Bardet-Biedl Syndrome

Evgeny N. Suspitsin\textsuperscript{a,b} Evgeny N. Imyanitov\textsuperscript{a–d}

\textsuperscript{a} N.N. Petrov Institute of Oncology, \textsuperscript{b} St. Petersburg Pediatric Medical University, \textsuperscript{c} I.I. Mechnikov North-Western Medical University, and \textsuperscript{d} 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, brachydaupply 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 compensation 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.

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; Hiran-no 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://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; Shoe-mark 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 [Reddin 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 cilium 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.
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 \textit{BBS1} and \textit{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 \textasciitilde80\% 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].

\textbf{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,
Bardet-Biedl Syndrome

| Gene (synonym), chromosome localization | Contribution to BBS pathogenesis | Genotype-phenotype correlations |
|----------------------------------------|---------------------------------|-------------------------------|
| BBS1 (BBS2L2), 11q13                  | 23%                             | Recurrent variants, Subcellular localization, function |
| BBS2 (BBS), 16q21                     | 8%                              | Higher frequency in Iran (29%) [Fatihah et al., 2014] |
| BBS3 (ARL6, RP55), 3q11.2             | 0.4%                            | Small GTPase, participates in BBSome assembly |
| BBS4, 15q22.3q23                      | 2%                             | BBSome c.77_220del144, Iran [Mykytyn et al., 2001] |
| BBS5, 2q31                           | 0.4%                            | McKusick-Kaufman syndrome [Schaefer et al., 2011] |
| BBS6 (MKKS, MKS), 20p12               | 6%                              | Chaperonin complex, Patients with mutations in BBS6, BBS10 or BBS2, syndrome had more severe renal or Meckel-like syndrome [Karmous-Benailly et al., 2005] |
| BBS7 (FLJ10715, BBS2L1), 4q27          | 2%                              | BBSome c.1967_1968delTAinsC (p.L656Pfs*18), Russia [Suspitsin et al., 2015] |
| BBS8 (TTC8, RP51), 14q32.1            | 1%                              | Chaperonin complex, Patients with mutations in BBS7, BBS10 or BBS2, syndrome had more severe renal or Meckel-like syndrome [Karmous-Benailly et al., 2005] |

**Table 1. Genetics of BBS**

*Note: c.- denotes a deletion mutation, + denotes an insertion mutation.*

DOI: 10.1159/000445491
| Gene (synonyms), chromosome localization | Contribution to BBS morbidity* | Subcellular localization, function | Recurrent variants | Genotype-phenotype correlations | Other conditions caused by mutations in the same gene |
|-----------------------------------------|-------------------------------|-----------------------------------|-------------------|-------------------------------|-------------------------------------------------|
| **BBS9** (PTHB1, B1, D1, C18), 7p14 [Nishimura et al., 2005] | 6% | Basal body, participates in organization of the transition zone | | | |
| **BBS10** (C12orf58, FLI23560), 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 BBS10 mutations had significantly higher BMI-Z, greater visceral adiposity, and greater insulin resistance than those with BBS1 mutations [Feuillan et al., 2011]; A higher frequency of urogenital anomalies in patients with BBS10 vs. BBS1 mutations was observed [Castro-Sanchez et al., 2015]; Patients with mutations in BBS6, BBS10 or BBS12 genes had more severe renal disease [Imhoff et al., 2011] | |
| **BBS11** (TRIM32, HT2A, LGMD2H, TATIP), 9q31q34.1 [Chiang et al., 2006] | 0.1% | E3 ubiquitin ligase, involved in membrane trafficking | | | Limb-girdle muscular dystrophy type 2H, sarcotubular myopathy [Frosk et al., 2002] |
| **BBS12** (C4orf24, FLJ35630), 4q27 [Stoetzel et al., 2007] | 5% | Chaperonin complex | c.1156–1157CG>TA (p.Arg386*), Iran [Fatemi et al., 2014] | A higher frequency of cognitive impairment in patients with BBS12 vs. BBS1 mutations was observed [Castro-Sanchez et al., 2015]; Patients with mutations in BBS6, BBS10 or BBS12 genes had more severe renal disease [Imhoff et al., 2011] | |
| **BBS13** (MKS1, FLI20345), 17q23 [Leitch et al., 2008] | 4.5% | Basal body, participates in organization of the transition zone | | | Meckel syndrome [Consugar et al., 2007] |
| **BBS14** (CEP290, NPHP6, 3H11Ag, BBS14, CT87, IFT142, LCA10, MKS4, POCS3, SLN6, r106), 7q21.3 [Leitch et al., 2008] | 1% | Basal body, participates in organization of the transition zone and cilary entry of BBSome | | | Joubert syndrome, nephronophthisis, Senior-Loken syndrome, Meckel syndrome, Leber congenital amaurosis [Coppieters et al., 2010] |
| **BBS15** (WDPCP, C2orf56, CHDHPC, FRITZ, FRITZ2), 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] |
| **BBS16** (SDCCAG8, NPHP10, CCCCAP, CCAP SLN7, HSPO8, SY-CO-8, SLN7, hCCCAP), 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., 2013] |
| **BBS17** (LZTF1L), 3p21.3 [Marion et al., 2012; Schaefer et al., 2014] | ? | BBSome, participates in the Shh signaling | | | Mezoaxial polydactyly [Schaefer et al., 2014] |
| **BBS18** (BRIP1, BBIP10, hAS4H5.3, NCRNA00081), 1q25.2 [Scheidecker et al., 2014] | ? | BBSome | | | |
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 [Suspsitsin 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 [Suspsitsin 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 variations 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 Kuligina 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).
Alvarez-Satta M, Castro-Sanchez S, Pereiro I, Pniero-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 epithetic 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 (2013).

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, Iclioglu N, Woolf AS, Parker D, Flinter 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 mutation 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, Siemiatkowska AM, Liu Q, Place E, et al.: Mutations in IFT172 cause isolated retinal degeneration and Bardet-Biedl syndrome. Am J Hum Genet 72:463–464 (2003).

Carmi R, Rokhina T, Kwait-Black AE, Elbedour K, Nishimura D, et al.: Molecular diagnoses of Meckel-Gruber syndrome highlights phenotypic differences between MKS1 and MKS3. Hum Genet 121:591–599 (2007).

Coppeters P, Lefever S, Leroy BE, 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 Hejtmancik 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, Akyur C, 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, BBS5, BBS9, BBS10 genes. Eur J Med Genet 58:689–694 (2015).

Estrada-Cuzzano 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, Boroevic 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, Ayme S, de Heredia ML, Maffei P, McCafferty S, et al.: EURO-WABB: an EU rare disease project seeking small GTP binding proteins causes Bardet-Biedl syndrome. BMC Pediatr 13:130 (2013).

Fattahi Z, Rostami P, Najmabadi A, Mohseni M, Fakhrizadeh A, Jalas C, Abeliovich D, Krakovský Y, Ekshtain 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, Wettsch 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, Arding RA, Wallace SE, Amemiya A, et al. (eds): GeneReviews® [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 83:482–488 (2011).

Frook P, Weiler T, Nylens 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, Jager M, Robinson PN, Vanita V: Confirmation of T7C8 as a disease gene for nonsyndromic 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 IFTT172 cause Jeune and Mainzer-Saldino syndromes in humans. Am J Hum Genet 93:915–925 (2013).

Héon E, Westall C, Carmi R, Elbedour K, Panton C, et al.: Ocular phenotypes of three genetic variants of Bardet-Biedl syndrome. Am J Med Genet A 132A:283–287 (2005).

Hirchi 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. Clin Genet 87:1533–1543 (2015).

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, Gronskov K, Rosenberg T, Bøndum-Nielsen K, Olsen JH: Risk for cancer in patients with Bardet-Biedl syndrome. Eur J Hum Genet 15:1001–1009 (2007).

Hjortshøj TD, Grønskov K, Rosenberg T, Bøndum-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).
Karmous-Benailly H, Gronskov K, Brondum-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, Gronskov 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, Hølter 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, Redd 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. Am J Hum Genet 76:493–504 (2005).

Katani S, 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).

Katani S, 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).

Katani S, Eichers ER, Ansley SJ, Lewis RA, Kayserli 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, Bennis F, et al: Large homozygous deletions of the 2q13 region are a major cause of juvenile nephronophthisis. Hum Mol Genet 5:367–371 (1996).

Kwitek-Black AE, Carmi R, Duyk GM, Buetow KH, Eldedour 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 S, 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 triallelic. Eur J Hum Genet 14:1195–1203 (2006).

Leitch CC, Zaghloul NA, Davis EE, Stoetzel C, Diaz-Font A, et al: Hypomorphic mutations in syndromic encephalophegic genes are associated with Bardet-Biedl syndrome. Nat Genet 40:443–448 (2008).

Leppert M, Baird L, Anderson KL, Otterud B, Lamers WH, et al: Pharmacological modulation of the 2q13 region are a major cause of juvenile nephronophthisis. Hum Mol Genet 5:435–438 (2006).

Laurier S, Stoetzel C, Muller J, Thibault C, Corbani S, et al: Identiﬁcation of the gene that, when mutated, causes the human obesity syndrome. 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, Leitch CC, et al: Comparative genomics identiﬁes a ﬂagellar and basal body proteome that includes the BBS5 human disease gene. Cell 117:541–552 (2004).

M’hamdi O, Ouertani I, 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 5:351–56 (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 287:37345–37349 (2012).

Møller KD, Oggerup S, 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).

Müller 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, Nishimura DY, Searby CC, Beck G, Buğke 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, Arikir R, Chaki M, Zhou W, et al: Candidate exome capture identifies mutation of SDCCAG8 as the cause of a retinal-ciliary lipodystrophy. Nat Genet 42:840–850 (2010).

Pawlik B, Mir A, Iqbal H, Li Y, Nürnberg G, et al: Novel familial BBS2 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, Audollent 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 NMV: Next-generation sequencing for research and diagnostics in kidney disease. Nat Rev Nephrol 10:433–444 (2014).

Riese 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 WDCP in a girl with polysyndactyly, coarctation of the aorta, and tongue hamartomas. Am J Med Genet A 167A:421–427 (2015).

Sathy Na, 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, Zaloszcz 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).

Susptisim/Imyantiyov
Schaefer E, Lauer J, Durand M, Pelletier V, Obinger C, et al: Mesoaxial polydactyly is a major 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 mutation confirms the implication of IFT172 (BBS20) in Bardet-Biedl syndrome. J Hum Genet (2016), DOI: 10.1159/000445491.

Seo S, Guo DF, Bugge K, Morgan DA, Rahmouni K, Sheffield VC: Requirement of Bardet-Biedl syndrome proteins for leptin receptor signaling. Hum Mol Genet 18:1323–1331 (2009).

Shevach E, Ali M, Mizrahi-Meissonnier L, McKibbin M, El-Asrag M, et al: Association between missense mutations in the BBS2 gene and nonsyndromic retinitis pigmentosa. JAMA Ophthalmol 133:312–318 (2015).

Shoemark A, Dixon M, Beales PL, Hogg CL: Bardet-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).

Slootvink AM, Stone EM, Molytkyn K, Heckenlively JR, Green JS, et al: Mutations in MKKS cause Bardet-Biedl syndrome. Nat Genet 26:15–16 (2000).

Slavotinek AM, Stone EM, Molytkyn K, Heckenlively JR, Green JS, et al: Identification of a novel BBS gene (BBS12) highlights the major role of a vertebrate-specific branch of chaperonin-related proteins in Bardet-Biedl syndrome. Am J Hum Genet 80:1–11 (2007).

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).

Young TL, Woods MO, Parfrey PS, Green JS, Heferton D, Davidson WS: A founder effect in the Newfoundland population reduces the Bardet-Biedl syndrome 1 (BBS1) interval to 1 cM. Am J Hum Genet 65:1680–1687 (1999).

Zaghloul NA, Katsanis N: Mechanistic insights into Bardet-Biedl syndrome, a model ciliopathy. J Clin Invest 119:428–437 (2009).

Zaghloul 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).