The Phenotype in Norwegian Patients With Bardet-Biedl Syndrome With Mutations in the BBS4 Gene

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Objective: To describe the phenotype of the Bardet-Biedl syndrome in patients with mutations in the BBS4 gene.

Methods: We examined 3 pairs of siblings with Bardet-Biedl syndrome in whom 3 different mutations in the BBS4 gene were detected, 2 of which were homozygous for the mutation.

Results: All patients had an increased body mass index. The obesity varied between families from moderate to severe. All of the males had hypogenitalism. All had brachydactyly and similar dental anomalies. Polydactyly was present in 5 of the 6 patients. The number and location of the extra digits varied even between siblings. The intelligence varied between families and was within the normal range in 4 individuals. One male had spinal stenosis with paraparesis of his legs. Four patients had increased blood pressure, but only 1 had impaired renal function. Severe retinitis pigmentosa with onset in early childhood was present in all patients. There were few abnormal retinal pigmentary deposits even at advanced stages.

Conclusions: The phenotype of patients with BBS4 mutations consists of severe retinitis pigmentosa, variable obesity, brachydactyly with variable polydactyly, small or missing teeth, genital hypoplasia, and cardiovascular disease. The combinations of clinical signs are mostly independent of the individual BBS4 mutation and can vary even within pairs of siblings. It is possible that there is a characteristic appearance of the ocular fundus in patients with BBS4 mutations.

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Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder with the cardinal features of retinitis pigmentosa, obesity, dental anomalies, brachydactyly and polydactyly, hypogenitalism, and renal disorder. The syndrome is also associated with intellectual impairment, cardiac disease, and hypertension.

There is, however, considerable variation in the clinical picture, even in patients with BBS within the same family. Intelligence can be nearly normal and polydactyly is absent in some patients. Overlapping with Laurence-Moon syndrome and Alstrom syndrome has been observed.

The syndrome is genetically heterogeneous and can be caused by mutations in at least 6 different genes: BBS1 to BBS6. The BBS6 and BBS2 genes and newly also the BBS4 gene have been identified. The BBS6 gene is identical with the MKKS gene involved in McKusick-Kaufman syndrome.

The BBS4 gene consists of 16 exons and spans approximately 52 kilobases. That study included the identification of BBS4 gene mutations in 3 Norwegian families with 6 affected members. In 2 of the sibships the affected subjects were homozygous, while the 2 affected individuals in the third sibship were heterozygous for a mutation in the BBS4 gene. It is the aim of this report to describe the phenotype of these individuals to examine phenotype-genotype relationships.

Patients and Methods

In 6 patients, 3 pairs of siblings from 3 families, mutations in the BBS4 gene were newly documented. The method of this documentation was described earlier. These patients were previously included in comprehensive studies of 44 Scandinavian individuals with BBS (families IV, VIII, and IX). We reanalyzed both the extracocular phenotypes (obesity, mental status, abnormalities of extremities and teeth, genital status, blood pressure, renal function) and the ocular characteristics (age at onset, visual acuity, refraction, slitlamp and ophthalmoscopic findings, electroretinographic measurements, and the course of the disease) in these 6 patients. In addition, we updated earlier findings by means of a questionnaire.
The 3 families had the following BBS4 mutations in affected members: Family IV had a heterozygous 2-base pair insertion in exon 8 and shared haplotypes with microsatellite markers D15S125, D15S131, D15S204, and D15S114, which span the BBS4 locus. Family VIII had a homozygous A→C transversion in exon 7 splice acceptor position –2. Family IX had a homozygous G→C transversion in the exon 4 splice donor site position +1.7

EXTRAOCULAR PHENOTYPE

We found obesity in all patients, with a mean body mass index (weight in kilograms divided by the square of height in meters) of 37 (reference value, ≤25). In the patients in family VIII, the obesity was more pronounced than in the other families (Table). All 6 patients had brachydactyly and 5 had postaxial polydactyly. The polydactyly was limited to 1 extremity in 2 persons and was bilateral in 3. The extra digit was located in the hands in 3 and in the feet in 2 individuals, and both the number and the location varied between siblings (Table). All 6 patients had typical dental anomalies in the form of missing permanent teeth and/or short roots. One patient in family IX had episodes of paraparesis of his legs caused by spinal stenosis; he had also been treated for a growth hormone–producing pituitary adenoma.

Intelligence, based on the level of school and social performance, was considered reduced in the affected siblings in family VIII but within normal limits in the remaining patients (Table). Four patients from the 3 families had increased blood pressure, but only 1 had an abnormal serum creatinine level. All patients had a rod-cone retinal dystrophy according to the course of the disease. The mean age at onset of nyctalopia was 4 years (range, 2-7 years). Earlier electroretinographic recordings had shown no photopic or scotopic amplitude in any of the patients,1 including the youngest at age 13 years.

The visual status is listed in the Table. Best-corrected visual acuity was severely reduced in all patients; therefore, optotype measurements and visual fields could be obtained only in the 2 teenagers, and the latter were constricted to 10° to 30° from fixation. Five patients had myopic astigmatism, as shown in the Table as the mean of the spherical equivalent in the 2 eyes.

The course of the visual function was followed in each individual for 9 years and showed a rapid decline through the teenage years, with only a minor variation between the siblings in family IV.

Posterior capsular cataract was noted in 4 affected individuals from families IV, VIII, and IX at ages from 16 to 33 years. The ocular fundus showed a waxy pale optic disc, attenuated vessels, and fine granular pigment in the macula (Figure 1). Abnormal pigmentation in the periphery was seen only in the patients from families VIII and IX who were older than 30 years, and the pigments were sparse and uncharacteristic of retinitis pigmentosa in general (Figure 2).

The diversity of the clinical findings in BBS has been highlighted earlier.1 Clinical examination of patients with BBS in general has previously shown significant variation in the features even between siblings.4 Attempts to define a specific phenotype corresponding to a specific mutation have so far been unconvincing.1,8

The BBS4 gene is expressed in all tissues examined, and expression is highest in the kidney.7 We present herein a detailed study of the general and ocular characteristics of patients with identified BBS4 gene mutations.

Our study showed that obesity was profuse in the patients from the 3 families who were older than 30 years, and the latter were constricted to 10° to 30° from fixation. Five patients had postaxial polydactyly. The site of the extra digit included hands and feet but varied even between siblings. The number of extra digits varied between 0 and 2. It is therefore

### RESULTS

### MUTATIONS

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sible that the polydactyly in patients with BBS4 mutations is less pronounced than in other patients with BBS.1

Our estimate of intelligence was based on the level of school and social performance, and only the siblings of family VIII were considered mentally retarded. The 2 siblings in family IV attended high school, and the 2 adult patients in family IX were able to live independently. The presence of near-normal intelligence in these patients with BBS is in accordance with the findings in some other patients with BBS.1

Increased blood pressure was present in most of our patients. Renal function was normal in 5 of 6 patients on the basis of measurements of creatinine in serum. However, we did not examine the kidneys with ultrasound. In future studies of patients with BBS4 gene mutations, examination of renal function should be intensified, since the BBS4 gene has its highest expression in the kidney. Furthermore, renal disease has been shown to be a major cause of death in patients with BBS.1

Nearly all men with BBS have hypogenitalism,1 and this was also the case in the males in our study. Hypogenitalism thus does not separate the patients with BBS who have BBS4 mutations from other patients with BBS.

The finding of dental anomalies, such as missing permanent teeth and short dental roots, was universal in our patients, but this has also been documented in other individuals with BBS.1,9

Ocular examination documented a serious rod-cone retinal dystrophy with very early presentation of nyctalopia and a rapid decrease in visual function similar to that reported in other patients with BBS.10 The sparse amount of abnormal retinal pigment deposits was noted in all 6 of our patients with BBS4 mutations, even in advanced stages when visual acuity was reduced to light perception. In addition, the appearance of the pigment deposits was not of the typical bone spicule type found in many other patients with BBS,1 but rather is best described as “amorphous.” This finding has not been characteristic of most other patients with advanced BBS1 and might possibly be typical of the retinal dystrophy in cases with BBS4 mutations, although it could also reflect the nature of the mutations in these families, all of which are consistent with loss of function.7

Refraction in our patients showed myopic astigmatism in 5 patients, but one of the siblings in family VIII was hypermetropic. An increased tendency to myopia has been
demonstrated in other patients with BBS and might be connected to the severity of the retinitis pigmentosa.11

The 3 affected pairs of siblings had different mutations in the BBS4 gene, and one of them in family IV remains to be identified.7 The phenotypes of the homozygous and the presumed compound heterozygous patients with BBS, however, could not be distinguished from each other on the basis of clinical examination. The uniform and slightly unusual appearance of the ocular fundus in our patients could be a typical feature of the BBS4 gene, but this requires confirmation with a larger series of patients.

The BBS4 gene is expressed in the retina,7 and it remains to be seen why the disorder is so consistently severe and rapidly progressive. The amount of within-family variation in most of the clinical features indicates that individual modifying genes or stochastic12 or epigenetic factors may also influence the phenotype.

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REFERENCES


ARCHIVES Web Quiz Winner

Congratulations to the winner of our July quiz, Josh Litwin, MD. The correct answer to our July challenge was bacterial keratitis. For a complete discussion of this case, see the Clinicopathologic Reports, Case Reports, and Small Case Series section in the August ARCHIVES (Cho BJ, Lee YB. Infectious keratitis manifesting as a white plaque on the cornea. Arch Ophthalmol. 2002;120:1091-1093).

Be sure to visit the Archives of Ophthalmology World Wide Web site (http://www.archophthalmol.com) and try your hand at our Clinical Challenge Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of the book One Hundred Years of JAMA Landmark Articles.