Identification of Compound Heterozygous Mutations in the \textit{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 (\textit{BBS1-14, SDCCAG8}) have been identified, accounting for 70-76\% of BBS cases. Among them, \textit{BBS 1, 2, 10}, and \textit{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 \textit{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 (\textit{BBS1-BBS14}) from all family members by Sanger sequencing revealed that the proband and his brother shared the same compound heterozygous variants of the \textit{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 \textit{BBS7} gene intron 2 and exon 3 boundary. \textit{In silico} analysis of the mutant splice site using a neu-
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 pigmentation are present in the mid-periphery of the retina. Macular dystrophy is also observed in both eyes.

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]         |
|                               |                |               | Devault et al. [3]        |
| Gender (M:F)                  | Male           | Male          | 1.3:1                     |
| Age at diagnosis (yr, mean)   | 26             | 28            | 9                         |
|                               |                |               | 19.2                      |
| Primary features              |                |               |                           |
| 1. Visual disorder            | Yes            | Yes           | 100                       |
| Rod-cone dystrophy            | Yes            | Yes           | 93                        |
| 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/m²)  | (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                        |
|                               |                |               |                           |
| 7. Mild spasticity (especially lower limbs) | Yes | Yes | 47 |
|                               |                |               | -                         |
| 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           | 19                        |
| 14. Infections                | No             | No            | 32                        |
|                               |                |               |                           |
| 15. Miscellaneous             |                |               |                           |
| Emotional immaturity          | Yes            | Yes           | 18                        |
| Hypertension                  | Yes            | Yes           | 8                         |
| Deep vein thrombosis          | No             | Yes           | -                         |
| Retroperitoneal fibrosis      | No             | Yes           | -                         |

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