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Bardet-Biedl syndrome: an emerging pathomechanism of intracellular transport

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Abstract. From a handful of uncloned genetic loci 6 years ago, great strides have been made in understanding the genetic and molecular aetiology of Bardet-Biedl syndrome (BBS), a rare pleiotropic disorder characterised by a multitude of symptoms, including obesity, retinal degeneration and cystic kidneys. Presently, 11 BBS genes have been cloned, with the likelihood that yet more BBS genes remain undiscovered. In 2003, a major breakthrough was made when it was shown that BBS is likely caused by defects in basal bodies and/or primary cilia. Since then, studies in numerous animal models of BBS have corroborated the initial findings and, in addition, have further refined the specific functions of BBS proteins. These include roles in establishing planar cell polarity (noncanonical Wnt signaling) in mice and zebrafish, modulating intraflagellar transport and lipid homeostasis in worms, and regulating intracellular trafficking and centrosomal functions in zebrafish and human tissue culture cells. From these discoveries, a common theme has emerged, namely that the primary function of BBS proteins may be to mediate and regulate microtubule-based intracellular transport processes.

Keywords. Bardet-Biedl syndrome, cilia, centrosomes, intracellular trafficking, intraflagellar transport.

Introduction

In 1866, four siblings with obesity, retinal degeneration and mental retardation were reported by Laurence and Moon [1]. Over 50 years later, Bardet and Biedl found individuals who, in addition to the Laurence-Moon symptoms, presented with polydactyly [2, 3]. It is now generally accepted that Laurence-Moon syndrome and Bardet-Biedl syndrome are not distinct disorders, but rather are allelic [4, 5]. Bardet-Biedl syndrome (BBS; OMIM 209900) is a highly pleiotropic human disorder, characterised by a multitude of symptoms. Beales et al. [4] proposed that clinical diagnosis of BBS requires four of six primary symptoms (i.e. obesity, rod-cone dystrophy, renal abnormalities, polydactyly, male hypogonadism and learning disabilities), or three primary symptoms and at least two secondary symptoms, which include diabetes mellitus, hepatic fibrosis, ataxia/poor coordination/imbalance, speech disorder/delay, polyuria/polydipsia (nephrogenic diabetes insipidus), mild spasticity (especially lower limbs), dental crowding/hypodontia/small roots/high arched palate, left ventricular hypertrophy/congenital heart disease, hearing loss, anosmia, and situs inversus (for full description of BBS symptoms see [4, 6, 7].

Although many BBS symptoms are detectable at birth, a number of them only become manifest from childhood onwards (e.g. retinal degeneration, genital abnormalities, obesity). Given the clinical hypervariability of BBS, correct diagnosis requires careful phenotypic analysis, and for those symptoms that develop after childhood, due consideration must be given to the age of the patient. Indeed, phenotypic overlap with disorders such as Meckel syndrome has resulted in a number of BBS patients being

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misdiagnosed [8]. Interestingly, a recent report describes a new BBS-like disorder termed MORM syndrome (mental retardation, truncal obesity, retinal dystrophy and micrognathia) [9]. Although the genetic lesion responsible for MORM syndrome is not linked to any of the known BBS loci, the high degree of phenotypic overlap with BBS, together with the fact that additional BBS genes remain to be discovered, implies that an allelic association with BBS cannot be discounted for MORM syndrome.

BBS is a rare disorder, with a prevalence of 1 : 13,000–1 : 17,000 [6, 13]. However, in isolated communities with increased frequency of consanguinity, such as certain fishing communities in Newfoundland and the Bedouin tribes of Kuwait and Saudi Arabia, the incidence of BBS can be as high as 1 : 13,000–1 : 17,000 [6, 13]. Anderson and colleagues [35] found that BBS is a rare disorder, with a prevalence of 1 : 13,000–1 : 17,000 [6, 13].

Gene identification

BBS is a multigenic disorder, with 11 genes now associated with the syndrome. Standard positional cloning techniques were used to identify the first 3 BBS genes, BBS6 [14, 15], BBS2 [16] and BBS4 [17], and very recently, a similar approach uncovered BBS10 [18]. High-density single-nucleotide polymorphism (SNP) microarray genotyping was used to identify the most recently discovered BBS gene, BBS11 [19]. For the remaining 6 genes, bioinformatics- and genomics-based approaches were applied to probe uncloned BBS genetic loci for candidate BBS genes. BBS1 [20] and BBS7 [21] were identified based on limited protein sequence similarity to BBS2. BBS8 [22] was identified on account of protein sequence similarity to BBS4. Finally, BBS3 [23, 24], BBS5 [25] and BBS9 [26] were identified using comparative genomics analyses that exploited the fact that all known BBS genes have been lost from the genomes of certain organisms.

Globally, BBS1 and BBS10 are the most common BBS loci, accounting for 23–56% and 20% of BBS cases, respectively [18, 27–29]. Next is BBS2 at 8–16%, followed by BBS6 at 4–5%, with the remaining BBS loci each contributing <4% of cases [BBS3 (2–4%), BBS4 (3%), BBS5 (3%), BBS7 (3.5%), BBS8 (1–2%) and BBS-9 (not determined)] [21, 30–33]. The reported variation in the contribution of certain BBS genes, in particular BBS1, which accounts for only 20–30% of cases in Caucasians [27], suggests that other BBS genes remain to be identified. Interestingly, with regard to the obesity phenotype, the frequency of the most common BBS mutation, M390R, is identical among obese and non-obese individuals in a Newfoundland population, indicating that BBS mutations are unlikely to function in the pathogenesis of non-syndromic obesity [34]. Consistent with these findings, Anderson and colleagues [35] found that BBS6 mutations are not linked to obesity in a Danish population with juvenile onset obesity.

With the exception of BBS3, BBS6, BBS10 and BBS11, the primary sequences of the other seven BBS proteins have not provided significant functional clues. BBS1, BBS2 and BBS7 proteins have predicted β-propeller domains, which are relatively common motifs with multiple functions [36]. BBS4 and BBS8 harbour several tetra-tricopeptide repeat domains (TPRs), which are found in many different proteins and play important roles in protein-protein interactions [37]. BBS5 possesses two DM16 repeat motifs of unknown function, and BBS9 was previously annotated as human B1 protein whose function is not known. In contrast, BBS3 encodes ADP-ribosylation-like protein 6 (ARL6), a small GTPase of the Ras superfamily with likely regulatory functions [23, 24]. The entire BBS6 protein and limited regions within BBS10 show sequence homology to archaeal chaperonins and the eukaryotic CCT (chaperonin containing TCP-1) proteins, suggesting possible roles in protein folding or assembly [18, 38]. Finally, BBS11 is a member of the TRIM family, and the encoded protein has E3 ubiquitin ligase activity that suggests a role in the ubiquitin/proteasome system [19]. Interestingly, as will be discussed later on, all of the BBS genes are widely distributed in ciliated organisms such as Chlamydomonas reinhardtii, Caenorhabditis elegans and Drosophila melanogaster, with the exception of the chaperonin-like BBS6 and BBS10 genes, which appear to have emerged more recently in vertebrates [18, 38].

Genetic inheritance of BBS

The genetic heterogeneity and familial phenotypic variability of BBS has sparked considerable interest in its mode of inheritance. Classically, it appears that BBS is inherited in an autosomal recessive manner, with two mutations at a single locus sufficient to cause the disease. However, over the last 5 years, several studies have indicated that BBS can be transmitted in a complex, non-Mendelian fashion, requiring mutations at more than one locus. In the seminal study, Katsanis et al. [39] screened 163 BBS families for mutations in BBS2 and BBS6 and found four pedigrees with individuals possessing three BBS alleles, namely a pair of homozygous mutations in one BBS gene and a third mutation in a second BBS gene. Since BBS gene mutations are rare in the general population, the probability of discovering four pedigrees with three BBS alleles is extremely small, indicating, therefore, that the third alleles are likely linked to disease pathogenicity in these individuals. Consistent with a triallelic mode of inheritance, Katsanis and colleagues also identified unaffected individuals with two nonsense alleles of BBS2 (Q59X/Y22X), indicating that two null