Letter to the Editor
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Identification of Compound Heterozygous Mutations in the *BBS7* Gene in a Korean Family with Bardet-Biedl Syndrome

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Dear Editor,

Bardet-Biedl syndrome (BBS) (OMIM 209900) is an autosomal recessive, clinically and genetically heterogeneous ciliopathy [1, 2]. The prevalence of BBS is relatively low, ranging from 1:100,000 in the North American to 1:160,000 in the European population, and is rarely found in East Asia [3, 4]. To date, at least fifteen *BBS* genes (*BBS1-14, SDCCAG8*) have been identified, accounting for 70-76% of BBS cases. Among them, *BBS 1, 2, 10*, and *12* are considered the major causative genes [3-5]. Correlation between the BBS genotype and phenotype varies among and within families [1, 3]. Here, we report the first genetically confirmed BBS case in a Korean family with a compound heterozygous mutation of the *BBS7* gene.

A 26-yr-old Korean male (proband) was the second son of non-consanguineous Korean parents. He was blind, mentally retarded, and truncally obese. Past history showed that he had undergone an operation for an atrial septal defect at the age of four. A chest X-ray revealed cardiomegaly and pulmonary edema. Renal sonogram revealed bilateral small-sized kidneys, increased renal parenchymal echogenicity, and poor corticomedullary differentiation, together with laboratory findings, were indicative of an end-stage renal disease. Fundus examination revealed pigmentary changes as typically observed in retinitis pigmentosa with optic disc atrophy (Fig. 1). The proband was treated with maintenance hemodialysis and antihypertensive medications.

The proband's 28-yr-old brother showed similar clinical findings, but his parents, younger sister, and other blood relatives presented as non-specific (Fig. 2A). Clinical characteristics of the proband and his brother are summarized in Table 1, and both of their diagnoses were consistent with the BBS diagnostic criteria [1, 2]. However, his brother showed some different phenotypes: unilateral kidney agenesis with milder renal symptoms, no atrial septal defect with milder cardiovascular symptoms, and deep vein thrombosis of the left lower extremity.

Genetic studies conducted on the fourteen known *BBS* genes (*BBS1-BBS14*) from all family members by Sanger sequencing revealed that the proband and his brother shared the same compound heterozygous variants of the *BBS7* gene (NM_176824.2) (Fig. 2B). One of which was a novel variant (c.103-1G>A) in the consensus splice acceptor site, which altered the splicing recognition site of 'AG' to 'AA' at the *BBS7* gene intron 2 and exon 3 boundary. *In silico* analysis of the mutant splice site using a neu-

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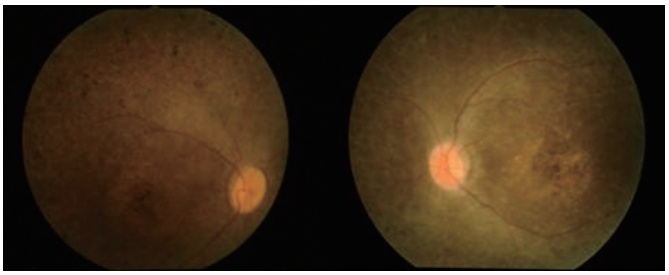

Fig. 1. Fundus photograph of the proband with Bardet-Biedl syndrome. Fundus examination showed optic disc atrophy with indistinct margins. Marked arteriolar narrowing is observed, and bone spicule pigmentations are present in the mid-periphery of the retina. Macular dystrophy is also observed in both eyes.

ral network splice site scoring program (NNSPLICE 0.9 version) predicted that the splice site would be abolished. The other variant was a c.728G>A (p.Cys243Tyr) missense mutation, which has been reported in a case describing juvenile retinitis pigmentosa, by Wang *et al*. [6]. The father was a heterozygous carrier for c.103-1G>A, and the mother was a heterozygous carrier for c.728G>A. Additionally, array comparative genomic hybridization analysis using the NimbleGen 3×720 K array (Roche NimbleGen Inc., Madison, WI, USA) revealed a normal hybridization pattern with no evidence of any significant chromosomal imbalance.

BBS is a ciliopathy involving multiple systems, characterized by a primarily autosomal recessive inheritance, but three mutational alleles in two *BBS* genes have been implicated (trialleic inheritance) in some families [4, 7]. No additional pathogenic allele was found in other *BBS* genes, from *BBS1* to *BBS14*, in this case. BBS proteins are known to play an important role in ciliary biogenesis and signaling [2, 8], and BBS7 protein dysfunctions or abnormalities can cause structural and functional defects in cilia, and as a result, affect variable organs in the body [9, 10].

The present case showed neither polydactyly, as usually seen in 69-82% of affected individuals, nor hypogonadism, usually seen in 16-96% of affected individuals according to previous reports (Table 1) [1, 3]. Interestingly, minor phenotypic variabilities, including renal and cardiac anomalies were also identified within the family. Therefore, further work is required to differentiate BBS from the other ciliopathies, because the spectrums of BBS can overlap with the other ciliopathies such as the McKusick-Kaufan syndrome, which involves the limb, cardiac and associated urogenital systems, with *BBS6* as the causative gene; or the Alström syndrome, which leads to obesity, retinal and endocrine systems with *ALMS1* as the causative gene [1-3].

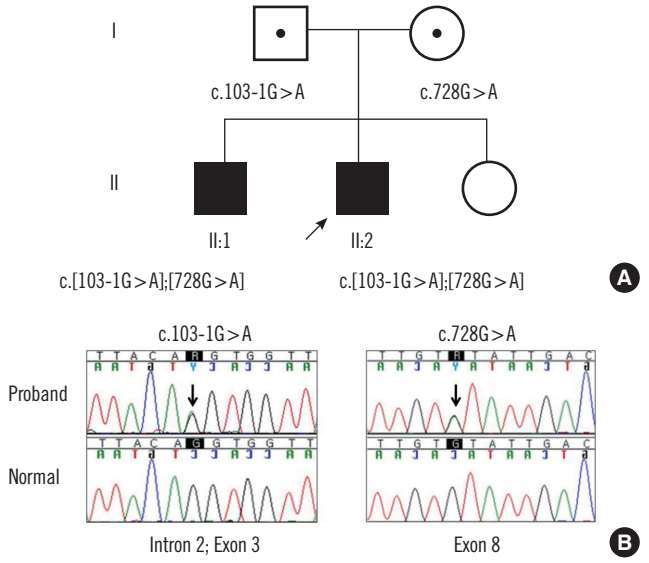

Fig. 2. Characterization of the family with Bardet-Biedl syndrome. (A) Pedigree showing the segregation of c.103-1G>A and c.728G>A variants. The arrow indicates the proband of the family. (B) Sequencing analysis revealed a compound heterozygous mutation of c.103-1G>A (a consensus splice acceptor site) at the intron 2 and the exon 3 boundary, and c.728G>A (p.Cys243Tyr) at the exon 8 of the *BBS7* gene.

Nevertheless, 24-30% of BBS cases show no mutations in *BBS* genes [3-5]. BBS phenotype could be affected not only by transcription of DNA mutations, but also by other etiologies not addressed in this study, such as protein defects associated with noncoding RNA regulatory mechanisms or methylation. Further studies are warranted to clarify these issues.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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Table 1. Features of the proband and his brother per the diagnostic criteria of Bardet–Biedl syndrome

Phenotype	II:2 (Proband)	II:1 (Brother)	Frequency (%) reported by	
			Beales *et al*. [1]	Deveault *et al*. [3]
Gender (M:F)	Male	Male	1.3:1	1:1
Age at diagnosis (yr, mean)	26	28	9	19.2
Primary features				
1. Visual disorder	Yes	Yes		100
Rod-cone dystrophy	Yes	Yes	93	15
Optic atrophy	Yes	Yes	-	-
Blindness	Yes	Yes	-	84
2. Limb defects	No	No	-	98
Postaxial polydactyly	No	No	69	82
3. Weight gain anomaly	Yes	Yes		93
Truncal obesity	Yes	Yes	52	-
Overweight	Yes	Yes	72	-
(Body mass index > 25 kg/m^2)	(29.75)	(29.74)		
4. Learning disabilities	Yes	Yes	62	-
5. Hypogonadism	No	No	96	16
6. Renal anomalies	Yes	Yes	46	53
Scarring	Yes	No	12	-
Cortex thinning	Yes	Yes	-	3
Unilateral agenesis	No	Yes	4	-
End stage renal failure	Yes	No	5	5
Secondary features				
1. Speech disorder	Yes	Yes	54	82
Disordered speech	Yes	Yes	-	-
Slow speech	Yes	Yes	-	-
2. Strabismus/cataract/astigmatism	No	No	-	-/44/-
3. Brachydactyly/syndactyly	No	No	-	20/15
4. Developmental delay	Yes	Yes	50	92
Delay in speech	Yes	Yes	47	-
Delay in walking	Yes	Yes	42	-
Delay in fine motor skills	Yes	Yes		-
Delay in gross motor skills	Yes	No	-	-
Delay in psychosocial skills	Yes	Yes	-	-
Delayed puberty	Yes	Yes	31	-
5. Polyuria/polydypsia	No	No	-	35/32
6. Ataxia/imbalance (wide-base gait)	Yes	Yes	40/33	-
7. Mild spasticity (especially lower limbs)	Yes	Yes	-	-
8. Diabetes mellitus	No	No	6	19
9. Dental anomalies	No	No	27	51
10. Cardiovascular anomalies	Yes	Yes	-	19
Atrial septal defect	Yes	No	-	3
Left ventricular hypertrophy	Yes	Yes	-	-
Congestive heart disease	Yes	No	-	-
11. Hepatic fibrosis	No	No	-	2
12. Hyposmia/anosmia	No	No	-	67
13. Nociception/thermosensation	No	No		
14. Infections	No	No		
15. Miscellaneous				
Emotional immaturity	Yes	Yes	-	18
Hypertension	Yes	Yes	8	32
Deep vein thrombosis	No	Yes	-	-
Retroperitoneal fibrosis	No	Yes	-	-

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