BARDET-BIEDEL SYNDROME

Phenotypic Characteristics Associated with the BBS4 Locus

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SUMMARY

Herein reported are the systemic and ophthalmologic features of four patients with Bardet-Biedl syndrome (BBS) from a consanguineous pedigree. Molecular genetic analyses showed linkage with the BBS4 locus (chromosome 15), and excluded linkage to the other known loci on chromosome 3 (BBS3), 11 (BBS1), and 16 (BBS2), respectively. Patients were 15 to 26 years old (M = 3; F = 1) at last examination, and follow-
up was up to 10 years. An array of clinical and functional tests were performed to characterize the ocular phenotype of this pedigree.

Mild obesity and dystrophic extremities were observed in all four subjects, and mild to moderate mental retardation was noted in three. All three male subjects had also cryptorchidism. Two siblings also had dental abnormalities. Renal function investigations were unrevealing.

Night blindness was the presenting symptom in all patients (onset: birth to 4 years of age). Visual acuity and color vision were severely affected early on in three subjects, moderately in the fourth. Further deterioration was documented in the follow-up. On ophthalmoscopy, retinal vessels were severely attenuated in all cases. Retinal pigmentary changes were mild and sectoral in all subjects in the earlier phases of the disease. Optic discs were pale (partial to complete atrophy) in all patients. Increasing retinal pigmentation and disc pallor was documented over the years. Maculas appeared initially healthy in all subjects, but mild abnormalities became ophthalmoscopically apparent over time. Goldmann visual fields were variably constricted, with good preservation of the inferior field in one subject as late as 26 years of age. Maximal electroretinogram responses were recordable only in two subjects at first examination, and suggested possible partial preservation of rod function in the early phases of the retinopathy. Later in the course of the disease, only cone-mediated function could be identified. Despite the healthy appearance on ophthalmoscopy, macular cone function was profoundly altered in all subjects.

In summary, the ophthalmologic manifestations of this BBS4 pedigree do not appear to be distinct from those of other reported BBS phenotypes. Systemic manifestations were only in part matching those described for other BBS4 kindreds, indicating substantial interfamilial heterogeneity. Particularly, obesity was not nearly as prominent a feature as reported for Arab-Bedouin BBS4 large consanguineous pedigrees. Intrafamilial variability was also noted, adding further to the complexity of this syndrome.

1. INTRODUCTION

Following the original descriptions in the late 1800s and early 1900s, several reports described in detail the ophthalmologic and systemic features associated with Bardet-Biedl syndrome [(BBS) see Iannaccone et al. for a review). The classic cardinal features of this autosomal recessive syndrome are: (1) pigmentary retinopathy, (2) dystrophic extremities, (3) obesity, (4) hypogenitalism, and (5) mental retardation. Evidence has accumulated over the past two decades to indicate that at least two additional features must be held as typical of BBS patients, i.e. (6) renal involvement and (7) dental abnormalities. With the exception of retinopathy, the other six features are not invariably present in each affected subject, and incomplete phenotypes are particularly frequent.

In the past several years, significant progress has been made in identifying several distinct loci associated with BBS pedigrees. This has demonstrated the genetic heterogeneity associated with this condition, and provided in part a rationale for the observed phenotypic variability. Reports on pedigrees with multiple affected individuals are few, and so are those describing the phenotypes associated with these recently characterized distinct loci.