his best-corrected visual acuity (BCVA) was 0.07 in the right eye and 0.2 in the left eye. At 28 years of age, his BCVA was 0.01 in the right eye and 0.04 in the left eye; he exhibited bilateral diffuse retinal degeneration, including macular atrophy, attenuated retinal vessels, and optic nerve head pallor with little pigmentary dispersion. His parents were not consanguineous. His mother showed

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no sign of BBS or rod-cone dystrophy. His father did not have symptoms of BBS.

All experimental procedures were approved by the Ethics Committee at Osaka University (No. 719-2, Osaka, Japan) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient (at the time of the report, a 28-year-old male) and his 61-year-old mother. Both individuals underwent ophthalmologic examinations: BCVA in decimal units, slit-lamp biomicroscopy, fundoscopy, visual field testing with Goldmann perimetry, optical coherence tomography (SSOCT; DRI OCT1, Topcon Corp., Tokyo, Japan), and fundus autofluorescence (Optos, Optos KK, Tokyo, Japan). Genomic DNA was extracted from blood samples using NucleoSpin Blood XL (Macherey-nagel, Düren, Germany). DNA libraries were constructed using SureSelectXT Human All Exon Kit V6 and SureSelectXT Reagent Kit (Agilent, Santa Clara, CA, USA) and then subjected to 100 bp paired-end sequencing on an Illumina HiSeq2500 Platform (Illumina, San Diego, CA, USA). Sequence reads were aligned to the reference human genome (UCSC hg19) in BWA (http://www.bio-bwa.sourceforge.net/) to align short reads after adaptor sequences were removed by Cutadapt (https://cutadapt.readthedocs.io/en/stable/). SAM tools (Version 0.1.17; http://www.samtools.sourceforge.net/) were used for sequence data conversion, sorting, and indexing. exclude duplicate reads, Picard (http://picard. То sourceforge.net) was used. Variants were determined using GATK (http://www.broadinstitute.org/gatk/). ANNOVAR

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	Age of onset	Clinical information	Intervention
Primary signs			
Rod-cone dystrophy	8 Years old	Visual acuities: 0.01 (right), 0.04 (left), (with mild myopia and astigmatism)	No medication
		Fundus finding: binocular diffuse retinal degeneration Visual field: centipede constriction (binocular) Optical coherence tomography: binocular diffuse thinning of outer retinal layer (+), macular atrophy $(+)$, macular edema $(-)$, cystic changes $(-)$, elipsoid zone $(-)$ Fundus autofluorescence: binocular mottled pattern $(+)$, perifoveal ring $(-)$	
Polydactyly	At birth	Both feet	Plastic surgery (19 months old)
Obesity	9 Years old	Height: 164 cm Weight: 78.1 kg Body mass index (BMI): 29 kg/m ²	No medication
Hypogonadism		Testosterone: 300–600 ng/dl	No medication
Renal anomalies	1 Week old	Cystic kidney Creatinine: 1.79 mg/dl BUN: 21 mg/dl eGFR cre: 37.2 mL/min/1.73 m ²	No medication
Mental retardation	No	-	-
Secondary signs			
Hirschsprung disease	3 Months old	-	Surgery (28 months old)
Abnormal glucose tolerance	9 Years old	HbA1c: 5.6%, 75 g oral glucose tolerance test: 82 mg/dL at 0 h, 185 mg/dL at 2 h	No medication
Exotropia	NA	-	Bilateral lateral rectus muscle recession (14 years old)
Hypertension	27 Years old	Blood pressure = 145/83 mm Hg	Oral medicine (Azilsartan 20 mg and Amlodipine besilate 3.47 mg per day
Cataract	NA	Binocular anterior sub-capsular cataract	-
Heart diseases	No	-	-
Liver fibrosis	No	-	-

Table 1 Primary and secondary	signs of	f BBS in	this patient
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(http://www.openbioinformatics.org/annovar/) was used to annotate the resulting genetic variants. Rare variants (minor allele frequency < 0.05) were selected using the Exome Sequencing Project, 1000 Genomes Project, and Human Genetic Variation databases; possible pathogenic variants, such as nonsynonymous, nonsense, and frameshift mutations, were extracted from among the retinal degenerative disease-related genes registered in the Ret.Net.TM database.

Ten candidate pathogenic rare variants in genes related to retinal degenerative diseases were detected in this patient. All were heterozygous variants; however, two novel nonsense (NM_001288781.1 [TTC8_v001]: c.226 C > T, p.Q76X) and frameshift (NM_001288781.1 [TTC8_v001]: c.309_310insTA, p.T103fs) mutations were located in the TTC8 gene (also known as BBS8). Both mutations were validated by direct sequencing of PCR products (Applied Biosystems 3730 DNA Analyzer; Thermo Fisher Scientific K.K., Tokyo, Japan). The primer sets used for PCR were as follows: c.226 C > T, 5'-TGG GTTTTAGGCAGCTTGGA-3' and 5'-ACCATAAGGCA GAACAGAAACCA-3'; c.308 309insAT, 5'-TAGGCCCT GGAACGTCTTTG-3' and 5'- ACCATAAGGCAGAAC AGAAACCA-3'. This mutation is likely to be pathogenic, because the TTC8 gene has been reported as a causative gene for BBS8⁴. The nonsense mutation was located in exon 3 of the TTC8 gene, thus producing a truncated protein without tetratricopeptide repeats 11 and 15, which are involved in pilus formation and twitching mobility. The frameshift mutation in exon 5 (c.309_310insTA) generates a premature stop codon in exon 6, which also produces TTC8 lacking normal tetratricopeptide repeats 11 and 15. The premature stop codon is located before the last exon; notably, a mRNA transcribed from a gene with a truncating mutation often undergoes nonsensemediated mRNA decay before translation⁵. Thus, transcripts with nonsense and frameshift mutations are likely to be rapidly degraded to reduce the translation of the truncated TTC8 protein. Therefore, this compound heterozygous patient would not have a functional TTC8 protein to support the formation of the BBSome, leading to the development of BBS. His mother exhibited the heterozygous nonsense mutation, but no frameshift mutation. Although the genetic and clinical data were not available from his father, this patient's BBS was determined to result from a compound heterozygous TTC8 gene mutation.

BBS patients with mutations in the *TTC8* gene comprise only 2.8% of all BSS patients^{6,7}. In Japan, the genetics of four BBS families have been reported: *BBS2*, *BBS5*, and *BBS7* homozygotes, as well as a *BBS10* compound heterozygote^{8,9}. To the best of our knowledge, this is the first BBS patient with a mutation in the *TTC8* gene in Japan. Thus far, 16 families with the *TTC8* genetic abnormality

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BakaraYesTGSNS1-2.4delTGCIonSplice siteYesYesYesYesNaSplice siteBakaraYesTCSNS1-2.4delTGCIonSplice siteYesYesYesYesYesYesYesBakaraNATCS187-1884EYIonSplice siteYesYesYesYesYesYesYesYesSudi ArabianNATCS187-1884EYIon64p Inframe delationYesYesYesYesNASpeechinentSudi ArabianNATCS187-1884EYIon64p Inframe delationYesYesYesNASpeechinentSudi ArabianNATCS187-1884EYIon64p Inframe delationYesYesYesNASpeechinentSudi ArabianNATCS187-1884EYIon64p Inframe delationYesYesYesNASpeechinentSudi ArabianYesTCS187-1884EYIon64p Inframe delationYesYesYesNASpeechinentSudi ArabianYesTCS187-1884EYIonSpeechinentYesYesYesYesYesYesSudi ArabianYesTCS187-1884EYIonSpeechinentYesYesYesYesYesYesSudi ArabianYesTCS187-1884EYIonSpeechinentYesYesYesYesYesYesSudi ArabianYes	Family 2	Pakistan	Yes	77C8	NS10 + 2_4deITGC	hom	Splice site	Yes	Yes	Yes	NA	Speech impediment	Developmental delay, brachycephaly	Ansley et al. ⁴
PakstanYesT/GNS10+2.4deffCInorSplite siteYesYesYesNeNeNeSplite siteSaudi ArabianNAT/G187-188deffYhom6 pinfame delationYesYesYesYesNoSpeechSaudi ArabianNAT/G187-188deffYhom6 pinfame delationYesYesYesNoSpeechSaudi ArabianNAT/G187-188deffYhom6 pinfame delationYesYesYesNoNoSaudi ArabianNAT/G187-188deffYhom6 pinfame delationYesYesYesNoNoSaudi ArabianNAT/G187-188deffYhom6 pinfame delationYesYesYesNoNoSaudi ArabianNAT/G187-188deffYhom6 pinfame delationYesYesYesNoNoSaudi ArabianNAT/G187-188deffYhom6 pinfame delationYesYesNoNoNoSaudi ArabianNAT/G187-188deffYhom6 pinfame delationYesYesNoNoSaudi ArabianNAT/G187-188deffYhom6 pinfame delationYesYesNoNoSaudi ArabianNAT/G187-188deffYhom6 pinfame delationYesYesNoNoNoSaudi ArabianNAT/G187-188deffYhom6 pinfame delationYesYes </td <td>Family 2</td> <td>Pakistan</td> <td>Yes</td> <td>77C8</td> <td></td> <td>mod</td> <td>Splice site</td> <td>Yes</td> <td></td> <td>Yes</td> <td></td> <td>Speech impediment</td> <td>Developmental delay, brachycephaly, Situs inversus</td> <td>Ansley, et al.⁴</td>	Family 2	Pakistan	Yes	77C8		mod	Splice site	Yes		Yes		Speech impediment	Developmental delay, brachycephaly, Situs inversus	Ansley, et al. ⁴
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Saudi Arabian Ni. TC3 IS7-188delEY hom 6 bp inframe delation Yes Yes Yes NA Speech impediment Saudi Arabian NA TC3 I87-188delEY hom 6 bp inframe delation Yes Yes NA Speech impediment Saudi Arabian NA TC3 I87-188delEY hom 6 bp inframe delation Yes Yes NA Speech impediment Saudi Arabian NA TC3 I87-188delEY hom 6 bp inframe delation Yes Yes NA Speech impediment Saudi Arabian Yes TC3 I87-188delEY hom 5 bp inframe delation Yes Yes NA Speech impediment Saudi Arabian Yes TC3 I87-188delEY hom 5 pice site Yes Yes NA Speech impediment Saudi Arabian Yes TC3 459 Yes Yes Yes NA NA NA NA NA NA NA NA NA NA </td <td>Family 3</td> <td>Saudi Arabiar</td> <td></td> <td>TTC8</td> <td></td> <td>hom</td> <td>6 bp Inframe delation</td> <td>Yes</td> <td>Yes</td> <td>Yes</td> <td>NA</td> <td>Speech impediment</td> <td>Developmental delay, brachycephaly</td> <td>Ansley, et al.⁴</td>	Family 3	Saudi Arabiar		TTC8		hom	6 bp Inframe delation	Yes	Yes	Yes	NA	Speech impediment	Developmental delay, brachycephaly	Ansley, et al. ⁴
Saudi ArabianMT/C3187-188deEVhom6 bp Inframe delationYesYesNeNeSpeechSaudi ArabianNAT/C3187-188deEVhom6 bp Inframe delationYesYesNASpeechSaudi ArabianNAT/C3187-188deEVhom6 bp Inframe delationYesYesNASpeechSaudi ArabianNAT/C3187-188deEVhom6 bp Inframe delationYesYesNANASpeechSaudi ArabianNAT/C38/35/15/4hom5 plice siteYesYesNANANANANorth AfricanYesT/C38/35/15/4hom5 plice siteYesNANANANANANorth AfricanYesT/C38/35/15/5/4hom5 plice siteNANANANANANAUnisianNAT/C38/35/15/5/4homPro101Led/X12NANANANANANAUnisianNAT/C38/35/15/5/4homPro101Led/X12NANANANANANAUnisianNAT/C38/35/15/5/4homPro101Led/X12NANANANANANAUnisianNAT/C38/35/15/5/4homPro101Led/X12NANANANANANAUnisianNAT/C38/35/15/5/4homPro101Led/X12NANANANANA </td <td>Family 3</td> <td>Saudi Arabiar</td> <td></td> <td>77C8</td> <td></td> <td>hom</td> <td>6 bp Inframe delation</td> <td>Yes</td> <td>Yes</td> <td>Yes</td> <td>NA</td> <td>Speech impediment</td> <td>Developmental delay, brachycephaly</td> <td>Ansley, et al.⁴</td>	Family 3	Saudi Arabiar		77C8		hom	6 bp Inframe delation	Yes	Yes	Yes	NA	Speech impediment	Developmental delay, brachycephaly	Ansley, et al. ⁴
Saudi ArabianNATC8187-188deEVhom6 bp Inframe delationYesYesNASpeechSaudi ArabianNATC8187-188deEVhom6 bp Inframe delationYesYesNANASpeechSaudi ArabianNATC8187-188deEVhom6 bp Inframe delationYesYesNANASpeechNorth AfricanYesTC8459 G>Ahom5 plice siteYesYesNANANANorth AfricanYesTC8459 G>Ahom5 plice siteYesNANANANorth AfricanYesTC8459 G>Ahom5 plice siteYesNANANANANorth AfricanYesTC8459 G>Ahom5 plice siteNANANANANANorth AfricanYesTC8459 G>Ahom5 plice siteNANANANANALebaneseYesTC8459 F1 G>Ahom5 plice siteNANANANANALunsianNATC8459 F1 G>AhomPiol101eef/S121NANANANANALunsianNATC8459 F1 G>AhomPiol101eef/S121NANANANANALunsianNATC8355 F1 G>AhomPiol101eef/S121NANANANANALunsianNATC8459 F1 G>AhomPiol0101eef/S121	Family 3	Saudi Arabiar		77C8		mod	6 bp Inframe delation	Yes		N		nent	Developmental delay, brachycephaly, deafness	Ansley, et al. ⁴
Sauch AbabianNATrG $137-188$ delEYhom 6 pp Inframe delationYesYesNotNoNaSpeechNorth AfricanYesTrG 459 G>AhomSplice siteYesYesNANASpeechNaNorth AfricanYesTrG 459 G>AhomSplice siteYesYesNANAYesNANorth AfricanYesTrG 459 G>AhomSplice siteYesNANAYesNANorth AfricanYesTrG 459 G>AhomSplice siteYesNANANANANorth AfricanYesTrG 459 G>AhomSplice siteNANANANANAUnsianNATrG 459 F1G>AhomPo101LeufSX12NANANANANALebaneseYesTrG 459 F1G>AhomPo101LeufSX12NANANANANALuisianNATrG 459 F1G>AhomPo101LeufSX12NANANANANALuisianNATrG 355 SistinsGGTGGAAGGChomTrA14ArdfSX12NANANANANALuisianNATrG 355 SistinsGGTGGAAGGChomPo101LeufSX12NANANANANALuisianNATrG 355 SistinsGGTGGAAGGChomPo101LeufSX12NANANANALuisianNATrG <td>Family 4</td> <td>Saudi Arabiar</td> <td></td> <td>77C8</td> <td></td> <td>hom</td> <td>6 bp Inframe delation</td> <td>Yes</td> <td></td> <td>NA</td> <td>AN</td> <td></td> <td>Developmental delay, brachycephaly, hyposadias</td> <td>Ansley, et al.⁴</td>	Family 4	Saudi Arabiar		77C8		hom	6 bp Inframe delation	Yes		NA	AN		Developmental delay, brachycephaly, hyposadias	Ansley, et al. ⁴
North AfricanYesTTG459 G > ANorthAfricanYesNANACognitiveNorth AfricanYesTTG459 G > ANorthAfricanYesNANANACognitiveNorth AfricanYesTTG459 G > ANorthSplice siteYesYesNAYesNANorth AfricanYesTTG459 G > ANorthSplice siteYesYesNAYesNANorth AfricanYesTTG859 L G > ANorthSplice siteNANANAYesNALebaneseYesTTG859 L 1 G > ANorthSplice siteNANANANANANALunisianNATTG859 L 1 G > ANonPro101 LeufsX12NANANANANANALunisianNATTG859 L 1 G > ANonPro101 LeufsX12NANANANANANALunisianNATTG859 L 1 G > ANonNANANANANANALunisianNATTG859 L 1 G > ANonNANANANANANALunisianNATTG859 L 1 G > ANonNANANANANANALunisianNATTG859 L 1 G > ANaNANANANANANALunisianNATTG850 L G > ANANANANA<	Family 4	Saudi Arabiar		77C8		mod	6 bp Inframe delation	Yes	Yes	NA	AN		Developmental delay, brachycephaly, asthma	Ansley, et al. ⁴
North AfricanYesTTG 459 G5 AhomSplice siteYesYesNAYesYesNANorth AfricanYesTTG 459 G5 AhomSplice siteYesYesNAYesNANorth AfricanYesTTG 856 H_LG5 AhomSplice siteYesYesNAYesNALebaneseYesTTG 856 H_LG5 AhomSplice siteNANANAYesNALunsianNATTG 459 H 16 AhomPro101LeufsX12NANANANANANATunisianNATTG 459 H 16 AhomPro101LeufsX12NANANANANANATunisianNATTG 355 S56insGGTGGAGGGhomYe1124Arg5X43NANANANANANATunisianNATTG 355 S56insGGTGGAGGGhomYe1124Arg5X43NANANANANATunisianNATTG 355 S56insGGTGGAGGGhomYe124Arg5X43NANANANANATunisianNATTG 355 S56insGGTGGAGGGhomYe13Ye13Ye13Ye13Ye13Ye13UnisianNATTG 355 S56insGGTGGAGGGhomYe134rg5X43NANANANANAUnisianYe13Ye13Ye13Ye13Ye13Ye13Ye13Ye13Ye13Ye13Ye13NA <td>Family 5</td> <td>North African</td> <td></td> <td>77C8</td> <td></td> <td>mod</td> <td>Splice site</td> <td>Yes</td> <td></td> <td>AN NA</td> <td>NA</td> <td>Cognitive impairment</td> <td>Micropenis</td> <td>Stoetzel, et al.⁷</td>	Family 5	North African		77C8		mod	Splice site	Yes		AN NA	NA	Cognitive impairment	Micropenis	Stoetzel, et al. ⁷
North AfricanYesT/C8 459 G-3homSplice siteYesYesNAYesNAYesNALebaneseYesT/C8N/S6 + 1_G S AhomSplice siteNA	Family 5	North African		77C8		hom	Splice site	Yes	Yes	٨A		NA	Hydrometrocolpos	Stoetzel, et al. ⁷
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CaucasianNoTTC8 $V56 + 1-2delGT$ hetSplice siteNA <td>Family 6</td> <td>Lebanese</td> <td>Yes</td> <td>77C8</td> <td></td> <td>hom</td> <td>Splice site</td> <td>NA</td> <td>NA</td> <td>AN</td> <td></td> <td>NA</td> <td>NA</td> <td>Stoetzel, et al.⁷</td>	Family 6	Lebanese	Yes	77C8		hom	Splice site	NA	NA	AN		NA	NA	Stoetzel, et al. ⁷
TunisianNATC8 $459 + 1G > A$ homPro101Leuf5X12NANANANANANANANATunisianNATC8 $459 + 1G > A$ homPro101Leuf5X12NANANANANANANANATunisianNATC8 $355 \cdot 356 insGGTGGAGGGhomPro101Leuf5X12NANANANANANANANANANANANANANANANATurkeyYesTC8355 \cdot 356 insGGTGGAGGGhomW41XYesYesYesYesNoNANANATC8122 \cdot G > AhomSplice siteYesYesYesYesYesYesHispanicNATC8852 + 1 G > AhomSplice siteNANANANANANAUnisianYesTC8329 \cdot G > AhomSplice siteNANANANANAUnisianYesTC8329 \cdot G > AhomSplice siteYesYesYesYesYesUnisianYesTC8459 + 1 \cdot G > AhomSplice siteYesYesYesYesYesYesUnisianYesTC8459 + 1 \cdot G > AhomSplice siteYesYesYesYesYesYesUnisianYesTC8459 + 1 \cdot G > AhomSplice siteYesYesYesYesYes$	Family 7	Caucasian	No	77C8		het	Splice site	NA		NA		NA	NA	Stoetzel, et al. ⁷
TunisianNA $TC8$ $459 + 1$ G>AhomPro101 Leu(5X12NANANANANANATunisianNA $TC8$ 355_{-356} insGGTGGAAGGChom $Pro101$ Leu(5X12NANANANANANATurkeyYes $TC8$ 355_{-356} insGGTGGAAGGChom $W41X$ YesYesYesNoNANANANA $TC8$ 122 G>Ahom $W41X$ YesYesYesYesNoYesNANA $TC8$ 122 G>Ahom $W41X$ YesYesYesYesYesYesHispanicNA $TC8$ 452 H G>AhomSplice siteNANANANANAHispanicNA $TC8$ 329 G>AhomSplice siteNANANANANATunisianYes $TC8$ 329 G>AhomSplice siteYesYesYesYesYesYesTunisianYes $TC8$ 459 H G>AhomSplice siteYesYesYesYesYesYesTunisianYes $TC8$ 459 H G>AhomSplice siteYesYesYesYesYesYesTunisianYes $TC8$ 459 H G>AhomSplice siteYesYesYesYesYesYesUnisianYes $TC8$ 459 H G>AhomSplice siteYesYesYesYesYes<	Family 8	Tunisian	NA	77C8		hom	Pro101LeufsX12	NA	NA	٨A		NA	NA	Smaoui, et al. ¹⁰
Tunisian NA <i>TTC8</i> 355_356insGGTGGAAGGC hom Thr124ArgtsX43 NA NA NA NA NA NA NA TTC8 355_356insGGTGGAAGGC hom $VH1X$ Yes Yes Yes Yes Yes No NA VE Hispanic NA <i>TTC8</i> 122G>A hom $VH1X$ Yes	Family 9	Tunisian	AN	77C8		hom	Pro101LeufsX12	NA	NA	AN		NA	NA	Smaoui, et al. ¹⁰
Turkey Yes TC8 122 G > A hom W41X Yes Yes Yes No No Na NA NA TTC8 MS2 + 1 G > A hom Splice site Yes Yes Yes No No Yes Hispanic NA TTC8 485 delG & 1000 delA hom Splice site Yes <td>Family10*</td> <td>Tunisian</td> <td>NA</td> <td>77C8</td> <td>nsGGTGGAAGGC</td> <td>hom</td> <td>Thr124ArgfsX43</td> <td>AN</td> <td>NA</td> <td>AN</td> <td>AN</td> <td>AN</td> <td>AA</td> <td>Smaoui, et al.¹⁰</td>	Family10*	Tunisian	NA	77C8	nsGGTGGAAGGC	hom	Thr124ArgfsX43	AN	NA	AN	AN	AN	AA	Smaoui, et al. ¹⁰
NA NA TTC8 NS2+1G>A hom Splice site Yes Yes? No No Yes Hispanic NA TTC8 485delG & 1000delA comp. het G162fsX4 & 1334fsX1 Yes Yes Yes Yes Yes Yes Yes Yes Yes Tunisian Yes TTC8 329G>A hom Splice site NA NA NA NA NA NA NA NA Tunisian Yes TTC8 459+1G>A hom Splice site Yes Yes Yes Yes Yes NA	Family 11	Turkey	Yes	TTC8		hom	W41X	Yes	Yes	Yes	No	AN	Yes but details unknown	Harville, et al. ¹¹
Hispanic NA <i>TTC8</i> 485delG & 1000delA comp. het G162fsX4 & 133dfsX1 Yes Yes Yes Yes Yes Yes Tunisian Yes <i>TTC8</i> 329G>A hom Splice site NA NA NA NA NA NA NA Tunisian Yes <i>TTC8</i> 459+1G>A hom Splice site Yes Yes Yes Yes Yes Yes Na	Family 12	NA	AN	77C8		hom	Splice site	Yes	Yes	No		Yes	Asthma, nasal cephalocele	Janssen, et al. ¹²
Tunisian Yes 77C8 329.G > A hom Splice site NA NA NA NA NA NA NA Tunisian Yes 77C8 459+1.G > A hom Splice site Yes Yes Yes Yes Yes Na	Family 13	Hispanic	NA	77C8	485delG & 1000delA	comp. het	G162fsX4 & I334fsX1	Yes	Yes	Yes		Yes	Fatty liver, gall stones	
Tunisian Yes 77C8 459+1G>A hom Splice site Yes Yes Yes Yes Ne	Family 14	Tunisian	Yes	77C8		hom	Splice site	NA		AN		NA	NA	Redin, et al. ¹³
	Family 15	Tunisian	Yes	77C8		hom	Splice site	Yes		Yes		NA	Dental anomalies, hypertension	M'hamdi O, et al. ¹⁴

Family Ethnic	Ethnic	Consan- guineous	Gene	Consan- Gene Nucleotide alteration(s) Z guineous	Zygosity state	Zygosity Alteration(s) in state coding sequence	Rod-cone dystrophy	Polydactyly	Obesity	Hypo- gonadism	Renal anomalies	Mental retardation	Rod-cone Polydactyly Obesity Hypo- Renal Mental Secondary signs dystrophy gonadism anomalies retardation	Reference
amily 16	amily 16 Pakistan	Yes	TTC8	77C8 1347 G > C	hom	GIn449His	Yes	Yes	Yes	Yes	No	Congnitive Clinodactyly impairment	Clinodactyly	Ullah, et al. ¹⁵
⁻ amily 16	Pakistan	Yes	77C8	1347 G > C	hom	GIn449His	Yes	Yes	Yes	Yes	NA	Congnitive impairment	Congnitive Clinodactyly impairment	Ullah, et al. ¹⁵
⁻ amily 16	Pakistan	Yes	77C8	77C8 1347 G > C	hom	GIn449His	Yes	Yes	Yes	NA	No	Congnitive impairment	NA	Ullah, et al. ¹⁵

have been reported (Table 2)^{4,7,10–15}. Most of these families have homozygous mutations; only our patient and a Hispanic family were compound heterozygotes. Although full clinical information was not available for some cases, most of the cases in these 16 families exhibit classical BBS without obvious differences in phenotypes.

In summary, we identified a novel compound heterozygous mutation in a Japanese BBS patient by WES. Our findings suggest that WES may be a useful tool for genetic diagnosis and characterization of BBS.

HGV database

The relevant data from this Data Report are hosted at the Human Genome Variation Database at https://doi.org/10.6084/m9.figshare.hgv.2528; https://doi.org/10.6084/m9.figshare.hgv.2531

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Conflict of interest

The authors declare that they have no conflict of interest.

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