

# Bardet-Biedl Syndrome

Evgeny N. Suspitsin<sup>a, b</sup> Evgeny N. Imyanitov<sup>a–d</sup>

<sup>a</sup>N.N. Petrov Institute of Oncology, <sup>b</sup>St. Petersburg Pediatric Medical University, <sup>c</sup>I.I. Mechnikov North-Western Medical University, and <sup>d</sup>St. Petersburg State University, St. Petersburg, Russia

## Key Words

Bardet-Biedl syndrome · Ciliopathy · Ethnic variations · Recurrent mutations · Review · Treatment

## Abstract

Bardet-Biedl syndrome (BBS) is a rare autosomal recessive genetic disorder. It is characterized by heterogeneous clinical manifestations including primary features of the disease (rod-cone dystrophy, polydactyly, obesity, genital abnormalities, renal defects, and learning difficulties) and secondary BBS characteristics (developmental delay, speech deficit, brachydactyly or syndactyly, dental defects, ataxia or poor coordination, olfactory deficit, diabetes mellitus, congenital heart disease, etc.); most of these symptoms may not be present at birth but appear and progressively worsen during the first and second decades of life. At least 20 BBS genes have already been identified, and all of them are involved in primary cilia functioning. Genetic diagnosis of BBS is complicated due to lack of gene-specific disease symptoms; however, it is gradually becoming more accessible with the invention of multigene sequencing technologies. Clinical management of BBS is largely limited to a symptomatic treatment. Mouse experiments demonstrate that the most debilitating complication of BBS, blindness, can be rescued by topical gene therapy. There is a published case report describing the delay of BBS symptoms by nutritional compen-

sation of the disease-related biochemical deficiencies. Progress in DNA testing technologies is likely to rapidly resolve all limitations in BBS diagnosis; however, much slower improvement is expected with regard to BBS treatment.

© 2016 S. Karger AG, Basel

## Epidemiology

Bardet-Biedl syndrome (BBS) is a rare genetic disorder with severe multiorgan impairment. Its frequency in Europe and North America falls below 1:100,000 [Forsythe and Beales, 2013]. Some isolated human communities are characterized by unusually high occurrence of this disease [Sheffield, 2004]. For example, 13 BBS patients were registered among 48,000 inhabitants of the Faroe Islands, leading to disease frequency estimates of 1:3,700 [Hjortshøj et al., 2009]. BBS prevalence in Newfoundland was reported to approach 1:18,000 [Moore et al., 2005]. BBS is relatively common in the Middle East, with a frequency of 1:13,500 in some Bedouin communities and a noticeable number of families identified in several other populations [Farag and Teebi, 1989; M'hamdi et al., 2011]. Ashkenazi Jews, being apparently the most genetically studied founder community, have not yet been subjected to an exhaustive BBS epidemiologic research [Fedick et al., 2014]. It is important to comment that many of the re-

ported frequency estimates were not explicitly tailored to the DNA-based diagnosis; therefore, the available figures should be treated with caution. Up to now, only a few instances of BBS have been reported in Eastern Europe, Asia, South America, and Africa, and systematic BBS studies still remain to be done in these regions [Khan et al., 2013; Xing et al., 2014; Ece Solmaz et al., 2015; Hirano et al., 2015; Suspitsin et al., 2015]. There are (1) the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS) at the Marshfield Clinic ([https://www.marshfieldclinic.org/services/bardet-biedl-syndrome-\(bbs\);](https://www.marshfieldclinic.org/services/bardet-biedl-syndrome-(bbs);) <https://cribbs.marshfieldclinic.org/>), (2) the European-based EURO-WABB registry [Farmer et al., 2013], and a number of robust international studies [Deveault et al., 2011; Ajmal et al., 2013; Fattahi et al., 2014] attempting to attract unstudied patients to BBS research.

### Clinical Manifestations

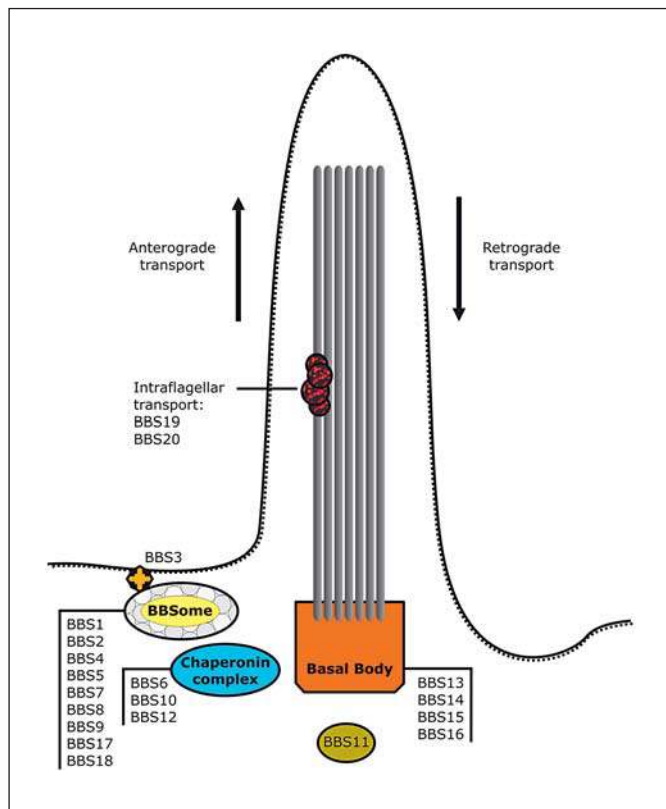
The description of essential clinical manifestations and corresponding diagnostic criteria is largely based on a seminal study of Beales et al. [1999]. It is important to acknowledge that these diagnostic algorithms were developed before the discovery of BBS genes and based on phenotypic presentations of this syndrome [Forsythe and Beales, 2013]. The disease symptoms may significantly vary between the patients; therefore, the diagnosis relies on the number of primary and secondary features of BBS. Multiple articles summarize the data on frequencies of various symptoms in BBS patients [Beales et al., 1999; Forsythe and Beales, 2013; M'hamdi et al., 2014]. However, it is very important to realize that almost all clinical studies analyzed patients of various ages. Many individuals with BBS look virtually healthy at birth unless they were born with a polydactyly. Other symptoms of BBS tend to gradually emerge during or after the first decade of life; thus, patients diagnosed at early childhood tend to have fewer clinical features of the disease. For example, rod-cone dystrophy was reported to affect 'only' 93% of BBS patients; however, those who did not have eye abnormalities were younger than 8 years at the time of the study [Beales et al., 1999].

There are 6 primary features of BBS, i.e. rod-cone dystrophy, polydactyly, obesity, genital abnormalities, renal defects, and learning difficulties. Secondary features include developmental delay, speech deficit, brachydactyly or syndactyly, dental defects, ataxia or poor coordination, olfactory deficit, diabetes mellitus, and congenital heart disease [Forsythe and Beales, 2013]; some authors also

mention hypertension, liver abnormalities, bronchial asthma, otitis, rhinitis, craniofacial dysmorphism, etc. [Baker and Beales, 2009; Forsythe and Beales, 2013; Shoemark et al., 2015; Khan et al., 2016]. It is recommended to assign BBS diagnosis to patients bearing at least 4 out of 6 primary features of the disease. If only 3 primary features are detected, 2 secondary features are required to confirm the presence of BBS. These criteria describe BBS mainly as a clinical entity; they do not fully account to the existence of patients with attenuated forms of the disease as well as to possible gene-specific manifestations of BBS [Pawlik et al., 2010; Estrada-Cuzcano et al., 2012]. It is likely that the increasing number of patients with incomplete diagnostic criteria for this syndrome will be subjected to BBS gene testing in the future, thanks to the improving availability of multigene sequencing. Furthermore, given that only polydactyly and renal abnormalities are often diagnosed at or before birth, the relaxed criteria for antenatal genetic screening are warranted [Putoux et al., 2010]. There is also a noticeable phenotypic overlap with some other ciliopathies, e.g. Alström syndrome, Joubert syndrome, Meckel syndrome, McKusick-Kaufman syndrome, or Senior-Loken syndrome, which further complicates the clinical and genetic diagnosis of BBS [Reidin et al., 2012].

### BBS Genes

The first 5 BBS loci were identified via linkage analysis of large BBS pedigrees [Kwitek-Black et al., 1993; Leppert et al., 1994; Sheffield et al., 1994; Carmi et al., 1995; Young et al., 1999] with corresponding genes cloned some years later [Mykytyn et al., 2001, 2002; Nishimura et al., 2001; Chiang et al., 2004; Fan et al., 2004; Li et al., 2004]. The first gene assigned to BBS was *MKKS* (*MKS*) already known to induce McKusick-Kaufman syndrome; given that it did not belong to previously identified BBS loci, it was named *BBS6*. At present, there are already 21 known BBS genes (*BBS1–BBS20* and *NPHP1*), and their number is likely to increase due to the invention of exome sequencing and analysis of previously unstudied populations (table 1). Strikingly, all BBS genes participate in cilia functioning (fig. 1), being a part of BBSome (*BBS1*, *BBS2*, *BBS4*, *BBS5*, *BBS7*, *BBS8*, *BBS9*, *BBS17*, and *BBS18*), chaperonin complex (*BBS6*, *BBS10* and *BBS12*), basal body (*BBS13*, *BBS14*, *BBS15*, and *BBS16*) or having some related biological function (*BBS3*, *BBS11*, *BBS19*, *BBS20*, and *NPHP1*). These genes apparently lack redundancy, and the disruption of any of them lead to cilia impairment



**Fig. 1.** BBS proteins, see comments in the text and in table 1.

[Tayeh et al., 2008]. It is frequently stated that the clinical presentation of BBS does not significantly depend on the identity of genes involved; therefore, prioritization of gene testing based on phenotypic characteristics of the affected patient is not advised [Forsythe and Beales, 2013]. However, most of the available BBS patients are *BBS1* and *BBS10* biallelic mutation carriers, while other genetic types of the disease are described in very small patient series or even in single families. There are multiple studies emphasizing genotype-phenotype correlations, i.e. specific disease presentation in carriers of particular alleles (table 1).

It is usually stated that the analysis of known BBS genes detects biallelic mutations in ~80% of BBS patients [Billingsley et al., 2011; Forsythe and Beales, 2013; Glöckle et al., 2014]. There are a number of limitations related to this issue. First, many of the identified mutations are not overtly deleterious (i.e. frameshifts, premature stop codons or alterations at splice sites), but are represented by amino acid substitutions [Muller et al., 2010; Pereiro et al., 2010; Deveault et al., 2011; Álvarez-Satta et al., 2014;

Lindstrand et al., 2014]. The evaluation of the true pathogenic impact of missense mutations is highly complicated and usually relies on the segregation analysis, various bioinformatics tools and functional assays. None of these approaches is sufficiently precise, especially when only one is performed [Muller et al., 2010]. Secondly, most of the current DNA sequencing protocols have some deficiencies, i.e. they are unable to cover all potentially important regions of BBS genes [Redin et al., 2012]. Thirdly, BBS genetic studies usually do not involve MLPA or equivalent methods. For this reason, some large gene rearrangements are likely to be missed [Muller et al., 2010; Lindstrand et al., 2014]. In agreement with this, some studies report the increased occurrence of BBS gene heterozygotes among BBS patients, leaving the possibility that the mutation in the second allele remains to be overlooked due to technical limitations [Fauser et al., 2003; Hichri et al., 2005; Hjortshøj et al., 2010].

### Mode of Inheritance

Early studies on BBS suggested the classical mode of autosomal recessive inheritance, and this model was confirmed in the initial gene discovery studies [Kwitek-Black et al., 1993; Leppert et al., 1994; Young et al., 1999]. Further research added complexity to the genetics of BBS. There are occasional observations on biallelic BBS gene mutation carriers, who remain healthy by the time of the investigation; this suggests incomplete penetrance at least for some genes and/or types of mutations [Katsanis et al., 2001; Beales et al., 2003; Estrada-Cuzcano et al., 2012]. At the same time, those patients who are affected by the disease and carry a homozygous mutation in one of the BBS genes often carry an additional heterozygous mutation in another BBS gene. These sensational observations were defined as a 'triallelic inheritance' and became a subject of intensive studies [Katsanis et al., 2001]. Some data sets confirm increased coincidence of homozygous and heterozygous BBS gene mutations in BBS patients, while others deny this relationship [Katsanis et al., 2002; Badano et al., 2003a; Beales et al., 2003; Fauser et al., 2003; Mykytyn et al., 2003; Hichri et al., 2005; Laurier et al., 2006; Smaoui et al., 2006; Hjortshøj et al., 2010; Abu-Safieh et al., 2012; Daniels et al., 2012; Redin et al., 2012]. Furthermore, the mechanistic basis for the pathogenic impact of heterozygous mutations remains largely elusive. The existing statistics may be compromised by the fact that the majority of available studies put both protein-truncating and presumably pathogenic missense mutations in one basket,

**Table 1.** Genetics of BBS

| Gene (synonyms), chromosome localization  | Contribution to BBS morbidity <sup>a</sup>                       | Subcellular localization, function            | Recurrent variants  | Genotype-phenotype correlations  | Other conditions caused by mutations in the same gene  |
|---|--|---|---|--|--|
| <i>BBS1</i> ( <i>BBS2L2</i> ), 11q13 [Leppert et al., 1994; Mykytyyn et al., 2002; Müller et al., 2010]           | 23%  | BBSome  | c.1169T>G (p.M390R), people of Northern European descent [Mykytyyn et al., 2003]; c.1091+3G>C; Faroe Islands [Hjortshøj et al., 2009]                                   | Milder phenotype for <i>BBS1</i> compared to <i>BBS2</i> and <i>BBS10</i> [Hjortshøj et al., 2010]; Better visual acuity and larger ERG amplitudes compared to patients with mutations in other BBS genes [Daniels et al., 2012]; Among patients with p.M390R mutation, homozygotes showed a relatively more severe ocular phenotype than compound heterozygotes [Castro-Sanchez et al., 2015]; Patients with missense mutations in <i>BBS1</i> had a lower level of biochemical cardiovascular disease markers compared to patients with <i>BBS10</i> and other <i>BBS1</i> mutations [Forsythe et al., 2015] | Nonsyndromic retinitis pigmentosa [Estrada-Cuzcano et al., 2012]   |
| <i>BBS2</i> ( <i>BBS</i> ), 16q21 [Kwitek-Black et al., 1993; Katsanis et al., 2001; Nishimura et al., 2001]      | 8% higher frequency in Iran (29%) [Fattahi et al., 2014]         | BBSome  | c.472-2A>G, Hutterites [Innes et al., 2010]; c.565C>T (p.R189*), Tunisia [M'hamdi et al., 2014]; c.311A>C (p.D104A) and c.1895G>C, Ashkenazi Jews [Fedick et al., 2014] | Biallelic <i>BBS2</i> mutations were detected in some antenatal cases presenting with cystic kidneys and polydactyly and/or hepatic fibrosis but no encephalocoele; these fetuses were mostly diagnosed as having Meckel or Meckel-like syndrome [Karmous-Benaïly et al., 2005]; Nonsyndromic retinitis pigmentosa [Shevach et al., 2015]  |  |
| <i>BBS3</i> ( <i>ARL6</i> , <i>RP55</i> ), 3q11.2 [Sheffield et al., 1994; Chiang et al., 2004; Fan et al., 2004] | 0.4% higher frequency in India (18%) [Sathya Priya et al., 2014] | Small GTPase, participates in BBSome assembly | c.272T>C (p.I91T), India [Sathya Priya et al., 2014]  | Myopia was associated with <i>BBS3</i> and <i>BBS4</i> , but not <i>BBS2</i> mutations [Héon et al., 2005]   | Nonsyndromic retinitis pigmentosa [Aldahmesh et al., 2009]   |
| <i>BBS4</i> , 15q22.3q23 [Carmi et al., 1995; Mykytyyn et al., 2001]  | 2%   | BBSome  | c.77_220del144, Iran [Mykytyyn et al., 2001]  | Characteristic ocular phenotype (sparse amount of abnormal retinal pigment deposits even in advanced disease stage; amorphous appearance of the deposits) [Riise et al., 2002]; Myopia was associated with <i>BBS3</i> and <i>BBS4</i> , but not <i>BBS2</i> mutation [Héon et al., 2005]  | Biallelic <i>BBS4</i> mutations were detected in some antenatal cases presenting with cystic kidneys and polydactyly and/or hepatic fibrosis but no encephalocoele; these fetuses were mostly diagnosed as having Meckel or Meckel-like syndrome [Karmous-Benaïly et al., 2005]  |
| <i>BBS5</i> , 2q31 [Young et al., 1999; Li et al., 2004]  | 0.4%   | BBSome  |   |  |  |
| <i>BBS6</i> ( <i>MKS</i> , <i>MKS</i> ), 20p12 [Katsanis et al., 2000; Slavotinek et al., 2000]                   | 6%   | Chaperonin complex                            |   | Patients with mutations in <i>BBS6</i> , <i>BBS10</i> or <i>BBS12</i> genes had more severe renal disease [Imhoff et al., 2011]  | McKusick-Kaufman syndrome [Schaefer et al., 2011]; Biallelic <i>BBS6</i> mutations were detected in some antenatal cases presenting with cystic kidneys and polydactyly and/or hepatic fibrosis but no encephalocoele; these fetuses were mostly diagnosed as having Meckel or Meckel-like syndrome [Karmous-Benaïly et al., 2005] |
| <i>BBS7</i> ( <i>FLJ10715</i> , <i>BBS2L1</i> ), 4q27 [Badano et al., 2003b]                                      | 2%   | BBSome  | c.1967_1968delT AinsC (p.L656Pfs*18), Russia [Suspitsin et al., 2015]   |  |  |
| <i>BBS8</i> ( <i>TTC8</i> , <i>RP51</i> ), 14q32.1 [Ansley et al., 2003]  | 1%   | BBSome  | c.459+1G>A, Tunisia [M'hamdi et al., 2014]  |  | Nonsyndromic retinitis pigmentosa [Goyal et al., 2016]   |

**Table 1 (continued)**

| Gene (synonyms), chromosome localization   | Contribution to BBS morbidity <sup>a</sup> | Subcellular localization, function  | Recurrent variants  | Genotype-phenotype correlations   | Other conditions caused by mutations in the same gene  |
|--|--|---|---|---|--|
| <i>BBS9</i> ( <i>PTHL1, BI, DI, CI8</i> ), 7p14 [Nishimura et al., 2005]   | 6%   | BBSome  |   |   |  |
| <i>BBS10</i> ( <i>CI2orf58, FLJ123560</i> ), 12q21.2 [Stoetzel et al., 2006]   | 20%  | Chaperonin complex  | c.271_272insT (p.C91Lfs*5), people of European descent [Stoetzel et al., 2006; Muller et al., 2010; Billingsley et al., 2011] | Patients with <i>BBS10</i> mutations had significantly higher BMI-Z, greater visceral adiposity, and greater insulin resistance than those with <i>BBS1</i> mutations [Feuillan et al., 2011];<br>A higher frequency of urogenital anomalies in patients with <i>BBS10</i> vs. <i>BBS1</i> mutations was observed [Castro-Sanchez et al., 2015];<br>Patients with mutations in <i>BBS6</i> , <i>BBS10</i> or <i>BBS12</i> genes had more severe renal disease [Imhoff et al., 2011] |  |
| <i>BBS11</i> ( <i>TRIM32, HT2A, LGMD2H, TATIP</i> ), 9q31q34.1 [Chiang et al., 2006]   | 0.1%                                       | E3 ubiquitin ligase, involved in membrane trafficking                                       |   |   | Limb-girdle muscular dystrophy type 2H, sarcofubular myopathy [Frosk et al., 2002]   |
| <i>BBS12</i> ( <i>C4orf24, FLJ35630</i> ), 4q27 [Stoetzel et al., 2007]  | 5%   | Chaperonin complex  | c.1156–1157CG>TA (p.Arg386*), Iran [Fattahi et al., 2014]   | A higher frequency of cognitive impairment in patients with <i>BBS12</i> vs. <i>BBS1</i> mutations was observed [Castro-Sanchez et al., 2015];<br>Patients with mutations in <i>BBS6</i> , <i>BBS10</i> or <i>BBS12</i> genes had more severe renal disease [Imhoff et al., 2011]   |  |
| <i>BBS13</i> ( <i>MKS1, FLJ20345</i> ), 17q23 [Leitch et al., 2008]  | 4.5%                                       | Basal body, participates in organization of the transition zone                             |   |   | Meckel syndrome [Consugar et al., 2007]  |
| <i>BBS14</i> ( <i>CEP290, NPHP6, 3H11Ag, BBS14, CT87, JBT55, LCA10, MKS4, POC3, SLSN6, rd16</i> ), 12q21.3 [Leitch et al., 2008]                 | 1%   | Basal body, participates in organization of the transition zone and ciliary entry of BBSome |   |   | Joubert syndrome, nephronophthisis, Senior-Loken syndrome, Meckel syndrome, Leber congenital amaurosis [Coppeters et al., 2010]  |
| <i>BBS15</i> ( <i>WDPCP, C2orf86, CHDTHP, FRITZ, FRTZ</i> ), 2p15 [Kim et al., 2010]   | 1%   | Basal body, involved in regulation of septins localization and ciliogenesis                 |   |   | Exome sequencing identified a compound heterozygous mutation in a young girl with polysyndactyly, coarctation of the aorta, and tongue hamartomas [Saari et al., 2015] |
| <i>BBS16</i> ( <i>SDCCAG8, NPHP10, CCCAP, CCCAP SLSN7, HSPC085, NY-CO-8, SLSN7, hCCCAP</i> ), 1q43 [Otto et al., 2010; Billingsley et al., 2012] | 1%   | Basal body, regulates pericentriolar material recruitment to the centrosomal region         |   | Absence of polydactyly [Schaefer et al., 2011]  | Senior-Loken syndrome [Otto et al., 2010]  |
| <i>BBS17</i> ( <i>LZTFL1</i> ), 3p21.3 [Marion et al., 2012; Schaefer et al., 2014]  | ?  | BBSome, participates in the Shh signaling   |   | Mesoaxial polydactyly [Schaefer et al., 2014]   |  |
| <i>BBS18</i> ( <i>BBIP1, BBIP10, bA348N5.3, NCRNA00081</i> ), 10q25.2 [Scheidecker et al., 2014]   | ?  | BBSome  |   |   |  |



**Table 1 (continued)**

| Gene (synonyms), chromosome localization   | Contribution to BBS morbidity <sup>a</sup> | Subcellular localization, function   | Recurrent variants   | Genotype-phenotype correlations   | Other conditions caused by mutations in the same gene   |
|--|--|--|--|---|---|
| <i>BBS19</i> ( <i>IFT27, RAYL, RABL4</i> ), 22q12 [Aldahmesh et al., 2014]   | ?  | G-protein, involved in intraflagellar transport  |  |   |   |
| <i>BBS20</i> ( <i>IFT172, NPHH17, SRTD10SLB, wim, RP71, osm-1</i> ), 2p23.3 [Bujakowska et al., 2015; Schaefer et al., 2016] | ?  | Involved in intraflagellar transport   |  |   | Jeune syndrome, Mainzer-Saldino syndrome [Halbritter et al., 2013]; Nonsyndromic retinitis pigmentosa [Bujakowska et al., 2015] |
| <i>BBS21</i> ( <i>?</i> ) ( <i>NPHH1, NPH1, JBTS4, SLN1</i> ), 2q13 [Lindstrand et al., 2014]                                | ?  | Mediates anchoring of the basal body to the plasma membrane and assembly of the primary cilium | 290-kb deletion, people of Northern European descent [Konrad et al., 1996] | One BBS patient described by Lindstrand et al. [2014] carried a homozygous <i>NPHH1</i> deletion together with a homozygous benign variant in <i>BBS2</i> ; BBS patients from another pedigree demonstrated a combination of a heterozygous deletion in <i>NPHH1</i> and a heterozygous null mutation in <i>BBS10</i> | Nephronophthisis [Renkema et al., 2014]; Senior-Loken syndrome, Joubert syndrome [Hildebrandt et al., 2011]                     |

<sup>a</sup> Forsythe and Beales [1993, 2013].

leaving the possibility that some of the accounted variants are actually benign. It is beyond any doubt, that at least a part of the observed phenotypic variability is not at all related to conventional genetic factors; for example, Beales et al. [1999] described monozygotic twins; one boy presented with polydactyly in 3 limbs, while his brother did not have additional fingers at all.

There is experimental evidence that some of the BBS mutations may render dominant-negative effect, e.g. by affecting the function of the remaining (wild-type) gene allele [Zaghloul et al., 2010]. The dominant-negative model may explain the increased incidence of heterozygous BBS gene mutation carriers in patients with BBS syndrome as well as the role of single-copy gene alterations in triallelic inheritance [Fauser et al., 2003; Hichri et al., 2005; Hjortshøj et al., 2010]. Some reports indicate an increased incidence of isolated BBS-related symptoms in parents of BBS patients and/or heterozygous carriers of the BBS gene mutations, while other studies disagree with this statement [Croft et al., 1995; Beales et al., 1999; Cox et al., 2003; Hjortshøj et al., 2007; Kim et al., 2007; Webb et al., 2009].

### Founder Mutations

Many of genetically diagnosed BBS patients carry founder mutations. Missense M390R mutation in the *BBS1* gene is characteristic for patients of European descent, while *BBS10* p.C91Lfs\*5 truncation was detected in several ethnic groups [Zaghloul and Katsanis, 2009]. Biallelic *BBS1* M390R carriers may have an attenuated form of the disease or even remain healthy [Hjortshøj et al., 2010; Estrada-Cuzcano et al., 2012]. Other recurrent alleles appear to be more ethnically specific. There are *BBS1* c.1091+3G>C in the Faroe Islands [Hjortshøj et al., 2009], *BBS2* c.472-2A>G in Hutterites [Innes et al., 2010], *BBS2* p.R189\* and *BBS8* c.459+1G>A in Tunisia [M'hamdi et al., 2014], *BBS2* c.311A>C (p.D104A) and c.1895G>C in Ashkenazi Jews [Fedick et al., 2014], *BBS3* c.272T>C (p.I91T) in India [Sathya Priya et al., 2015], *BBS4* c.77\_220del144 and c.1156-1157 CG>TA (p.Arg386\*) in Iran [Mykytyn et al., 2001; Fattahi et al., 2014], and *BBS7* c.1967\_1968delTAinsC in Russia [Suspitsin et al., 2015].

Founder mutations can be easily detected by rapid and cheap PCR tests; therefore, they may be tested at the beginning of diagnostic procedures or even for screening purposes [Suspitsin et al., 2015]. However, the majority of BBS cannot be explained by the inheritance of founder alleles and still requires exhaustive multigene testing.

## Experimental Therapeutics

Management of patients with BBS symptoms is largely restricted to symptomatic treatment and is unable to prevent the development of the most debilitating complication, i.e. blindness. Topical delivery of the missing BBS gene, e.g. by subretinal injection of BBS-containing adenovirus construct, rescued rhodopsin mislocalization and preserved the function of the eyes in experimental mice [Simons et al., 2011; Seo et al., 2013]. There were also some attempts to prevent apoptosis of photoreceptor cells by various pharmacological compounds [Mockel et al., 2012]. Administration of the melanocortin receptor agonist, melanotan II, attenuated obesity in BBS knockout mice, probably due to the activation of downstream leptin receptor signaling [Seo et al., 2009]. The inhibition of specific signaling molecules, such as mTOR by rapamycin or selected cyclin-dependent kinases by roscovitine, partially restored renal structure and function in zebrafish BBS models [Tobin and Beales, 2008]. There is an exceptionally interesting case report on a BBS-affected 21-month-old girl, who underwent comprehensive testing for biochemical deficiencies and was subsequently subjected to appropriate nutritional correction. Astonishingly, this child experienced a remarkable improvement of vision, resolution of obesity, normalization of behavior and mood, and restoration of normal development during the following 2 years and remained virtually healthy by the time of publication, i.e. being 7 years old [Genuis and Lobo, 2011]. While already established organ anomalies are notoriously difficult to treat, the mere delaying of BBS symptoms, if started from birth, may eventually turn out to be a feasible strategy.

## Perspectives

The invention of next-generation sequencing offers an opportunity to discover new BBS loci and thus explain the missing heritability in BBS patients without mutations in *BBS1*–*BB20* genes [Billingsley et al., 2011]. It has to be remembered that the most popular next-generation sequencing technology, whole-exome sequencing, is currently unable to reliably detect large gene rearrangements. Searching for gross alterations in already known and novel BBS genes currently requires different arrays of molecular tests, and they remain to be performed in BBS patients with unknown genetic causes of the disease. The existence of significant ethnic varia-

tions in the spectrum of affected genes calls for collection of patients and their genetic analysis in yet unstudied communities across the world. We are eagerly awaiting interventional trials in humans. Some of them, especially the ones based on gene therapy, may take years to come due to safety concerns as well as difficulties in organizing sophisticated gene-specific procedures for such a rare and heterogeneous multiorgan disease. Other approaches, e.g. as in the above-mentioned case based on nutritional correction [Genuis and Lobo, 2011], deserve rapid clinical assessment. In addition, population-based genetic screening is gradually becoming more achievable, thanks to decreasing costs and improving throughput for DNA-based assays. Routine identification of carriers of BBS mutations may eventually reduce the disease burden by revealing families at-risk and taking appropriate preventive actions [Genuis and Lobo, 2011; Baker et al., 2013].

## Acknowledgments

This work was supported by the Russian Scientific Fund (grant 15-15-00079). We are cordially thankful to Dr. Ekatherina Kuliagina for her help in preparing the figure.

## Disclosure Statement

The authors have no conflicts of interest to disclose.

## References

- Abu-Safieh L, Al-Anazi S, Al-Abdi L, Hashem M, Alkuraya H, et al: In search of triallelism in Bardet-Biedl syndrome. *Eur J Hum Genet* 20: 420–427 (2012).
- Ajmal M, Khan MI, Neveling K, Tayyab A, Jaffar S, et al: Exome sequencing identifies a novel and a recurrent *BBS1* mutation in Pakistani families with Bardet-Biedl syndrome. *Mol Vis* 19:644–653 (2013).
- Aldahmesh MA, Safieh LA, Alkuraya H, Al-Rajhi A, Shamseldin H, et al: Molecular characterization of retinitis pigmentosa in Saudi Arabia. *Mol Vis* 15:2464–2469 (2009).
- Aldahmesh MA, Li Y, Alhashem A, Anazi S, Alkuraya H, et al: *IFT27*, encoding a small GTPase component of IFT particles, is mutated in a consanguineous family with Bardet-Biedl syndrome. *Hum Mol Genet* 23:3307–3315 (2014).

- Álvarez-Satta M, Castro-Sánchez S, Pereiro I, Piñeiro-Gallego T, Baiget M, et al: Overview of Bardet-Biedl syndrome in Spain: identification of novel mutations in *BBS1*, *BBS10* and *BBS12* genes. *Clin Genet* 86:601–602 (2014).
- Ansley SJ, Badano JL, Blacque OE, Hill J, Hoskins BE, et al: Basal body dysfunction is a likely cause of pleiotropic Bardet-Biedl syndrome. *Nature* 425:628–633 (2003).
- Badano JL, Kim JC, Hoskins BE, Lewis RA, Ansley SJ, et al: Heterozygous mutations in *BBS1*, *BBS2* and *BBS6* have a potential epistatic effect on Bardet-Biedl patients with two mutations at a second BBS locus. *Hum Mol Genet* 12:1651–1659 (2003a).
- Badano JL, Ansley SJ, Leitch CC, Lewis RA, Lupski JR, Katsanis N: Identification of a novel Bardet-Biedl syndrome protein, *BBS7*, that shares structural features with *BBS1* and *BBS2*. *Am J Hum Genet* 72:650–658 (2003b).
- Baker K, Beales PL: Making sense of cilia in disease: the human ciliopathies. *Am J Med Genet C Semin Med Genet* 151C:281–295 (2009).
- Baker TM, Sturm EL, Turner CE, Petersen SM: Diagnosis of Bardet-Biedl syndrome in consecutive pregnancies affected with echogenic kidneys and polydactyly in a consanguineous couple. *Case Rep Genet* 2013:159143 (2013).
- Beales PL, Elcioglu N, Woolf AS, Parker D, Flintner FA: New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. *J Med Genet* 36:437–446 (1999).
- Beales PL, Badano JL, Ross AJ, Ansley SJ, Hoskins BE, et al: Genetic interaction of *BBS1* mutations with alleles at other BBS loci can result in non-Mendelian Bardet-Biedl syndrome. *Am J Hum Genet* 72:1187–1199 (2003).
- Billingsley G, Deveault C, Héon E: BBS mutational analysis: a strategic approach. *Ophthalmic Genet* 32:181–187 (2011).
- Billingsley G, Vincent A, Deveault C, Héon E: Mutational analysis of SDCCAG8 in Bardet-Biedl syndrome patients with renal involvement and absent polydactyly. *Ophthalmic Genet* 33:150–154 (2012).
- Bujakowska KM, Zhang Q, Siemiakowska AM, Liu Q, Place E, et al: Mutations in *IFT172* cause isolated retinal degeneration and Bardet-Biedl syndrome. *Hum Mol Genet* 24:230–242 (2015).
- Carmi R, Rokhlina T, Kwitek-Black AE, Elbedour K, Nishimura D, et al: Use of a DNA pooling strategy to identify a human obesity syndrome locus on chromosome 15. *Hum Mol Genet* 4:9–13 (1995).
- Castro-Sánchez S, Álvarez-Satta M, Cortón M, Guillén E, Ayuso C, Valverde D: Exploring genotype-phenotype relationships in Bardet-Biedl syndrome families. *J Med Genet* 52:503–513 (2015).
- Chiang AP, Nishimura D, Searby C, Elbedour K, Carmi R, et al: Comparative genomic analysis identifies an ADP-ribosylation factor-like gene as the cause of Bardet-Biedl syndrome (*BBS3*). *Am J Hum Genet* 75:475–484 (2004).
- Chiang AP, Beck JS, Yen HJ, Tayeh MK, Scheetz TE, et al: Homozygosity mapping with SNP arrays identifies *TRIM32*, an E3 ubiquitin ligase, as a Bardet-Biedl syndrome gene (*BBS11*). *Proc Natl Acad Sci USA* 103:6287–6292 (2006).
- Consugar MB, Kubly VJ, Lager DJ, Hommerding CJ, Wong WC, et al: Molecular diagnostics of Meckel-Gruber syndrome highlights phenotypic differences between *MKS1* and *MKS3*. *Hum Genet* 121:591–599 (2007).
- Coppieters F, Lefever S, Leroy BP, De Baere E: *CEP290*, a gene with many faces: mutation overview and presentation of *CEP290base*. *Hum Mutat* 31:1097–1108 (2010).
- Cox GF, Hansen RM, Quinn N, Fulton AB: Retinal function in carriers of Bardet-Biedl syndrome. *Arch Ophthalmol* 121:804–810 (2003).
- Croft JB, Morrell D, Chase CL, Swift M: Obesity in heterozygous carriers of the gene for the Bardet-Biedl syndrome. *Am J Med Genet* 55:12–15 (1995).
- Daniels AB, Sandberg MA, Chen J, Weigel-DiFranco C, Fielding Hejtmancic J, Berson EL: Genotype-phenotype correlations in Bardet-Biedl syndrome. *Arch Ophthalmol* 130:901–907 (2012).
- Deveault C, Billingsley G, Duncan JL, Bin J, Theal R, et al: BBS genotype-phenotype assessment of a multiethnic patient cohort calls for a revision of the disease definition. *Hum Mutat* 32:610–619 (2011).
- Ece Solmaz A, Onay H, Atik T, Aykut A, Cerrah Gunes M, et al: Targeted multi-gene panel testing for the diagnosis of Bardet Biedl syndrome: identification of nine novel mutations across *BBS1*, *BBS2*, *BBS4*, *BBS7*, *BBS9*, *BBS10* genes. *Eur J Med Genet* 58:689–694 (2015).
- Estrada-Cuzcano A, Koenekoop RK, Senechal A, De Baere EB, de Ravel T, et al: *BBS1* mutations in a wide spectrum of phenotypes ranging from nonsyndromic retinitis pigmentosa to Bardet-Biedl syndrome. *Arch Ophthalmol* 130:1425–1432 (2012).
- Fan Y, Esmail MA, Ansley SJ, Blacque OE, Borovich K, et al: Mutations in a member of the Ras superfamily of small GTP-binding proteins causes Bardet-Biedl syndrome. *Nat Genet* 36:989–993 (2004).
- Farag TI, Teebi AS: High incidence of Bardet Biedl syndrome among the Bedouin. *Clin Genet* 36:463–464 (1989).
- Farmer A, Aymé S, de Heredia ML, Maffei P, McCafferty S, et al: EURO-WABB: an EU rare diseases registry for Wolfram syndrome, Alström syndrome and Bardet-Biedl syndrome. *BMC Pediatr* 13:130 (2013).
- Fattahi Z, Rostami P, Najmabadi A, Mohseni M, Kahrizi K, et al: Mutation profile of BBS genes in Iranian patients with Bardet-Biedl syndrome: genetic characterization and report of nine novel mutations in five BBS genes. *J Hum Genet* 59:368–375 (2014).
- Fausser S, Munz M, Besch D: Further support for digenic inheritance in Bardet-Biedl syndrome. *J Med Genet* 40:e104 (2003).
- Fedick A, Jalas C, Abeliovich D, Krakinovsky Y, Ekstein J, et al: Carrier frequency of two *BBS2* mutations in the Ashkenazi population. *Clin Genet* 85:578–582 (2014).
- Feuillan PP, Ng D, Han JC, Sapp JC, Wetsch K, et al: Patients with Bardet-Biedl syndrome have hyperleptinemia suggestive of leptin resistance. *J Clin Endocrinol Metab* 96:E528–E535 (2011).
- Forsythe E, Beales PL: Bardet-Biedl Syndrome; in Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, et al (eds): *GeneReviews*<sup>®</sup> [Internet]. (University of Washington, Seattle 1993). <http://www.ncbi.nlm.nih.gov/books/NBK1363/>.
- Forsythe E, Beales PL: Bardet-Biedl syndrome. *Eur J Hum Genet* 21:8–13 (2013).
- Forsythe E, Sparks K, Hoskins BE, Bagkeris E, McGowan BM, et al: Genetic predictors of cardiovascular morbidity in Bardet-Biedl syndrome. *Clin Genet* 87:343–349 (2015).
- Frosk P, Weiler T, Nylén E, Sudha T, Greenberg CR, et al: Limb-girdle muscular dystrophy type 2H associated with mutation in *TRIM32*, a putative E3-ubiquitin-ligase gene. *Am J Hum Genet* 70:663–672 (2002).
- Genuis SJ, Lobo RA: Potential amelioration of morbidity in patients with chromosomal anomalies: relevance to Bardet-Biedl syndrome. *Clin Genet* 79:482–488 (2011).
- Glöckle N, Kohl S, Mohr J, Scheurenbrand T, Sprecher A, et al: Panel-based next generation sequencing as a reliable and efficient technique to detect mutations in unselected patients with retinal dystrophies. *Eur J Hum Genet* 22:99–104 (2014).
- Goyal S, Jäger M, Robinson PN, Vanita V: Confirmation of *TTC8* as a disease gene for non-syndromic autosomal recessive retinitis pigmentosa (RP51). *Clin Genet* 89:454–460 (2016).
- Halbritter J, Bizet AA, Schmidts M, Porath JD, Braun DA, et al: Defects in the IFT-B component IFT172 cause Jeune and Mainzer-Saldino syndromes in humans. *Am J Hum Genet* 93:915–925 (2013).
- Héon E, Westall C, Carmi R, Elbedour K, Pantan C, et al: Ocular phenotypes of three genetic variants of Bardet-Biedl syndrome. *Am J Med Genet A* 132A:283–287 (2005).
- Hichri H, Stoetzel C, Laurier V, Caron S, Sigaudy S, et al: Testing for triallelism: analysis of six BBS genes in a Bardet-Biedl syndrome family cohort. *Eur J Hum Genet* 13:607–616 (2005).
- Hildebrandt F, Benzing T, Katsanis N: Ciliopathies. *N Engl J Med* 364:1533–1543 (2011).
- Hirano M, Satake W, Ihara K, Tsuge I, Kondo S, et al: The First Nationwide Survey and Genetic Analyses of Bardet-Biedl Syndrome in Japan. *PLoS One* 10:e0136317 (2015).
- Hjortshøj TD, Grønsvov K, Rosenberg T, Brøndum-Nielsen K, Olsen JH: Risk for cancer in patients with Bardet-Biedl syndrome and their relatives. *Am J Med Genet A* 143A:1699–1702 (2007).



- Hjortshøj TD, Grønskov K, Brøndum-Nielsen K, Rosenberg T: A novel founder *BBS1* mutation explains a unique high prevalence of Bardet-Biedl syndrome in the Faroe Islands. *Br J Ophthalmol* 93:409–413 (2009).
- Hjortshøj TD, Grønskov K, Philp AR, Nishimura DY, Riise R, et al: Bardet-Biedl syndrome in Denmark – report of 13 novel sequence variations in six genes. *Hum Mutat* 31:429–436 (2010).
- Imhoff O, Marion V, Stoetzel C, Durand M, Holder M, et al: Bardet-Biedl syndrome: a study of the renal and cardiovascular phenotypes in a French cohort. *Clin J Am Soc Nephrol* 6:22–29 (2011).
- Innes AM, Boycott KM, Puffenberger EG, Redl D, MacDonald IM, et al: A founder mutation in *BBS2* is responsible for Bardet-Biedl syndrome in the Hutterite population: utility of SNP arrays in genetically heterogeneous disorders. *Clin Genet* 78:424–431 (2010).
- Karmous-Benaïly H, Martinovic J, Gubler MC, Sirot Y, Clech L, et al: Antenatal presentation of Bardet-Biedl syndrome may mimic Meckel syndrome. *Am J Hum Genet* 76:493–504 (2005).
- Katsanis N, Beales PL, Woods MO, Lewis RA, Green JS, et al: Mutations in *MKKS* cause obesity, retinal dystrophy and renal malformations associated with Bardet-Biedl syndrome. *Nat Genet* 26:67–70 (2000).
- Katsanis N, Ansley SJ, Badano JL, Eichers ER, Lewis RA, et al: Triallelic inheritance in Bardet-Biedl syndrome, a Mendelian recessive disorder. *Science* 293:2256–2259 (2001).
- Katsanis N, Eichers ER, Ansley SJ, Lewis RA, Kayserili H, et al: *BBS4* is a minor contributor to Bardet-Biedl syndrome and may also participate in triallelic inheritance. *Am J Hum Genet* 71:22–29 (2002).
- Khan S, Ullah I, Irfanullah, Touseef M, Basit S, et al: Novel homozygous mutations in the genes *ARL6* and *BBS10* underlying Bardet-Biedl syndrome. *Gene* 515:84–88 (2013).
- Khan SA, Muhammad N, Khan MA, Kamal A, Rehman ZU, Khan S: Genetics of human Bardet-Biedl syndrome, an update. *Clin Genet* (2016), DOI: 10.1111/cge.12737.
- Kim LS, Fishman GA, Seiple WH, Szlyk JP, Stone EM: Retinal dysfunction in carriers of Bardet-Biedl syndrome. *Ophthalmic Genet* 28:163–168 (2007).
- Kim SK, Shindo A, Park TJ, Oh EC, Ghosh S, et al: Planar cell polarity acts through septins to control collective cell movement and ciliogenesis. *Science* 329:1337–1340 (2010).
- Konrad M, Saunier S, Heidet L, Silbermann F, Bennessy F, et al: Large homozygous deletions of the 2q13 region are a major cause of juvenile nephronophthisis. *Hum Mol Genet* 5:367–371 (1996).
- Kwittek-Black AE, Carmi R, Duyk GM, Buetow KH, Elbedour K, et al: Linkage of Bardet-Biedl syndrome to chromosome 16q and evidence for non-allelic genetic heterogeneity. *Nat Genet* 5:392–396 (1993).
- Laurier V, Stoetzel C, Muller J, Thibault C, Corbani S, et al: Pitfalls of homozygosity mapping: an extended consanguineous Bardet-Biedl syndrome family with two mutant genes (*BBS2*, *BBS10*), three mutations, but no triallelism. *Eur J Hum Genet* 14:1195–1203 (2006).
- Leitch CC, Zaghoul NA, Davis EE, Stoetzel C, Diaz-Font A, et al: Hypomorphic mutations in syndromic encephalocele genes are associated with Bardet-Biedl syndrome. *Nat Genet* 40:443–448 (2008).
- Leppert M, Baird L, Anderson KL, Otterud B, Lupski JR, Lewis RA: Bardet-Biedl syndrome is linked to DNA markers on chromosome 11q and is genetically heterogeneous. *Nat Genet* 7:108–112 (1994).
- Li JB, Gerdes JM, Haycraft CJ, Fan Y, Teslovich TM, et al: Comparative genomics identifies a flagellar and basal body proteome that includes the *BBS5* human disease gene. *Cell* 117:541–552 (2004).
- Lindstrand A, Davis EE, Carvalho CM, Pehlivan D, Willer JR, et al: Recurrent CNVs and SNVs at the *NPHP1* locus contribute pathogenic alleles to Bardet-Biedl syndrome. *Am J Hum Genet* 94:745–754 (2014).
- Marion V, Stutzmann F, Gérard M, De Melo C, Schaefer E, et al: Exome sequencing identifies mutations in *LZTFL1*, a BBSome and smoothed trafficking regulator, in a family with Bardet-Biedl syndrome with situs inversus and insertional polydactyly. *J Med Genet* 49:317–321 (2012).
- M'hamdi O, Ouertani I, Maazouf F, Chaabouni-Bouhamed H: Prevalence of Bardet-Biedl syndrome in Tunisia. *J Community Genet* 2:97–99 (2011).
- M'hamdi O, Ouertani I, Chaabouni-Bouhamed H: Update on the genetics of Bardet-Biedl syndrome. *Mol Syndromol* 5:51–56 (2014).
- Mockel A, Obringer C, Hakvoort TB, Seeliger M, Lamers WH, et al: Pharmacological modulation of the retinal unfolded protein response in Bardet-Biedl syndrome reduces apoptosis and preserves light detection ability. *J Biol Chem* 287:37483–37494 (2012).
- Moore SJ, Green JS, Fan Y, Bhogal AK, Dicks E, et al: Clinical and genetic epidemiology of Bardet-Biedl syndrome in Newfoundland: a 22-year prospective, population-based, cohort study. *Am J Med Genet* 132A:352–360 (2005).
- Muller J, Stoetzel C, Vincent MC, Leitch CC, Laurier V, et al: Identification of 28 novel mutations in the Bardet-Biedl syndrome genes: the burden of private mutations in an extensively heterogeneous disease. *Hum Genet* 127:583–593 (2010).
- Mykytyn K, Braun T, Carmi R, Haider NB, Searby CC, et al: Identification of the gene that, when mutated, causes the human obesity syndrome *BBS4*. *Nat Genet* 28:188–191 (2001).
- Mykytyn K, Nishimura DY, Searby CC, Shastri M, Yen HJ, et al: Identification of the gene (*BBS1*) most commonly involved in Bardet-Biedl syndrome, a complex human obesity syndrome. *Nat Genet* 31:435–438 (2002).
- Mykytyn K, Nishimura DY, Searby CC, Beck G, Bugge K, et al: Evaluation of complex inheritance involving the most common Bardet-Biedl syndrome locus (*BBS1*). *Am J Hum Genet* 72:429–437 (2003).
- Nishimura DY, Searby CC, Carmi R, Elbedour K, Van Maldergem L, et al: Positional cloning of a novel gene on chromosome 16q causing Bardet-Biedl syndrome (*BBS2*). *Hum Mol Genet* 10:865–874 (2001).
- Nishimura DY, Swiderski RE, Searby CC, Berg EM, Ferguson AL, et al: Comparative genomics and gene expression analysis identifies *BBS9*, a new Bardet-Biedl syndrome gene. *Am J Hum Genet* 77:1021–1033 (2005).
- Otto EA, Hurd TW, Airik R, Chaki M, Zhou W, et al: Candidate exome capture identifies mutation of *SDCCAG8* as the cause of a retinal-renal ciliopathy. *Nat Genet* 42:840–850 (2010).
- Pawlik B, Mir A, Iqbal H, Li Y, Nürnberg G, et al: Novel familial *BBS12* mutation associated with a mild phenotype: implications for clinical and molecular diagnostic strategies. *Mol Syndromol* 1:27–34 (2010).
- Pereiro I, Valverde D, Piñeiro-Gallego T, Baiget M, Borrego S, et al: New mutations in *BBS* genes in small consanguineous families with Bardet-Biedl syndrome: detection of candidate regions by homozygosity mapping. *Mol Vis* 16:137–143 (2010).
- Putoux A, Mougou-Zerelli S, Thomas S, Elkhartoufi N, Audoulet S, et al: *BBS10* mutations are common in 'Meckel'-type cystic kidneys. *J Med Genet* 47:848–852 (2010).
- Redin C, Le Gras S, Mhamdi O, Geoffroy V, Stoetzel C, et al: Targeted high-throughput sequencing for diagnosis of genetically heterogeneous diseases: efficient mutation detection in Bardet-Biedl and Alström syndromes. *J Med Genet* 49:502–512 (2012).
- Renkema KY, Stokman MF, Giles RH, Knoers NV: Next-generation sequencing for research and diagnostics in kidney disease. *Nat Rev Nephrol* 10:433–444 (2014).
- Riise R, Tornqvist K, Wright AF, Mykytyn K, Sheffield VC: The phenotype in Norwegian patients with Bardet-Biedl syndrome with mutations in the *BBS4* gene. *Arch Ophthalmol* 120:1364–1367 (2002).
- Saari J, Lovell MA, Yu HC, Bellus GA: Compound heterozygosity for a frame shift mutation and a likely pathogenic sequence variant in the planar cell polarity–ciliogenesis gene *WDPCP* in a girl with polysyndactyly, coarctation of the aorta, and tongue hamartomas. *Am J Med Genet A* 167A:421–427 (2015).
- Sathya Priya C, Sen P, Umashankar V, Gupta N, Kabra M, et al: Mutation spectrum in *BBS* genes guided by homozygosity mapping in an Indian cohort. *Clin Genet* 87:161–166 (2015).
- Schaefer E, Zaloszyk A, Lauer J, Durand M, Stutzmann F, et al: Mutations in *SDCCAG8/NPHP10* cause Bardet-Biedl syndrome and are associated with penetrant renal disease and absent polydactyly. *Mol Syndromol* 1:273–281 (2011).

- Schaefer E, Lauer J, Durand M, Pelletier V, Ob-  
ringer C, et al: Mesoaxial polydactyly is a ma-  
jor feature in Bardet-Biedl syndrome patients  
with *LZTFL1* (*BBS17*) mutations. *Clin Genet*  
85:476–481 (2014).
- Schaefer E, Stoetzel C, Scheidecker S, Geoffroy V,  
Prasad MK, et al: Identification of a novel mu-  
tation confirms the implication of *IFT172*  
(*BBS20*) in Bardet-Biedl syndrome. *J Hum*  
*Genet* (2016), DOI: 10.1038/jhg.2015.162.
- Scheidecker S, Etard C, Pierce NW, Geoffroy V,  
Schaefer E, et al: Exome sequencing of Bardet-  
Biedl syndrome patient identifies a null muta-  
tion in the BBSome subunit *BBIP1* (*BBS18*). *J*  
*Med Genet* 51:132–136 (2014).
- Seo S, Guo DF, Bugge K, Morgan DA, Rahmouni  
K, Sheffield VC: Requirement of Bardet-Biedl  
syndrome proteins for leptin receptor signal-  
ing. *Hum Mol Genet* 18:1323–1331 (2009).
- Seo S, Mullins RF, Dumitrescu AV, Bhattarai S,  
Gratie D, et al: Subretinal gene therapy of  
mice with Bardet-Biedl syndrome type 1. *Invest*  
*Ophthalmol Vis Sci* 54:6118–6132  
(2013).
- Sheffield VC: Use of isolated populations in the  
study of a human obesity syndrome, the Bar-  
det-Biedl syndrome. *Pediatr Res* 55:908–911  
(2004).
- Sheffield VC, Carmi R, Kwitek-Black A, Rokhlina  
T, Nishimura D, et al: Identification of a Bar-  
det-Biedl syndrome locus on chromosome 3  
and evaluation of an efficient approach to ho-  
mozygosity mapping. *Hum Mol Genet* 3:  
1331–1335 (1994).
- Shevach E, Ali M, Mizrahi-Meissonnier L, Mc-  
Kibbin M, El-Asrag M, et al: Association be-  
tween missense mutations in the *BBS2* gene  
and nonsyndromic retinitis pigmentosa.  
*JAMA Ophthalmol* 133:312–318 (2015).
- Shoemark A, Dixon M, Beales PL, Hogg CL: Bar-  
det Biedl syndrome: motile ciliary phenotype.  
*Chest* 147:764–770 (2015).
- Simons DL, Boye SL, Hauswirth WW, Wu SM:  
Gene therapy prevents photoreceptor death  
and preserves retinal function in a Bardet-  
Biedl syndrome mouse model. *Proc Natl*  
*Acad Sci USA* 108:6276–6281 (2011).
- Slavotinek AM, Stone EM, Mykytyn K, Hecken-  
lively JR, Green JS, et al: Mutations in *MKKS*  
cause Bardet-Biedl syndrome. *Nat Genet* 26:  
15–16 (2000).
- Smaoui N, Chaabouni M, Sergeev YV, Kallel H, Li  
S, et al: Screening of the eight BBS genes in  
Tunisian families: no evidence of triallelism.  
*Invest Ophthalmol Vis Sci* 47:3487–3495  
(2006).
- Stoetzel C, Laurier V, Davis EE, Muller J, Rix S, et  
al: *BBS10* encodes a vertebrate-specific chap-  
eronin-like protein and is a major BBS locus.  
*Nat Genet* 38:521–524 (2006).
- Stoetzel C, Muller J, Laurier V, Davis EE, Zaghoul  
NA, et al: Identification of a novel BBS gene  
(*BBS12*) highlights the major role of a verte-  
brate-specific branch of chaperonin-related  
proteins in Bardet-Biedl syndrome. *Am J*  
*Hum Genet* 80:1–11 (2007).
- Suspitsin EN, Sokolenko AP, Lyazina LV, Pre-  
obrazhenskaya EV, Lepenchuk AY, Imyanitov  
EN: Exome Sequencing of a family with Bar-  
det-Biedl Syndrome identifies the common  
Russian mutation c.1967\_1968delTAinsC in  
*BBS7*. *Mol Syndromol* 6: 96–98 (2015).
- Tayeh MK, Yen HJ, Beck JS, Searby CC, Westfall  
TA, et al: Genetic interaction between Bardet-  
Biedl syndrome genes and implications for  
limb patterning. *Hum Mol Genet* 17:1956–  
1967 (2008).
- Tobin JL, Beales PL: Restoration of renal function  
in zebrafish models of ciliopathies. *Pediatr*  
*Nephrol* 23:2095–2099 (2008).
- Tobin JL, Beales PL: The nonmotile ciliopathies.  
*Genet Med* 11:386–402 (2009).
- Webb MP, Dicks EL, Green JS, Moore SJ, Warden  
GM, et al: Autosomal recessive Bardet-Biedl  
syndrome: first-degree relatives have no pre-  
disposition to metabolic and renal disorders.  
*Kidney Int* 76:215–223 (2009).
- Xing DJ, Zhang HX, Huang N, Wu KC, Huang  
XF, et al: Comprehensive molecular diagnosis  
of Bardet-Biedl syndrome by high-through-  
put targeted exome sequencing. *PLoS One*  
9:e90599 (2014).
- Young TL, Woods MO, Parfrey PS, Green JS, Hef-  
ferton D, Davidson WS: A founder effect in  
the Newfoundland population reduces the  
Bardet-Biedl syndrome I (*BBS1*) interval to  
1 cM. *Am J Hum Genet* 65:1680–1687 (1999).
- Zaghoul NA, Katsanis N: Mechanistic insights  
into Bardet-Biedl syndrome, a model ciliopa-  
thy. *J Clin Invest* 119:428–437 (2009).
- Zaghoul NA, Liu Y, Gerdes JM, Gascue C, Oh  
EC: Functional analyses of variants reveal a  
significant role for dominant negative and  
common alleles in oligogenic Bardet-Biedl  
syndrome. *Proc Natl Acad Sci USA* 107:  
10602–10607 (2010).