Bardet–Biedl syndrome: A model for translational research in rare diseases

Robert M. Haws, Anthony D. Krentz, Rachel V. Stankowski, Robert D. Steiner

1. Introduction
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In 1920, French physician Georges Louis Bardet submitted his thesis on hypothalamic obesity with a description of two French girls with polydactyly, obesity, and retinitis pigmentosa [9]. Two years later, Hungarian pathologist Artur Biedl further described the phenotype with cognitive impairment, polydactyly, and obesity [12]. The Bardet–Biedl Syndrome (BBS; MIM 209900), named after these two astute physicians, has a diverse phenotype with primary features of post-axial polydactyly, truncal obesity, degenerative retinal disease, learning disabilities, male hypogonadism, and renal anomalies. The prevalence of BBS in non-consanguineous populations in Northern Europe and America ranges between one in 100,000 (North America) and one in 160,000 (Switzerland) (Forsythe and Beales, 2014), qualifying BBS as one of the more than 7000 recognized rare diseases that cumulatively impact millions of lives.

As is typical of many rare diseases, descriptive reports provided the initial foundation for later discovery. Clinical reports of the diverse manifestations of BBS emerged throughout the twentieth century. Critical breakthroughs in the late twentieth century, including the discovery of the first of at least nineteen unique BBS genes and establishment of diagnostic criteria for the syndrome, further advanced the understanding of BBS ([11,10,14,45,58]). In the twenty-first century, rapid expansion of the understanding of genetic and proteomic mechanisms underlying this pleiotropic condition has positioned BBS as a mechanistic model for ciliopathies [70], a group of conditions ranging from the common disorder of autosomal dominant polycystic kidney disease to the ultra-rare Alström syndrome (Fig. 1).

Translational research in the ciliopathies remains limited and established therapies are few and in most ciliopathies nonexistent. Despite the paucity of recognized therapies, increased understanding of underlying defects in BBS and the mechanistic overlap between BBS and other ciliopathies positions BBS as an important model for therapeutic discovery. Furthermore, the prevalence of alterations of BBS genes in individuals impacted by common disorders, such as diabetes mellitus and obesity [46], suggests that translational research in BBS may also have wide ranging implications for common disorders.

2. Clinical features

BBS, like most ciliopathies, has diverse multisystem manifestations affecting nearly every organ system [7,36]. In 1999, Beales carried out a comprehensive survey of 109 BBS patients in the United Kingdom [10]. The diagnostic criteria established in that report remain widely accepted (Fig. 2). A large, multi-ethnic, international survey further documented the pleiotropic disease manifestations as well as phenotype overlap with other ciliopathies; specifically Alström and McKusick–Kaufman syndromes [21]. Clinical features of BBS and other ciliopathies share important implications for quality of life as well as increased morbidity and premature mortality. While many of the symptoms of BBS have been described, the typical natural history of disease over the

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![Fig. 1. Known ciliopathies and common overlapping symptoms.](image-url)
lifespan is currently not well-documented and current translational research activities are focused on better defining the course of BBS, as described below. Importantly, there is significant intra- and interfamilial phenotypic variability in BBS, with considerable symptomatic differences noted even between affected siblings.

3. Genetics

BBS is inherited in an autosomal recessive manner. It has been proposed that BBS has an oligogenic inheritance pattern in the form of triallelism [40]. The triallelism hypothesis states that three pathogenic alleles at two loci are necessary to produce a phenotype. This hypothesis potentially explains variable clinical expression patterns and the fact that several individuals with BBS have been found to have a third rare, possibly pathogenic variant in a second BBS gene [40,39,44], but evidence for triallelic inheritance has not been observed in all patient cohorts [1,61]. Family structures are typically not large enough to adequately test the triallelic hypothesis and in the majority of documented cases, two pathogenic variants in one gene appear to be sufficient to cause disease. Disease severity may, however, be modulated by an additional mutant allele at another locus. For genetic counseling purposes, it is recommended to use an autosomal recessive model [28].

BBS is a genetically heterogeneous disorder known to be caused by mutations in at least 19 different BBS genes, including ARL6/BBS3, BBIP1/BBS18, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, CEP290/BBS14, IFT27/BBS19, LZTFL1/BBS17, MKKS/BBS6, MKS1/BBS13, SDCCAG8/BBS16, TRIM32/BBS11, TTC8/BBS8, and WDPCP/BBS15 [28]. However, no known pathogenic variants are identified in approximately 20% of individuals with BBS, suggesting that additional BBS-related genes have yet to be discovered (Fig. 3). It is possible that such variants are in known BBS loci, but in regions of the genome not interrogated and/or analyzed by most sequencing assays, such as deep intrinsic variants or variants in regulatory regions. Considering the genetic heterogeneity of BBS, the possibility of genetic modifiers, and genetic and phenotypic overlap of BBS with other ciliopathies, a molecular testing approach that interrogates all known BBS genes simultaneously would be ideal. Several ciliopathies, including nephronophthisis, Leber congenital amaurosis, and McKusick–Kaufman, Meckel–Gruber, Joubert, and Senior–Løken syndromes are allelic disorders to BBS. In fact, there are reports of individuals within the same family with different ciliopathies. Zaki et al. [71] reported two such families. In one family, three members had nephronophthisis and one had Joubert syndrome. In the second family, one individual had BBS and two siblings had Joubert syndrome [71]. Mutations in CEP290 have been implicated in BBS, Joubert syndrome, Meckel–Gruber syndrome, Senior–Løken syndrome, nephronophthisis, and Leber congenital amaurosis [5]. In addition to CEP290, pathogenic variants in MKS1 are known to cause both Meckel–Gruber syndrome and BBS [44,41,43,69]. Similarly, MKKS/BBS6 is the only gene known to cause McKusick–Kaufman syndrome and is also responsible for approximately 6% of BBS cases [19,60,62]. Finally, variants in SDCCAG8 can cause Senior-Løken syndrome and BBS [55]. Although major strides in the genetic characterization of BBS and other ciliopathies have been made in recent years, genotype–phenotype correlations in BBS to date are not very strong. Some studies suggest that certain ocular phenotypes may be correlated with certain genes [17,34,52], but additional attempts to correlate genotype and phenotype have been largely unsuccessful. The lack of strong genotype–phenotype correlations is likely due to the fact that many of the BBS proteins interact and function together in a complex, and disruption of any protein in that complex will ultimately influence cellular physiology in a similar way [70,29]. However, the modifying elements that influence severity of phenotype and symptom constellation remain to be elucidated.

4. Cellular biology

Understanding of the disrupted cellular biology in BBS continues to evolve providing new and novel targets for therapeutic intervention. The cilium–centrosome complex is a critical structure that mediates disease expression in all ciliopathies, including BBS. This organelle is a ubiquitous, highly conserved, antennae-like structure that projects from the plasma membrane and is tethered to the centrosome-derived basal body. The microtubules that comprise the cilia structure can exist in two different configurations, resulting in function as either primary or motile cilia. Motile cilia disorders include primary ciliary dyskinesia and Kartagener’s syndrome. Disorders of primary cilia represent a larger, more diverse group of disorders, of which BBS provides a
mechanistic and potentially a therapeutic model for translational research.

In patients with BBS, reduced cilia number and function have been documented in numerous tissues and organs, including the kidney, pancreas, thyroid, spleen, liver, nose, neural tube, and developing limbs [2,30,42,63]. Cilia relay diverse signals ranging from photosensation, mechanosensation, osmosensation, thermosensation, nociception, and olfactory sensation to hormonal signaling [36,42,63,70]. Under normal circumstances, the cilia–centrosome complex serves as a cellular hub for receiving and processing a wide variety of external signals and the pleiotropic features of BBS have been attributed primarily to defects in this cilia–centrosome messaging [3,7,10,36]. The cilia–centrosome complex regulates movement of proteins and molecules along the cilium by means of a process termed intraflagellar transport (IFT), which permits transfer of external signals into the cell. Disrupted IFT is observed in BBS and accounts for reduced leptin signaling with associated lack of satiety and development of obesity [32,51,56], reduced arginine vasopressin receptor 2 (AVPR2) density and development of polyuria [49], and diminished insulin receptor signaling and development of insulin resistance [30]. Some proteins encoded by BBS genes have also been identified to interact with carrier molecules necessary for ciliogenesis and intraflagellar transport [8,18,50].

The understanding of the cellular biology of ciliopathies has been further expanded by examining the role of the basal body proteasomes. Separate from the cilia structure, proteasomes are multisubunit enzyme complexes that play a critical role in protein regulation, cell-cycle progression, and apoptosis. Liu et al. [47] demonstrated that several proteins implicated in BBS and oral-facial-digital syndrome 1 interact with the proteasome and that loss of these proteins results in depletion of multiple proteasome subunits. This alteration in proteasome composition was associated with dysfunction of multiple basal-body mediated paracrine pathways, including pathways demonstrated to be pertinent to renal cyst formation, retinal degeneration, and embryonic development. Proteasome malaise may account for the intracellular protein accumulation and cellular dysfunction observed in ciliopathies [47,70]. As such, augmenting proteasomal function in ciliopathies may be an important target for therapeutic development.

Although BBS proteins primarily localize to the cilia–centrosome complex, some BBS proteins have also been identified in the cell nucleus. In the nucleus, these proteins can influence DNA transcription and alter cellular and tissue homeostasis [47]. Loss of function of BBS genes and their protein products can therefore impact both ciliary and non-ciliary pathways [47,51,70]. Increased understanding of BBS proteins in non-ciliary processes, including DNA transcription, may provide additional targets for therapeutic intervention.

5. Translational medicine

Numerous opportunities for translation of research to clinical care exist for BBS as well as other ciliopathies. These opportunities include (1) development of specialized centers of excellence for the management of these often rare disorders with pleiotropic clinical manifestations, (2) establishment of rare disease patient registries linked to genomic databases and biorepositories, (3) development of pharmacologic agents targeting the disrupted cellular mechanisms underlying BBS and other ciliopathies, and (4) gene therapies to restore normal BBS protein synthesis. Each of these areas of opportunity will be discussed separately.
5.1. Development of centers of excellence

Translational medicine is most effective when it directly impacts patient care. Most ciliopathies are rare diseases and delayed or incorrect diagnosis is common. Patients are often frustrated by the delayed diagnosis and by fragmented care from local clinicians who often have little or no experience dealing with their disease. Specialized programs established in Europe and North America provide patients with unified multi-disciplinary care teams that can work with local primary care providers to ensure that diagnosis is accurate and that care is delivered in a comprehensive and cost-effective manner.

Recognizing the geographic dispersion of individuals with BBS as well as other ciliopathies, treatment guidelines for use by local medical providers have been developed [20,28]. The centers of excellence in BBS care established in the US and Europe are working to ensure that despite the distance between patients and lack of local expertise, best care practices are continuously improved and local providers are well-informed. Future longitudinal studies of disease progression, identification of high risk subpopulations with BBS, and improved understanding of genotype-phenotype relationships will help to refine future comprehensive care guidelines for BBS. Future opportunities for translational activities related to the centers for excellence include improved methods for dissemination of guidelines to make them readily available to the families, educators, dieticians, therapists, and clinicians involved in the care of individuals with BBS. Improved dissemination of treatment guidelines through web-based resources will provide an important method to facilitate translational implementation of guidelines and rapid incorporation of new findings into home-based clinical care.

5.2. Rare disease registries and biorepositories

Rare disease registries and biorepositories can be powerful tools for translational research in rare diseases. Integration of longitudinal patient health information with rare disease biorepositories has been enthusiastically endorsed by the U.S. Office of Rare Diseases Research at the National Institutes of Health and the European Union’s International Rare Diseases Research Consortium [27,53,65,67]. The aim of global registry platforms is to accelerate collaborative opportunities for clinicians, scientists, epidemiologists, and pharmaceutical developers to gain access to de-identified patient data, genomic data, information on biomaterial availability, and research/trial data sets [65]. Data standardization and interoperability for rare disease databases is essential to the effort. The Global Rare Diseases Patient Registries Data Repository (GRDR®) has made foundational contributions to data standardization and has released Common Data Elements (CDEs) that are now freely available on the NIH/NCATS GRDR® website (https://grdr.ncats.nih.gov/index.php?option=com_content&view=article&id=38&Itemid=5) [54]. In the future, simultaneous computer-based analysis of multiple rare disease databases may uncover patterns, unknown correlations, disease trends, and therapeutic responses. The analytic findings may lead to new therapeutic development, improved patient care, and improved research efficiency while offering a competitive advantage over randomized trials with the associated expense, complexity, and difficulty of enrolling individuals with rare diseases due to geographic dispersion of patients.

The importance of involving patients and families in the research process and registry design has been emphasized in recent publications [13,31,64,68]. The Clinical Registry Investigating Bardet–Biedl Syndrome (CRIBBS) provides a model for patient and researcher cooperative efforts. CRIBBS is a longitudinal natural history registry that captures both self-reported patient data and validated health information from clinics and hospitals. The effort combines a focus on patient-related information, dissemination of information to patient support groups, and development of translational studies with the involvement of the United States BBS Family Association. CRIBBS participates in both the RD-Connect and GRDR® programs and provides de-identified patient health data for availability in the GRDR. Biomedical informaticians at the Marshfield Clinic Research Foundation have provided an opensource registry platform to the GRDR and continue to refine a structured environment incorporating established common data and disease-specific elements.

5.3. Pharmacologic therapy

Development of pharmacotherapies to address the numerous morbidities of BBS is critically needed. A readily apparent opportunity for translational research is well-designed clinical trials in the BBS population examining the safety and efficacy of medications with previously approved indications in the general population. The growing pandemic of obesity in the world has led to the development of several pharmacologic therapies for obesity management, some of which may be appropriate for use in the context of BBS. Despite some anecdotal experience with orlistat, an agent available for more than two decades, employment in the BBS population has not been reported or critically examined. Other anti-obesity agents, such as liraglutide, a glucagon like peptide 1 agonist; lorcaserin, a selective 5-HT2c receptor agonist; and the combination agent phentermine/topiramate, represent agents licensed in the last 10 years that would be appropriate drugs for examination in clinical trials. Clinical trials examining the efficacy, adverse reactions, and pharmacology of these drugs may serve not only the BBS population but other syndromic obesity disorders as well.

In addition to potential pharmacologic therapies for obesity, animal models of BBS suggest new opportunities for employing natural compounds with established disease indications in the treatment of BBS. The low potential for toxicity of these agents is particularly encouraging. Liu et al. [47] employed sulforaphane (SFN), a phytochemical derived from cruciferous vegetables, such as broccoli and cabbage, to stimulate proteasome activity. The authors reported that SFN ameliorated morphologic BBS features in zebra fish BBS4 morphants. Similar results were observed with mevalonate, another proteasomal activator [47]. SFN has been employed in humans in the investigational treatment of neurodegenerative disease and cancer as well as in a rat model of diabetic nephropathy, but has a short half-life and low bioavailability limiting its utility as a clinically effective product [15,22,66]. Curing strategies combining SFN or its derivatives as well as unrelated proteasome agonists may offer potential opportunities for therapeutic trials in BBS.

Another natural compound, taurosodeoxycholic acid (TUDCA), is a water-soluble bile acid derivative currently approved in Europe for the treatment of cholestasis and hepatic steatosis, conditions that are common in BBS patients. TUDCA has a favorable adverse drug effect profile and has been used safely in high risk populations, including liver transplant recipients [4,25,26] and premature infants [35]. TUDCA may offer important therapeutic potential for multiple disease manifestations of BBS, including insulin resistance and retinal degeneration. TUDCA increases insulin sensitivity in obese patients in the muscle and liver by approximately 30%, but does not exert the same response in adipose tissue [38]. This magnitude of increased insulin sensitivity is similar to currently available diabetes medications, such as thiazolidinediones and metformin. In addition, TUDCA has non-specific anti-apoptotic effects that may provide benefit in degenerative retinal conditions, including BBS. Drack et al. [23] demonstrated that TUDCA delayed photoreceptor degeneration and slowed the diminution of the electroretinogram amplitudes in a BBS1 murine model. The authors also observed that
TUDCA-treated BBS1 mice had significantly less weight gain compared to the untreated BBS1 control littermates [23]. However, in a four week trial of TUDCA in obese, but otherwise healthy humans, there was no significant effect of TUDCA treatment on body fat or weight [38]. Translational studies examining TUDCA as a novel pharmacologic approach to this pleiotropic condition are anticipated.

Chronic kidney disease is a primary cause for premature death in BBS and approximately 10% of the BBS population will require some form of renal replacement therapy during their lifetime. Common pathologic pathways may be shared in BBS and the more common ciliopathy of autosomal dominant polycystic kidney disease (ADPKD). Current recommendations to avoid drugs, including desmopressin acetate (DDAVP), foskolin, and calcium channel inhibitors, in ADPKD are generally considered prudent in the case of BBS as well, but have not been specifically examined in the BBS population. Likewise, pharmacologic agents showing favorable impact for the treatment of ADPKD, including somatostatin analogs, niacinamide, vasopressin 2 receptor antagonists, and mTOR inhibitors, may hold promise for BBS. Because only a minority of patients with BBS progress to advanced stages of chronic kidney disease, it will be critical to identify high risk patients before initiating pharmacologic trials. The longitudinal data currently being collected in CRIBBS shows promise in this respect.

5.4. Gene therapy

Gene therapy is of particular interest to clinicians and scientists dealing with BBS. The adeno-associated vector (AAV) has been safely used for transgene insertion into a variety of tissues for more than 25 different disorders, including individuals affected by the ciliopathy Leber congenital amaurosis (LCA), a non-syndromic form of autosomal recessive blindness that shares overlapping features with the retinal disease in BBS [24]. LCA is caused by mutations in at least 19 different genes. Gene therapy was successfully employed in individuals possessing the 65 kDa mutated retinal pigment epithelium-specific protein (RPE65) with reported improvement in vision [6,33,48]. Unfortunately, a recent report of progressive diminution of vision in RPE65-associated LCA patients treated with gene therapy demonstrates that hurdles to the use of gene therapy remain [37]. Limited, but encouraging functional and histologic results from subretinal injection of BBS transgenes into murine models of BBS1 and BBS4 have been reported [57,59], but human trials have yet to be conducted. Roadblocks to implementation of gene therapy in BBS include the diversity of affected genes in BBS and multiple organ system involvement. Of particular concern in the case of BBS, as described by Seo et al. [57], is that gene replacement therapy for a gene whose product is a member of a large multiprotein complex may result in changes in protein stoichiometry and disruption of the function of the complex. Additional challenges to successful implementation of gene therapy for retinal disorders have been outlined by several authors [16,23,24,37]. Natural immunity to adenovirus limits efficacy of systemic transgene-AAV delivery directly into blood stream as well as direct delivery into the brain, kidney, liver, and muscle. The subretinal space is relatively immune protected, however, and development of transgene delivery systems in the eye may allow gene therapy to be pioneered in other tissues as well.

6. Future perspectives for translational research in BBS

Advancements in genomics, proteomics, and transcriptomics will continue to unravel the mechanisms for disrupted cellular signaling pathways characteristic of BBS thus providing novel pharmacologic targets for drug repositioning and development. Despite current limitations, encouraging gene therapy results will likely yield new avenues to treat monogenic eye disease as well as treatments for other target organs. Clinical efforts to improve care, track longitudinal data, and characterize the affected population provide avenues for rapid transition of promising therapies to clinical trials in patients with BBS. Ongoing efforts to disseminate information on BBS to clinicians and development of treatment guidelines for the disorder will permit translational medicine to be generally applied while specialized centers implement and refine future health care guidelines.

7. Executive summary

• Ciliopathies are pleiotropic disorders characterized by disruption in cellular signaling pathways. BBS provides a mechanistic model for ciliopathies and increased understanding of the diverse function of the cilia–centrosome complex has advanced our current understanding of ciliopathies.

• It is thought that the lack of proteins essential to ciliogenesis and ciliary functions result in altered tissue modeling (e.g. cyst formation), accelerated apoptosis (e.g. tissue degeneration), and impaired response to extracellular signals (e.g. loss of cilia) and disrupted intracellular signaling pathways.

• The Clinical Registry Investigating Bardet–Biedl Syndrome (CRIBBS) provides a model for rare disease registries that can be connected to global registries such as the GRDR® and RD-Connect. Genomic databases and biomaterial availability linked to registries offer unique opportunities for collaboration for disease investigation and translational medicine.

• Multidisciplinary specialty clinics and development of guidelines for the treatment of BBS and other ciliopathies is critical for dissemination of information to practitioners and provides a model for rare disease care.

• Research into ciliopathies may yield new insights into common disorders including degenerative eye disease, obesity, and diabetes mellitus and facilitate novel drug development and new therapeutic approaches to these common diseases affecting large populations.

Conflict of interest statement

Author T.J.K. is an employee of Prevention Genetics. The authors report no additional conflicts of interest.

Ethical statement

The authors confirm that the submitted manuscript has not been published in any part or form in another publication of any type, nor is it under consideration by any other journal. Neither will it be submitted elsewhere unless and until it is declared unacceptable for publication by your journal.

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K. Agassandian, M. Patel, M. Agassandian, K.E. Steren, K. Rahmouni


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