Update on the Genetics of Bardet-Biedl Syndrome

O. M'hamdi^a I. Ouertani^{a, b} H. Chaabouni-Bouhamed^{a, b}

^aDepartment of Human Genetics, Faculty of Medicine, Tunis El-Manar University, and ^bDepartment of Hereditary and Congenital Disorders, Charles Nicolle Hospital, Tunis, Tunisia

Key Words

Bardet-Biedl syndrome · Molecular diagnosis · Next-generation sequencing

Abstract

Bardet-Biedl syndrome (BBS) is an autosomal recessive disease characterized by retinal dystrophy, obesity, postaxial polydactyly, learning disabilities, renal involvement, and male hypogonadism. BBS is genetically heterogeneous, and to date 18 genes (*BBS1–18*) have been described. Mutations in known BBS genes account for approximately 70–80% of cases, and triallelic inheritance has been suggested in about 5%. Many minor features can be helpful in making the clinical diagnosis. Recently, the use of next-generation sequencing technologies has accelerated the identification of novel genes and causative disease mutations in known genes. This report presents a concise overview of the current knowledge on clinical data in BBS and the progress in molecular genetics research. A future objective will be the development of BBS diagnosis kits in order to offer genetic counseling for families at risk.

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ties, and renal tract and genital anomalies as well as other minor frequent features such as anosmia, ataxia, or Hirschsprung disease. Clinical diagnosis is established if at least 4 major features are present in a patient [Beales et al., 1999]. The phenotypic spectrum and timing of the onset of BBS-associated symptoms are highly variable; some manifestations can appear during childhood. BBS is considered a rare disorder: its prevalence in Tunisia has been estimated at 1:156,000 [M'hamdi et al., 2011], and the current prevalence in North American and European populations ranges from 1:140,000–160,000 live births. Populations with a high rate of consanguinity or from isolated regions have been characterized with a higher frequency of BBS such as for Kuwait (1:17,000) and Newfoundland (1:18,000) [Farag and Teebi, 1989; Moore et al., 2005].

BBS is a genetically heterogeneous disorder. To date, 18 genes have been described (*BBS1–18*) [Scheidecker et al., 2013], and 7 BBS proteins (*BBS1*, 2, 4, 5, 7, 8, and 9) form a stable complex 'BBSome' [Nachury et al., 2007; Lechtreck et al., 2009]. BBS is considered an autosomal recessive disease. Oligogenic inheritance has been shown in some BBS families [Katsanis et al., 2001; Leitch et al., 2008; Zaghloul et al., 2010]. Mutations in *BBS1–18* account for 70–80% of affected BBS families [Zaghloul and Katsanis, 2009; Muller et al., 2010; M'hamdi et al., 2013]. Founder mutations were described in Tunisian BBS families [Smaoui et al., 2006], in the Hutterite population [Innes et al., 2010], and in the Faroe Islands [Hjortshøj et

Bardet-Biedl syndrome (BBS, OMIM 209900) is a pleiotropic genetic disorder characterized by a wide spectrum of clinical signs including progressive retinal degeneration, postaxial polydactyly, obesity, learning difficul-

Table 1. Clinical diagnosis features in Bardet-Biedl syndrome and their frequencies

Clinical feature	Frequency, %
<i>Major feature</i>	
Rod-cone dystrophy	90–100
Obesity	72–92
Polydactyly	63–81
Genital anomalies	59–98
Learning difficulties	50–61
Renal anomalies	20–53
<i>Minor feature</i>	
Speech delay	54–81
Developmental delay	50–91
Diabetes mellitus	6–48
Dental anomalies	51
Congenital heart disease	7
Brachydactyly/syndactyly	46–100
Ataxia/poor coordination	40–86
Cardiopathy	10
Deafness	11–12
Anosmia/hyposmia	60

al., 2009]. Recently, the advent of next-generation sequencing technologies has accelerated the identification of novel BBS genes and causative disease mutations in known genes [Otto et al., 2010; Marion et al., 2012; Redin et al., 2012; Ajmal et al., 2013; M'hamdi et al., 2013]. This report presents a concise overview on the current knowledge of BBS including clinical and molecular data as well as a discussion of the future research directions aimed at the management of molecular diagnosis.

Bardet-Biedl Syndrome: Clinical Summary

Bardet-Biedl syndrome is diagnosed if at least 4 of the main manifestations are present in a patient. Clinical evaluation during early infancy remains difficult as not all of the main manifestations are congenital but may occur later during childhood (table 1).

Retinal Degeneration

BBS is recognized as one of the major causes of syndromic retinal dystrophy which leads to a severe visual handicap before adulthood in BBS patients, and total blindness usually occurs before the second decade of life [Mockel et al., 2011]. Different forms of retinal dystrophy have been described, including a cone-rod dystrophy or

rod-cone dystrophy, choroidal dystrophy, and so-called 'global severe retinal dystrophy'. Cone-rod dystrophy is defined as a progressive retinal degeneration with initial decreased visual acuity, impaired color vision, and electroretinogram abnormalities with cone functions affected at an early stage prior to the rods. Furthermore, rod-cone dystrophies are characterized by initial rod involvement with subsequent cone alteration. Molecular genetics analysis has revealed unclear retinal genotype-phenotype correlations [Riise, 1987; Beales et al., 1999; Riise et al., 2002; Hamel, 2007; Gerth et al., 2008].

Obesity

Obesity is the second major feature in BBS patients; the current incidence of obesity in the BBS cohort has been estimated to be 72–92% [Riise et al., 1997; Beales et al., 1999; Moore et al., 2005; M'hamdi et al., 2013]. Usually beginning in early childhood and becoming severe with age, obesity appears to be widespread and diffuse [Forsythe and Beales, 2013]. Some BBS patients develop type 2 diabetes which can be related to the degree of obesity. The origin of obesity in BBS patients seems to be both central and peripheral as described by molecular and physiological studies [Mykytyn et al., 2001; Davis et al., 2007; Zhang et al., 2011]. BBS mouse models show leptin resistance; BBS proteins are required for leptin receptor localization in the hypothalamus. Moreover, primary cilium and BBS proteins play a key role in the differentiation of adipocytes, suggesting that a defect of adipogenesis contributes to the pathogenesis of obesity in BBS patients [Rahmouni et al., 2008; Marion et al., 2009; Seo et al., 2009].

Polydactyly Limb Anomalies

Polydactyly-type limb anomalies are the third major feature in BBS and may be the only clinical sign present at birth. Classically, polydactyly is postaxial (63–81%) in BBS patients. Other limb defects such as brachydactyly or syndactyly are frequently reported for both hands and feet. Limb malformations in BBS have been associated with a dysregulation of the Sonic hedgehog pathway which is a key developmental pathway implicated in limb development and left/right symmetry [McGlinn and Tabin, 2006; Bimonte et al., 2011; Mockel et al., 2011].

Hypogonadism and Genital Anomalies

Hypogonadism may manifest as delayed puberty or hypogonadism in males and genital abnormalities in females [Beales et al., 1999]. It may include hypoplastic fallopian tubes and uterus, vaginal atresia, and hydrometrocolpos. In some cases, the vaginal malformation has been

Table 2. List of the locus position, the OMIM reference, and the product function, if known, of the Bardet-Biedl syndrome genes cited in this review

Gene	Locus	Function	Gene/MIM number
<i>BBS1</i>	11q13	BBSome protein	209901
<i>BBS2</i>	16q21	BBSome protein	606151
<i>BBS3/ARL6</i>	3p12p13	GTPase	608845
<i>BBS4</i>	15q22.3q23	BBSome protein	600374
<i>BBS5</i>	2q31	BBSome protein	603650
<i>BBS6/MKKS</i>	20p12	part of chaperonin complex/BBSome assembly	604896
<i>BBS7</i>	4q27	BBSome protein	607590
<i>BBS8/TTC8</i>	14q32.1	BBSome protein	608132
<i>BBS9</i>	7p14	BBSome protein	607968
<i>BBS10</i>	12q21.2	part of chaperonin complex	610148
<i>BBS11/TRIM32</i>	9q31q34.1	E3 ubiquitin ligase	602290
<i>BBS12</i>	4q27	part of chaperonin complex	610683
<i>BBS13/MKS1</i>	17q23	basal body/centriole migration	609883
<i>BBS14/CEP290/NPHP6</i>	12q21.3	basal body: RPGR interaction	610142
<i>BBS15/WDPCP</i>	2p15	basal body: regulation of septins localization and ciliogenesis	613580
<i>BBS16/SDCCAG8</i>	1q43	basal body/interaction with OFD1	613615
<i>BBS17/LZTFL1</i>	3p21.3	BBSome: regulation of BBSome ciliary trafficking and Shh signaling	606568
<i>BBS18/BBIP1</i>	10q25.2	BBSome protein	613605

reported as leading to lethal abdominal tumors in neonates [Stoler et al., 1995]. Some BBS patients were reported to have given birth to healthy children [Klein and Amman, 1969; Beales et al., 1999].

Cognitive Impairment

Neuropsychiatric manifestations have been described in BBS patients, including intellectual disability, learning difficulties, speech deficits, and behavioral problems such as autistic traits and psychosis [Beales et al., 1999]. The primary cilium is one of the important organelle in human brain cells and is necessary for neurogenesis signaling and hippocampal development [Han et al., 2008]. A recent report showed a reduction of the volume of the hippocampus in BBS patients [Baker et al., 2011].

Renal Abnormalities

Renal failure is one of the primary features and a major cause of morbidity and mortality in BBS patients [Imhoff et al., 2010; Sowjanya et al., 2011]. The renal abnormalities are variable but classically manifest with cystic tubular disease and anatomical malformations. Most BBS patients have been characterized as having urinary concentration defects with normal renal function and no major cysts [Putoux et al., 2012; Marion et al., 2011]. The primary cilium is necessary for water absorption in the kidney [Marion et al., 2011]. In addition, a recent study re-

ported that the vasopressin receptor AV2R is located on the primary cilium and plays a chemosensory role in renal epithelial cells [Raychowdhury et al., 2009].

Genetics of Bardet-Biedl Syndrome

BBS is a genetic heterogeneous disease; up to date 18 genes have been described (*BBS1–18*) accounting for 70–80% of the BBS cases (table 2). Within the last decade, the introduction of robust genomics analysis technologies such as homozygosity mapping using SNPs arrays and high-throughput sequencing technologies have accelerated the discovery of novel BBS genes and mutations in known causative disease genes [Smaoui et al., 2006; Abu Safieh et al., 2010; Marion et al., 2012; Redin et al., 2012; M'hamdi et al., 2013; Scheidecker et al., 2013].

BBS Genes Epidemiology

All described BBS genes have been shown to be related to cilium biogenesis and/or function [Mockel et al., 2011]. The BBS mutation spectrum is divergent between populations. In European and Caucasian populations, the most commonly mutated BBS genes are *BBS1* and *BBS10*, together accounting for about 21–30% of the BBS cases in those populations [Badano et al., 2003; Janssen et al., 2011]. In the Tunisian population, the pathogenic muta-

Fig. 1. Suggested algorithm for the molecular analysis of Bardet-Biedl syndrome patients in clinical genetics practice.

tions have been most frequently found in *BBS1*, *BBS2*, and *BBS8* [Smaoui et al., 2006; M'hamdi et al., 2013], while *BBS1*, *BBS3*, and *BBS4* are frequently mutated in the population of Saudi Arabia [Abu Safieh et al., 2010, 2012], contributing to 33, 17, and 17% of disease-associated mutations, respectively. In north European BBS patients, 2 recurrent mutations are most common and predicted to result in the protein change p.M390R (*BBS1*) (50% of *BBS1* cases) and p.C91Lfs*5 (*BBS10*) [Kim et al., 2010]. In isolated and highly consanguineous populations, founder mutations in BBS genes have been reported as well; in Tunisia, 2 founder mutations have been described: p.R189* in *BBS2* and c.459 + 1G>A in *BBS8* [Smaoui et al., 2006;

Chen et al., 2011; M'hamdi et al., 2013]. In the Faroe Islands, 1 splice mutation c.1091 + 3G>C in *BBS1* was reported, and in the Hutterite population, 1 other founder mutation, c.472 – 2A>G in *BBS2*, was described [Hjortshoj et al., 2009; Innes et al., 2010]. Several BBS genes have been described in other ciliopathies: *BBS15* and *BBS13* have been reported in Meckel syndrome [Otto et al., 2010]. Similarly, mutations in *SDCCAG8* were reported in Meckel syndrome [Schaefer et al., 2011; Billingsley et al., 2012].

Triallelism and Modifier Alleles in Bardet-Biedl Syndrome

Triallelic inheritance in BBS was reported in 2001 in an affected BBS family with unaffected BBS siblings carrying 2 mutations in the *BBS2* gene, whereas the affected child was found to have a third mutation in either *BBS1* or *BBS6*. This was interpreted to mean that 3 mutations were necessary to cause the disease in these patients [Katsanis et al., 2001]. Several studies reported few BBS families for whom the third allele correlated with a more severe phenotype, suggesting the possible effect of modifier alleles. In a reported BBS family, 2 affected patients shared the homozygous mutation p.M390R (*BBS1*); the first patient, carrying an additional heterozygous missense mutation (*BBS6*), had an earlier onset of obesity and more severe mental retardation than her sister who carried only the homozygous p.M390R (*BBS1*) mutation. In addition, a BBS family has been described with p.M390R (*BBS1*) and an additional heterozygous mutation found in *BBS2* associated with a higher body mass index and a more severe retinal phenotype [Badano et al., 2003]. The frequency of identified triallelism in BBS has been overall low, and several studies suggest the absence of evidence of triallelism in BBS families [Badano et al., 2006; Smaoui et al., 2006; Abu Safieh et al., 2012]. Moreover, the *CCDC28B* gene (synonym *MGC1203*) has been reported to contribute epistatic alleles modifying the BBS phenotype [Badano et al., 2006]. Interestingly, other ciliopathy genes have been described to exhibit epistatic effects on BBS gene mutations, such as *MKS1*, *MKS3*, *CEP290*, and *AHI1* [Nachury et al., 2007; Pawlik et al., 2010; Zaghoul et al., 2010].

Genotype-Phenotype Correlation

For the majority of identified mutations, no clear-cut correlation could be established between the genotype and clinical expression of BBS. Several studies have suggested a milder phenotype in association with some BBS gene mutations [Riise et al., 2002; Hjortshoj et al., 2010; Pawlik et al., 2010]. For instance, a milder phenotype has

been associated with the recurrent mutation p.M390R (*BBS1*) [Hjortshøj et al., 2010]. Further, in a recent study, ocular phenotype evaluation for 37 BBS patients revealed that patients with *BBS1* mutations had a milder phenotype than patients with mutations in other BBS genes [Daniels et al., 2012]. Other reports suggested the association between mutations in *BBS1*, *BBS2*, *BBS3*, and *BBS4* and specific ocular phenotypes and digital malformations [Heon et al., 2005].

Molecular Analysis of Bardet-Biedl Syndrome: Future Directions

The extensive clinical and genetic heterogeneity of BBS generates difficulties for molecular diagnosis and genetic counseling. Within the last decade, many molecular strategies have been proposed to optimize the frequency of mutation detection. These strategies include homozygosity mapping using SNPs arrays in consanguineous families and screening of all BBS genes by direct sequencing [Abu Safieh et al., 2010; Billingsley et al., 2011; Janssen et al., 2011]. Recently, the implementation of next-generation sequencing has accelerated the molecular analysis

of BBS patients [Choi et al., 2009; Marion et al., 2012; Redin et al., 2012; M'hamdi et al., 2013]. Targeted exon capture strategy coupled with high-throughput sequencing of 30 ciliopathy genes including 16 BBS genes, 12 nephronophthisis genes, the *ALMS1* gene, and the *CCDC28B* gene showed high efficiency of mutation detection in BBS patients (70–80%) [Redin et al., 2012; M'hamdi et al., 2013]. Furthermore, the advent of strategies for scanning the human genome at high resolution coupled with the recognition of copy number variation has led to new methodologies in the identification of clinically relevant genes [Alkuraya, 2013; de Ligt et al., 2013]. We hope that these new molecular strategies will be adopted by medical geneticists. In figure 1 we propose a specific algorithm that could be applied to delineate the clinical and molecular diagnosis of BBS in the future.

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