

Mutations in *BBS1* or *BBS2* and Retinal Degeneration – an Overview

Introduction

Retinal degeneration, which shows a prevalence of about 1 in 3000, is characterized by progressive rod-cone dystrophy leading to vision loss and, eventually, blindness (1). Retinal degeneration can occur in isolation or as part of wider syndromes such as Bardet-Biedl syndrome (BBS), a recessively inherited developmental disorder with an incidence of about 1:140,000 births (1,2). Identifying BBS as the cause of retinal degeneration is important, since it can alert physicians and patients to the risk of other BBS-associated manifestations such as renal malformations, which affect about half of all BBS patients and are a leading cause of morbidity and mortality in individuals with BBS (2,3). Since BBS has been associated with autosomal recessive loss-of-function mutations in any one of several different genes (*BBS1* through *BBS11*), genetic testing can allow a definitive diagnosis of BBS in patients with retinal degeneration (4-16).

Molecular Pathophysiology

While different BBS genes code for different classes of proteins, such as chaperonin-like proteins (*BBS6* and *BBS10*) (10,11,15), an E3 ubiquitin ligase (*BBS11*) (16), or an ADP-ribosylation factor (*BBS3*) (6,7), all BBS gene products are believed to be involved in intracellular trafficking or, more specifically, intraflagellar transport (IFT) (17,18). IFT, or the active transport of proteins along the microtubules in cilia, is necessary for formation and maintenance of cilia, which have been shown to play a role not only in cell mobility, but also in transport of fluids over epithelial cells and in sensory perception. Defects in IFT have been implicated in male infertility, polycystic kidney disease, retinal degeneration, and disturbances in embryonic development (19). Given

the ubiquity of IFT in mammalian cells and the varied roles of cilia in different cell types, association of BBS with mutations in IFT components may explain the pleiotropic phenotype of the disorder. Inheritance of BBS is mainly autosomal recessive (20). In rare cases, digenic inheritance has been reported, where mutations in two different BBS genes are necessary for expression of the phenotype.

Diagnosis

BBS is associated with a range of primary and secondary features in addition to retinal degeneration, such as postaxial poly-, syn- or brachydactyly, early-onset obesity, cardiac and renal abnormalities, mild to moderate learning disabilities, anosmia, hypogonadism in males, genitourinary malformation in females, dental anomalies, nephrogenic diabetes insipidus, diabetes mellitus, and hypertension (2). Although symptoms such as postaxial polydactyly be present from birth, diagnosis of BBS is usually delayed until visual problems become apparent at about 8 years of age, typically presenting as night blindness. Genetic testing for pathogenic mutations in *BBS1* or *BBS2*, which are estimated to account for about 23% and 8% of all cases of BBS, respectively, can confirm a diagnosis of BBS (20).

Of note, the names Bardet-Biedl Syndrome and Laurence-Moon Syndrome are often used interchangeably or together (Laurence-Moon-Biedl-(Bardet) Syndrome) to describe BBS. However, Laurence-Moon Syndrome (LMS) has been defined as a separate entity characterized by retinal degeneration, mental retardation, hypogonadism, and spastic paraplegia, although a recent study questions this distinction between LMS and BBS (21).

References

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