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MUTATION ANALYSIS IN BARDET-BIEDL SYNDROME PATIENTS IN PAKISTAN: A REVIEW

Asma Arshad[*1], Muhammad Usman Arshad[2], Fiza Laraib[3], Sana Arshad[4]

[*1]*Molecular Biology Program, Dept. of Animal Sciences, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan*
[2]*Department of Health Sciences, Shalamar Medical and Dental College Lahore, Pakistan*
[3]*Molecular Biology Program, Dept. of Animal Sciences, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan*
[4]*Department of Gynecology, Sarwar Foundation, Hospital, Rajana, Pakistan*

[*1]asmaarshad@bs.qau.edu.pk, [2]m.usman148@gmail.com, [3]fizalaraib94@gmail.com, [5]sanaarshad1808@gmail.com

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Asma Arshad

Abstract
This study explores Bardet-Biedl Syndrome (BBS), a complex illness characterized by diversity in clinical manifestations and involvement of multiple organs. It draws attention to the genetic complexity of BBS and emphasizes the need for an all-encompassing approach to patient management. Future therapeutic approaches may be possible thanks to recent discoveries about the roles of the BBS protein. The research highlights the significance of genetic screening and counseling, especially in communities such as Pakistan where consanguineous marriages are common. It also includes an investigation of Pakistani population-specific BBS mutations. Ultimately, it seeks to raise awareness, encourage more study, and develop better diagnostic and treatment plans for people with BBS.

INTRODUCTION

Ciliopathies are defined as a group of disorders characterized by genetic mutations that produce faulty proteins and lead to compromised primary cilium formation or function. The advancement of genetic technologies has resulted in the identification of a growing number of genes associated with disorders of the primary cilia, thereby enhancing our understanding of the fundamental mechanisms that cause disease(Reiter & Leroux, 2017). One of the most specialized cellular organelles includes cilia which are significant to human development and health. Defects in the anatomy and physiology of cilia result in a wide range of developmental disorders. More than 150 different genes are known to cause genetic mutations that result in these defects(Wheway et al., 2019). Cilia are complex organelles, highly evolved having major roles in motility and signalling(Mitchison & Valente, 2017; Wheway et al., 2018). Cilia are broadly classified into two categories; motile and non-motile (primary) cilia each of which have distinct functions. Primary (Non-motile) Cilia are more pervasive and project as a single projection from the cell surface to the extracellular environment functioning as a sensory organelle with diverse roles in signal transduction. Defective primary cilia are characterized by retinitis pigmentosa, left-right asymmetry, polydactyly, speech deficit, cystic kidneys, and defects in the liver and pancreas(Singla & Reiter, 2006). On the other hand; Motile cilia are found in large numbers (around 200 cilia per cell) on respiratory epithelial cells, brain ventricles, and fallopian tubes where they help in the movement of essential fluids and gametes. Defects in motile cilia result in respiratory distress, situs inversus, bronchiectasis as well and infertility(Spassky & Meunier, 2017). Because the cilium is essential to both development and health, complicated multi-organ developmental abnormalities are frequently

observed in ciliopathies. Neurodevelopmental traits are present in the most severe-lethal ciliopathies, Meckel-Gruber syndrome (MKS)(Hartill et al., 2017), Joubert syndrome (JBTS)(Bachmann-Gagescu et al., 2015; Hartill et al., 2017), orofacial digital syndrome (OFD), and Bardet-Biedl syndrome (BBS)(Forsythe & Beales, 2013).These frequently coexist with additional characteristics such as skeletal

condition with significant interfamilial and intrafamilial variation affecting multiple organs of the body(Riise et al., 1997). It is an autosomal recessive genetic, oligogenic disorder belonging to a group of ciliopathies(Katsanis et al., 2001). As for other autosomal recessive diseases, negative family history of BBS is common. In 80 percent of the cases, the disease is carried in an autosomal recessive manner(Abu-Safieh et al., 2012; Manara et al., 2019). Initially known as Laurence-Moon-Bardet-Biedl syndrome (LMBBS) due to the presence of paraplegia, a condition similar to BBS patients. With

(Melluso et al., 2023; Priya et

al., 2016). Figure 1 depicts the key features associated with the syndrome. Mutations in genes that code for proteins involved in the maintenance of structure and functioning of cilia and important signaling pathways are known to cause BBS(Blacque & Leroux, 2006). BBS proteins in turn are then responsible for the disruption of function of cilia and chemical

abnormalities, renal dysplasia, and retinal degeneration. BBS is a disease of immotile cilia.(Forsythe & Beales, 2013).**An Insight into Bardet-Biedl Syndrome**

Bardet-Biedl Syndrome (BBS) is a rare, complex disorder known for its wide-ranging effects on the body, making it a prime example of ciliopathy. BBS is a genetic pleiotropic

the advent of understanding and salient features associated with BBS, Laurence-Moon Syndrome is now considered a separate entity as other features such as polydactyly and obesity are not found that form the main diagnostic criteria of BBS along with several other features(Mandal et al., 2021). Other conditions associated with BBS include hypogonadism, hypertension, cystic kidneys, speech deficits, rod-cone dystrophy, diabetes Mellitus, facial dysmorphism, teeth deformities, liver failure, and congenital heart defects

signaling pathways that are active throughout the developmental process, and sensual perception(Priya et al., 2016).

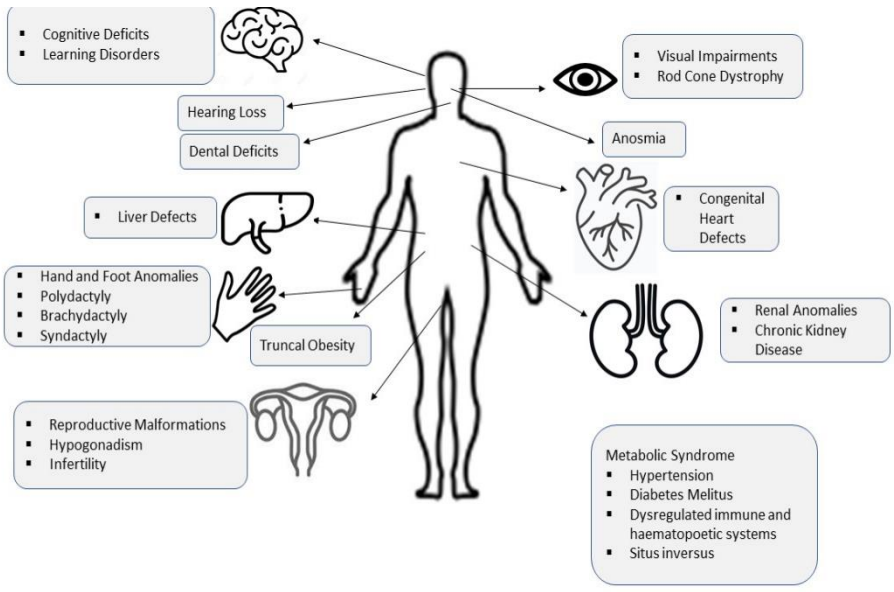


Figure 1: F eatures associated with Bardet Biedel Syndrome

Through the onset of structural and functional anomalies, BBS is usually manifested earlier in life. Within the first ten years of life, symptoms tend to appear, with a chief complaint being problems in

Clinical features of BBS

Retinal Degenreration

One of the ubiquitous handles suggesting the diagnosis of BBS phenotype is retinal degeneration, a symptom that is frequently found in many syndromic ciliopathies because of the role of cilium in the retina. The highly specialized nonmotile (primary) cilia are involved in the transmission of sensory signals to photoreceptor cells of the retina and other olfactory cells. At least about one-third of the non-syndromic inherited retinal dystrophies are linked to retinal cilium defects. Among these are the retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA)(Bujakowska et al., 2009; Estrada-Cuzcano et al., 2012).

limbs or either the upper or lower limbs are affected by postaxial polydactyly, which is frequent (63–81%) and can coexist with brachydactyly(46%) and/or syndactyly (8%)(Beales et al., 1999). The smoothened, frizzled family receptor (Smo) and the human patched 1 (Ptch1), which are important in limb formation, are two Hedgehog Pathway components with which the BBS1 gene interacts(Priya et al., 2016). however, mutations in the BSS17 (LZTFL1) gene are associated with the unusual mesoaxial polydactyly(Schaefer et al., 2014).

Obesity

Obesity is another significant clinical characteristic; it is estimated that 72–86% of BBS patients are obese while birth weight typically falls within the standard range(Hjortshøj et al., 2010). Early onset severe obesity is associated with polymorphisms in the BBS4 (rs7178130), BBS6 (rs6108572, rs221667), and BBS2 (rs4784675) genes, which may play a role in the development of the condition(Benzinou et al., 2006; Hjortshøj et al., 2010) Obesity in BBS is caused by disruption of leptin receptor trafficking, which reduces energy expenditure due to loss of BBS proteins and promotes hyperphagia(Guo et al., 2019).

Renal Abnormalities

After the discovery of the BBS, the association of renal anomalies remained completely overlooked for

vision at night. Nystagmus is also reported as an initial complaint in some of the BBS patients(Kumar et al., 2020). Figure 1, depicts the features associated with bardet biedel Syndrome.

Visual impairment is one of the features that is diagnosed early in life. Development of the rod-cone dystrophy with initial loss of rod photoreceptors that is then followed by loss of cone photoreceptors leading to a decline in color vision and visual acuity. Nyctalopia is also frequently encountered among such patients occurring between 4 to 8 years of age followed by progressive peripheral vision loss. Between the second and third decade of life, blindness occurs in most patients(Forsythe & Beales, 2013; Weihbrecht et al., 2017). Fundus examination shows atypical retinitis pigmentosa with macular involvement. Around 90% of the BBS patients present Retinitis pigmentosa(Ferrari et al., 2011). Strabismus, cataracts, and astigmatism are some of the conditions known to be associated with the disease

more than 50 years. With the work of McLoughlin and Shanklin in the late 1960s, attention was drawn towards renal involvement in BBS patients(McLoughlin & Shanklin, 1967). A significant cause of morbidity and mortality in BBS is renal abnormalities; thus, today these are included in the primary diagnostic feature of the disease.

Numerous BBS renal lesions have been documented including cystic tubular disease, calyceal clubbing, fetal lobulation, Polyuria, focal sclerosing glomerulonephritis, interstitial nephritis, and anatomical malformations. and chronic renal(Putoux et al., 2012). Today renal abnormalities are included in the primary features of BBS. Among BBS patients Kidney defects are often variable, non-specific and remain unnoticed until end-stage renal disease.

Hypogonadism

About 59% of the BBS subjects also present genitourinary abnormalities(Forsyth & Gunay-Aygun, 2020). Around 90% of male patients manifest hypogenitalism (delayed puberty). In females, the BBS phenotype represents an ambiguous genital area(Deveault et al., 2011).

Dental Anomalies

Dental crowding (46%), and a high-arched palate (35%), are frequently observed in BBS subjects. Other dental anomalies include hypodontia,

microdontia, malocclusion, and enamel hypoplasia(Kulaga et al., 2004; Panny et al., 2017) To differentiate BBS from Alstrom and McKusick-Kaufman syndromes knowledge of oral and dental anomalies would prove beneficial(Andersson et al., 2013; Yalcin & Ararat, 2019). According to Andersson et al., there is an 82.9% incidence of taurodontism, suggesting that taurodontism abnormalities should be incorporated into the BBS diagnostic characteristics(Yalcin & Ararat, 2019).

Cardiovascular Defects

Heart defects manifested in 7–50% of BBS patients are highly variable. Undiagnosed cardiomyopathy regurgitation, aortic stenosis, valvular stenosis, left ventricular hypertrophy, patent ductus arteriosus, and pericarditis are commonly encountered(Beales et al., 1999; Mauro et al., 2022; Rooryck & Lacombe, 2008).

Autoimmune disorders

Patients with BBS have a greater frequency of autoimmune disorders due to a defect in the BBSome transport mechanism that regulates B cell development and homeostasis. An increase in immature B cells, a decrease in the number of red blood cells and platelets count, and subsequently immunological dysfunction are caused by BBSome complex malfunction(Borna et al., 2020; Tsyklauri et al., 2021). Megaloblastic anemia, a rare occurrence in BBS patients, seemed to be linked to the disease. It could be attributed to a hereditary susceptibility or inadequate vitamin intake(Hassan et al., 2023).

Learning Disabilities

Cognitive impairment has been reported in 60–66% of BBS subjects(Beales et al., 1997). Speech problems could be exacerbated by hearing loss, which affects 17–21% of patients(Deveault et al., 2011). One important feature (86%) of the condition is decreased IQ. Magnetic resonance imaging reveals a decrease in the grey matter volume of the hippocampal region, as well as a loss of white matter volume in the right inferior longitudinal fasciculus, anterior temporal lobes, and medial orbitofrontal cortex(McIntyre et al., 2016; Priya et al., 2016).

Others

The following secondary clinical features have been reported: polycystic ovary syndrome, hypothyroidism, facial dysmorphism, laterality defects, mild spasticity, ataxia/poor coordination, anosmia, hepatic fibrosis/disease, developmental delay, behavioral abnormalities, and other gastrointestinal diseases(Mujahid et al., 2018). Among BBS patients, Insulin resistance is common, and type 2 diabetes is common and is correlated with obesity levels(Melluso et al., 2023). Numerous BBS cases have also been linked to autism spectrum disorders and obsessive-compulsive disorders(Beales et al., 1999). Many people with facial dysmorphism have mild features; they include hypertelorism, wide ears, enophthalmos, flat nasal bridge, anteverted nares, thin upper lip, and early frontal baldness in adult males(Beales et al., 1999; Forsythe & Beales, 2013). Although 50% of BBS patients have been reported to have anosmia or hyposmia, the actual rate may be greater because to the challenges associated with evaluating this condition in clinical settings. Experts in olfactory dysfunction assessment can benefit from MRI scanning of the olfactory bulb(Braun et al., 2016). Rarely, BBS patients have been reported to have PCOS (polycystic ovarian syndrome)(Mujahid et al., 2018).

Diagnostic Approach

Despite significant heterogeneity, the BBS phenotype progressively changes throughout the first ten years of life. The majority of patients are therefore diagnosed in their late youth or early adulthood. Moreover, the gradual emergence of all clinical symptoms makes an early diagnosis more challenging. As to Beales et al., the mean age at diagnosis is nine years old(Beales et al., 1999). The mean diagnostic age in the Clinical Registry Investigation of BBS (CRIBBS) is 5.8 years(Pomeroy et al., 2021).

According to the standards provided by Beales et al., at least four major factors or three major factors and two minor factors should be observed for the diagnosis of the condition(Beales et al., 1999). The primary and secondary diagnostic features are listed in Figure 2 (Beales et al., 1999; Forsythe & Beales, 2013)

Early detection of these rare syndromes is now feasible thanks to the quick advancements in fetal medicine, genetic testing, and ultrasonography (18–20 weeks scan). This aids in the early intervention and counseling of such newborns with disabilities. Using ultrasonography, polydactyly and hyperechogenic kidneys are most commonly detected(Sablok et al., 2020). Additionally, prenatal imaging can assist in detecting illness throughout

pregnancy. During prenatal examination, structural abnormalities, polydactyly, and renal abnormalities may be suspected and verified by genetic testing(Forsythe & Beales, 2013).

Sequencing of the genes associated with the BBS phenotype can help in the diagnosis of about 80% of the subjects through molecular analysis(Forsythe et al., 2023). The tremendous variation and expensive cost of sequencing the BBS genes, particularly in low-income nations, typically restrict access to this process.

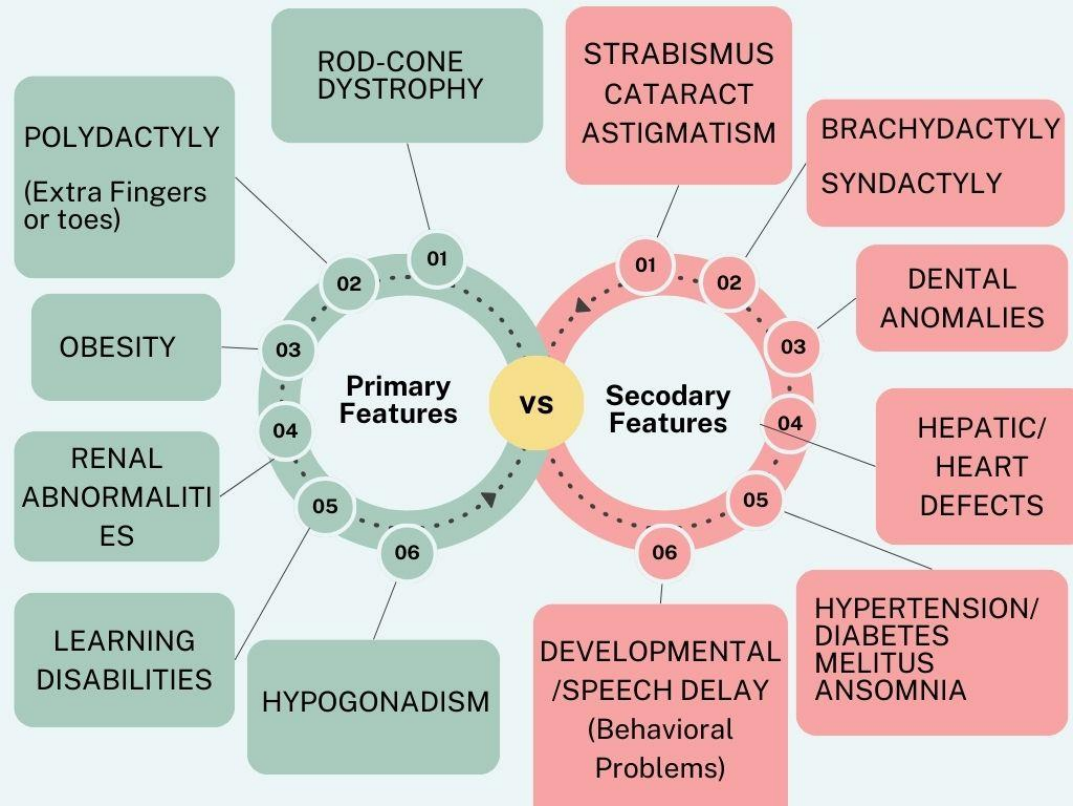


Figure 2: Diagnostic Features of Bardet Biedel Syndrome

Genetics of the disease

Attempts at genetic mapping between 1993 and 2000 found DNA sites linked to Bardet-Biedl Syndrome (BBS). An autosomal recessive mutation in one of the 26 genes connected to the disease causes a biallelic loss of function that results in the syndrome(Forsyth & Gunay-Aygun, 2020). Table 1 analyses the genes whose mutations are associated with Bardet Biedel Syndrome.

Gene	Name	Chromosomal Location	Localization of the Protein in the Cell	Aliases	Tissue Specificity	Protein Function
BBS1	Bardet-Biedl syndrome 1	11q13.2	• Cilium • Basal Body	BBS2L2	Low	Component of BBSome complex
BBS2	Bardet-Biedl syndrome 2	16q13	• Cilium • Basal Body	BBS, RP74	Low	Component of BBSome complex
BBS3/ARL6	ADP ribosylation factor like GTPase 6	3q11.2	• Cilium • Basal body • Cytosol • Transition zone	RP55	Low	GTP-binding protein involved in ciliary trafficking
BBS4	Bardet-Biedl syndrome 4	15q24.1	• Cilium • Basal Body		Low	Component of BBSome complex
BBS5	Bardet-Biedl syndrome 5	2q31.1	• Basal body		Low	Component of BBSome complex
BBS6/MKKS	Bardet-Biedl syndrome 6/ MKKS centrosomal shuttling protein	20p12.2	• Basal body • Cytosol	HMCS, KMS, MKS	Low	Chaperonin like protein Assist in BBSome formation
BBS7	Bardet–Biedl syndrome 7	4q27	• Cilium • Basal body	BBS2L1	Low	Component of BBSome complex
BBS8/TTC8	Bardet-Biedl syndrome 8/	14q31.3	• Cilium • IFT	RP51	Low	Component of BBSome complex

	tetratricopeptide repeat domain 8		• Basal body •				
BBS9	Bardet–Biedl syndrome 9	7p14.3	• Cilium		B1, C18, D1, PTHB1	Low	Component of BBSome complex
BBS10	Bardet-Biedl syndrome 10	12q21.2	• Basal body		C12orf58	Low	Chaperonin like protein assisting BBSome formation
BBS11/ TRIM32	Bardet- Biedl syndrome 11-tripartite motif containing 32	9q33.1	• Interme diate filaments		HT2A, LGMD2H, LGMDR8, TATIP	Low	E3 ubiquitin ligase; it promotes degradation of several targets
BBS12	Bardet–Biedl syndrome 12	4q27	• Basal body		C4orf24, FLJ35630, FLJ41559	Low	Chaperonins Assist in BBSome Formation
MKS1	MKS transition zone complex subunit 1	17q22	• Basal body		FLJ20345, BBS13, JBTS28, MES, MKS, POC12	Low	Component of the tectonic-like complex localized at the transition zone of primary cilium
BBS14/ CEP290	Bardet-Biedl syndrome 14/centrosomal protein 290	12q21.32	• Basal body • Centros ome		3H11Ag, CT87, JBTS5, LCA10, MKS4, NPHP6, POC3, SLSN6, rd16	Low	Centrosomal protein involved in primary cilium formation

BBS15/ WDPCP	Bardet-Biedl syndrome 15/WD repeat containing planar cell polarity effector	2p15	• Cytosol • Axoneme • Plasma membrane	C2orf86, CHDTHP, CPLANE 5, FRITZ, FRTZ	Low	Controls ciliogenesis
BBS16/ SDCCAG8	Bardet-Biedl syndrome 16/SHH signaling and ciliogenesis regulator SDCCAG8	1q43-q44	• Basal body • transition zone • Centriole	CCCAP, CCCAP SLSN7, HSPC085, NPHP10, NY-CO-8, SLSN7, hCCCAP	Low	Involved in ciliogenesis and Sonic Hedgehog signaling pathway
BBS17/ LZTFL1	Bardet-Biedl syndrome 17/leucine zipper transcription factor like 1	3p21.31	• Cilium • Basal body		Mainly in lymphoid tissue	Regulator of BBSome trafficking and Sonic Hedgehog signalling
BBS18/ BBIP1	Bardet-Biedl syndrome 18/BBSome interacting protein 1	10q25.2	• Cytosol	BBIP10, NCRNA00081, bA348N5.3	Mainly in testis	Component of BBSome complex
BBS19/IFT27	Bardet-Biedl syndrome 19/intraflagellar transport 27	22q12.3	• Cilium • IFT • Basal body	CFAP156, FAP156, RABL4, RAYL	Low	Intraflagellar trafficking (IFT-B) component
BBS20/IFT172	Bardet-Biedl syndrome 20/	2p23.3	• Vesicles	NPHP17, RP71,	Low	Intraflagellar trafficking (IFT-B) component

	intraflagellar transport 172				SLB, SRTD10, osm-1, wim		
BBS21/ CFAP418/ C8orf37	Bardet-Biedl syndrome 21/ cilia and flagella associated protein418	8q22.1	• Basal body • Ciliary root			Low	No Known Function

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BBS22 /IFT74	Bardet-Biedl syndrome 22/ intraflagellar transport 74	9p21.2	• Cilium • IFT • Basal body	CCDC2, CMG-1, CMG1, JBTS40, SPGF58	Low	Intraflagellar trafficking (IFT-B) component
CEP19	Centrosomal protein 19	3q29	• Centrosome		Low	Recruits the RABL2B GTPase to the ciliary base and intraflagellar transport (IFT) complex B
NPHP 1	Nephrocystin 1	2q13	• Transition zone	JBTS4, NPH1, SLSN1	Mainly in skeletal muscle	Cell-matrix signaling at focal adhesions
SCAP ER	S-phase cyclin A associated protein in the ER	15q24.3	• Endoplasmic reticulum • Ciliary tip		Low	Ciliary dynamics and disassembly
SCLT1	Sodium channel and clathrin linker 1	4q28.2	• Centriole	CAP-1A, CAP1A	Low	Component of distal appendages Involved in ciliogenesis

Table 1: Genes associated with Bardet Biedel Syndrome

MKKS, the first BBS gene, was discovered in 2000 because of its resemblance to McKusick-Kaufman syndrome (MKS)(Katsanis et al., 2000). A complex known as the BBSome is made up of eight of the 26 BBS proteins: BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9, and BBS18(Loktev et al., 2008). By controlling molecular trafficking to the ciliary surface, this complex preserves the structure and functionality of cilia. In order to aid in the production of BBSome, three other proteins—BBS6/MKKS, BBS10, and BBS12—form a chaperonin complex. Additional BBS proteins aid in guiding the BBSome to its destination.

Gene mutations in BBS1–BBS18 account for 70–80% of instances of Bardet-Biedl Syndrome (BBS) globally(M'hamdi et al., 2014). The BBSome genes (BBS1, 2, 4, 5, 7, 8, 9, 18) are the most often occurring and largest collection of mutations affecting BBS patients.

BBS1, BBS2, and BBS10 mutations account for about 50% of diagnosis in Western countries(Zacchia et al., 2021). However, the BBS1, BBS2, and BBS8 genes are known to have common harmful mutations in Tunisia. People from the Middle East and North Africa are extremely likely to have variations in BBS4, BBS5, and BBS8/TTC8(Billingsley et al., 2011). Many syndromes, including Joubert Syndrome (JS), Meckel Syndrome (MKS), Bardet-Biedl Syndrome (BBS), Leber Congenital Amaurosis (LCA), Senior-Loken Syndrome (SLS), and Nephronophthisis (NPH), share a large number of genes associated with ciliary dysfunction(Leitch et al., 2008). They might have the same mutations in genes such as NPHP6 and FTM (RPGRIP1L), for example.

MKKS mutations are frequently found in cases of Joubert syndrome and BBS(Katsanis et al., 2000). Mutations in the BBS2, BBS4, and BBS6 genes are shared by BBS and Meckel Syndrome(Karmous-Benailly et al., 2005). Furthermore, BBS traits may also result from mutations in MKS1, which are generally linked to Meckel syndrome, whereas MKS3 mutations are present in patients with both BBS and Joubert syndrome. Figure 3 shows a venn diagram depicting the genetic overlap between certain ciliopathies.

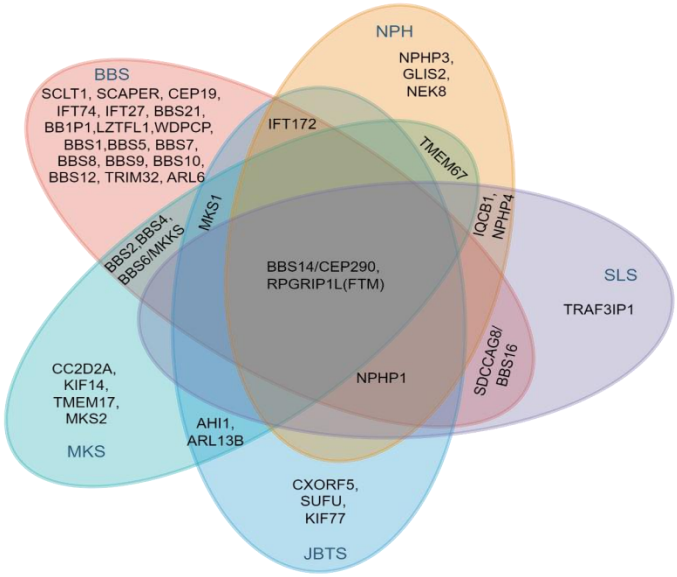


Figure Venn Diagram showing the overlapping of genes in certain ciliopathies

Molecular Analysis of BBS Patients

Molecular diagnosis and genetic counselling are made more difficult by the broad clinical and genetic variability of BBS. Numerous molecular techniques have been put forth in the previous ten years to maximize the frequency of identifying mutations. Among these tactics is the mapping of homozygosity using SNP arrays in consanguineous families and direct sequencing assessment of every BBS gene(Billingsley et al., 2011; Janssen et al., 2011). The use of next-generation sequencing has recently sped up the molecular analysis of BBS patients(M'hamdi et al., 2014; Marion et al., 2011). Methods for detecting copy number variations in the human genome and for high-resolution sequencing. has also resulted in the discovery of clinically significant genes, and medical geneticists ought to employ these novel molecular techniques(Alkuraya, 2013).

Through sequencing of the BBS genes diagnosis can be genetically confirmed. However due to excessive heterogeneity and high cost access to such sequencing is usually restricted, especially in low-income countries like Pakistan. Furthermore, the ratio of consanguineous marriages is higher in Pakistan than in other countries. About 60% of the marriages are consanguineous which then increases the ratio of autosomal recessive diseases(Hassan et al., 2023; Rao et al., 2023).

Management of the disease

One of the primary areas of focus in BBS is gene therapy research(Forsythe et al., 2018; Kenny et al., 2017). Animal models of BBS have been tested for the effective treatment of retinal degeneration through gene therapy(Seo et al., 2013). Certain BBS mutations affect splicing and may be corrected by splicing-correcting strategies such as RNA interference, snRNAs, and antisense oligonucleotides. Additionally, fibroblasts harboring a BBS1 mutation have shown potential therapeutic effects in vivo(Forsythe et al., 2018; Melluso et al., 2023).

Considering the pronounced heterogeneity for retinal impairments Electroretinography (ERG) is preferred(Forsythe & Beales, 2013), because it appears to be more sensitive and shows alterations that occur in the first two years of life, even before fundus abnormalities manifest(Denniston et al., 2014; Scheidecker et al., 2015). Ocular assessment, fundus examination, visual field testing, electroretinogram, and optical coherence tomography (OCT) are additional retinal assessments carried out in the course of the diagnosis(Denniston et al., 2014). One of the primary objectives is to correct refractive errors; for individuals who are photophobic, using tinted glasses is strongly advised(Caba et al., 2022).

It is advised that accessory digits be surgically removed. It is also advised to monitor BMI, dietary evaluations, head circumference, weight, height, and daily physical activity level to control obesity(Carey et al., 2020). All these parameters will be evaluated at each medical visit.

Melanocortin receptor agonists are another possible treatment option for Bardet-Biedl syndrome in the context of obesity management(Carey et al., 2020; Seo et al., 2009). The gonadotropic axis activity, which regulates the release of GnRH, aids in maintaining fertility in adults as well as during the fetal life period and the onset of puberty(Mujahid et al., 2018).

The early diagnosis of kidney defects can benefit from renal and bladder ultrasonography as well as blood pressure, CBC, urinary protein, and serum creatinine monitoring(Carey et al., 2020; Forsyth & Gunay-Aygun, 2020; Mujahid et al., 2018). To assess cardiomyopathy, a heart auscultation, electrocardiogram, and echocardiography are performed(Caba et al., 2022). In addition, patients with BBS may experience behavioral conditions such as anxiety, depression, bipolar disorder, emotional outbursts, hyperactivity, and frustration, all of which call for a mental health evaluation(Zelihić et al., 2020). Similarly, MRI is suitable for evaluating ataxia, hypotonia, and seizures.

BBS mutations in Pakistani Patients

Here in this review we particularly focused on the mutations presented in BBS patients in Pakistan. To our knowledge, no thorough analysis of all the known mutations causing BBS in the Pakistani population has yet been published. To gather information about mutations in BBS patients, including the type of mutation, location of the mutation, amino acid/protein change, and study protocol, all studies published up until March 2024 were evaluated at www.ncbi.nlm.nih.gov/pubmed. We identified 74 different types of BBS mutations presented in Table 2 whereas Figure 3 shows the frequency of reported genes in BBS patients across the Pakistani population.

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Genes	Exon/ Intron	Methodology	Type of Mutation	Variant at DNA level	Change at protein level	features	Refere
BBS1	Exon 1	Whole exome sequencing (WES)	Splice site	c.47+1G>T	p?	Retinitis pigmentosa, obesity, learning difficulties, polydactyly	(Ajma
BBS1	Exon 4	Whole exome sequencing (WES)	Missense	c.442G>A	p.Asp148Asn	Developmental delay, Retinitis pigmentosa, obesity, and learning difficulties, hypertensive	(Ajma
BBS1	Exon 12	Whole exome sequencing (WES)	Nonsense	c.1150 C>T	p.Glu384Ter	RP, Polydactyly, obesity, Hypogonadism, Renal failure, intellectual disability	(Rao e
BBS1	Exon 13	Whole exome sequencing (WES)	Missense	c.1339G>A	p.Ala447Thr	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism, Renal abnormality, Intellectual disability, Speech disability, Strabismus, cataract, astigmatism, Dental anomaly	(Nawa
BBS1	Exon 13	Whole exome sequencing (WES)	Missense	c.1339G>A	p.Ala447Thr	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism, Renal abnormality, Intellectual disability, Speech disability	(Nawa
BBS1	Exon 16	Whole exome sequencing (WES)	Splice site	c.951+1G>A	p?	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism, Renal abnormality, Intellectual disability, Speech disability, Strabismus, cataract, astigmatism	(Nawa
BBS2	Exon 3	Whole exome sequencing (WES)	Missense	c.443A>T	p.Ala148Ile	obesity, renal problems, intellectual disability (ID), and postaxial polydactyly	(Ali et
BBS2	Exon 12	Linkage analysis and Sequencing	Nonsense	c.1658C>T	p.R413X	RP, Polydactyly, obesity, developmental delay, mental retardation, , situs inversus, bipolar disorder	(Kord
BBS2	Exon 12	SNP array	Nonsense	c.1438C>T	p.Arg480Ter	IRD and extra-ocular symptoms such obesity, hypogonadism,	(Ur R

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						learning/developmental disabilities, post-axial polydactyly of hands and/or feet, and renal abnormalities	
BBS2	Exon 3	Whole exome sequencing (WES)	Splice site	c.471G>A	no protein	RP, Polydactyly, obesity, Hypogonadism, Nystagmus	(Rao e
BBS2	Exon 12	Dideoxy Sequencing(DS)	Nonsense	c.1658C>T	p.R413X	Vision impairment, obesity, polydactyly, developmental delay	(Chen
BBS2	Exon 11	Homozygosity Mapping	Missense	c.1237C>T	p.R413X	RP, Polydactyly, obesity, developmental delay, mental retardation, , situs inversus, bipolar disorder	(Harvi
BBS2	Exon 3	Whole exome sequencing (WES)	Missense	c.443A>T	p.Ala148Ile	obesity, renal problems, intellectual disability (ID), and postaxial polydactyly, diabetes mellitus, Speech delay	(Ali et
BBS3/ARL6	Intron 3	Dideoxy Sequencing(DS)	Frameshift	c.123+1118del53985†	p?	Congenital postaxial polydactyly, progressive night blindness, atypical retinitis pigmentosa (RP, rod-cone dystrophy), myopia and astigmatism	(Pawli
BBS3/ARL6	Exon 8	Targeted Exome sequencing	splice site	c.534A > G	p.Q178Q	RP, Polydactyly, Hypogonadism, Renal abnormalities, Elevated liver enzymes, abnormal ECG, gynaecomastia BBS like Syndrome	(Maria
BBS3/ARL6	Exon 1	Homozygosity mapping	Missense	c.281T>C	p.Ile94Thr	postaxial polydactyly, obesity and retinitis pigmentosa	(Khan
BBS3/ARL6	Exon 1	Whole exome sequencing (WES)	Frameshift	c.387_394delAAATAAAA	pAsn130GlyfsTer3	RP, polydactyly, obesity	(Rao e
BBS5	Exon 1	Whole exome sequencing (WES)	Missense	c. 2T>A	p.Met1Lys	strabismus, bilateral clinodactyly of fifth and sixth fingers in hands and bilateral postaxial polydactyly, bulging eyes	(Ali et
BBS5	Exon 3	Whole exome sequencing	frameshift	c.196delA	p.Arg66Glufs*12	intellectual disability, visual impairment, truncal obesity, postaxial polydactyly, and	(Khan

		(WES)				renal anomalies, hypogonadism	
BBS5	Exon 3	Whole exome sequencing (WES)	Frameshift	c.196delA	p.Arg66Glufs*12	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism, Renal abnormality, Intellectual disability, Speech disability, Ataxia, imbalance	(Nawa
BBS5	Exon 1	Whole exome sequencing (WES)	Missense	c.2T > A	p. Met1Lys	strabismus, bilateral clinodactyly of fifth and sixth fingers in hands and bilateral postaxial polydactyly, bulging eyes, Ataxia, imbalance	(Ullah
BBS5	Exon 1	Homozygosity mapping	Missense	c.2T>A	p.Met1Lys	RP, Polydactyly, obesity, hypogonadism, developmental delay, mental retardation, , situs inversus, bipolar disorder	(Harvi
BBS5	Exon 1	Homozygosity mapping	Missense	c.2T>A	p.Met1Lys	RP, Polydactyly, hypogonadism, developmental delay, mental retardation, , situs inversus, bipolar disorder	(Harvi
BBS5	Exon 9	Sanger sequencing using dye-termination chemistry	Frameshift	c.734_744del	p.E245Gfs*18	RP, Polydactyly, Intellectual Disability, Hypogonadism, Bilateral renal calculi, Hypodontia, syndactyly, brachydactyly, ataxia, speech disability, gall bladder calculi, hepatomegaly	(Maria
BBS5	Exon 9	Sanger sequencing using dye-termination chemistry	Frameshift	c.734_744del	p.E245Gfs*18	RP, Polydactyly, Hypogonadism, Developmental delay, irregular menstruation, low progesterone levels, diabetes, hepatomegaly with fatty infiltration, liver abnormalities	(Maria
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Frameshift	c.774delA	p.Thr259LeuTer21	RP, Polydactyly, obesity, Hypogonadism, Nystagmus	(Rao e
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Frameshift	c.774delA	p.Thr259LeuTer21	RP, Obesity, polydactyly	(Rao e
BBS6/MKKS	Exon 3	Whole exome sequencing	Missense	c.748G>A	p.gly250Arg	RP, Polydactyly, obesity, Nystagmus	(Rao e

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		(WES)					
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	frameshift	c.774delA	p.Thr259LeuTer21	RP, polydactyly, intellectual disability, obesity, nystagmus	(Rao e
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Missense	1226G>A	p.Gly409Glu	RP, Polyudactyly,	(Rao e
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Nonsense	c.119C>G	p.Ser40*	RP, polydactyly, obesity, hypogonadism, cognitive impairment, renal impairment, intellectual disability, speech difficulties, mild hearing problems, and slight mental retardation	(Ullah
BBS6/MKKS	Exon 3	Microsatellite-based genotyping and whole exome sequencing.	Frameshift	c.775delA	p. Thr259Leufs*21	polydactyly, had obesity, incomplete syndactyly , mild intellectual disability, poor vision and hypogonadism, Ataxia, imbalance	(Ullah
BBS6/MKKS	Exon 3	Microsatellite-based genotyping and whole exome sequencing.	Nonsense	c.119 C > G	p.Ser40*	polydactyly, had obesity, incomplete syndactyly , mild intellectual disability, poor vision and hypogonadism, Ataxia, imbalance	(Ullah
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Frameshift	c.775 delA	p.Thr259Leufs*21	strabismus (exotropia), retinitis pigmentosa, obesity, and intellectual disability, clinodactyly, postaxial polydactyly, Ataxia, imbalance	(Ullah
BBS6/MKKS	Exon 3	Homozygosity mapping+ Sanger sequencing	Frameshift	c.775-775delA	p.Thr259Leufs*21	polydactyly, learning difficulties, retinitis pigmentosa, truncal obesity, and hypogonadism, dental anomalie, sparse hairs on scalp	(Ullah
BBS6/MKKS	Exon 3	Homozygosity mapping+ Sanger sequencing	variant	c.287C>T	p.Ala96Val	polydactyly, learning difficulties, retinitis pigmentosa, truncal obesity, and hypogonadism, clinodactyly of toes	(Ullah
BBS6/MKKS	Exon 3	Whole exome sequencing	Frameshift	c.775delA	p.Thr259Leufs*21	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism,	(Nawa

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		(WES)				Renal abnormality, Intellectual disability, Speech disability, Strabismus, cataract, astigmatism, Diabetes mellitus	
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Nonsense	c.119C>G	p.Ser40*	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism, Intellectual disability, Speech disability, Strabismus, cataract, astigmatism	(Nawa
BBS6/MKKS	Exon 3	Microsatellite-based genotyping	Nonsense	c.775delA	p.Thr259Leufs*21	right foot polydactyly and 2/3digit incomplete syndactyly, strabismus, obesity, intellectual disability, poor vision and hypogonadism	(Ali et
BBS6/MKKS	Exon 3	SNP array	Missense	c.280T>C	p.Phe94Leu	obesity, hypogonadism, learning/developmental disabilities, post-axial polydactyly of hands and/or feet, and renal abnormalities	(Ur R
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Frameshift	c.775delA	p.Thr259Leufs*21	strabismus (exotropia), RP, obesity, weak vision, Intellectual Disability, Clinodactyly of 5th finger and postaxial polydactyly, bilateral brachydactyly	(Nawa
BBS6/MKKS	Exon 3	Microsatellite-based genotyping	Nonsense	c.119 C>G	p.Ser40*	right foot polydactyly and 2/3digit incomplete syndactyly, strabismus, obesity, mild intellectual disability, poor vision and hypogonadism	(Ali et
BBS7	Exon 16	Whole exome sequencing (WES)	splice-site	c.1677-1G > A	p. Arg559ArgfsTer3	facial dysmorphology, cutis laxa in the abdominal area, scoliosis, polydactyly, speech impairment, and walking difficulties	(Shaul
BBS7	Exon 11	Homozygosity Mapping followed by Sanger sequencing	Missense	c.719G>T	p.Gly240Val	hypertelorism, facial dysmorphism, hypogonadism, malar hypoplasia, obesity, mental retardation and poor analytical ability	(Hayat
BBS7	Exon 8	Whole exome sequencing	Missense	c.752G>T	p.Gly251Val	bulging eyes and misaligned teeth, bilateral clinodactyly ,hypertelorism	(Ali et

		(WES)					
BBS7	Exon 8	Whole exome sequencing (WES)	Missense	c.752G > T	p.Gly251Val	bulging eyes and misaligned teeth, facial anomalies including hypertelorism, postaxial polydactyly, obesity.Ataxia, imbalance	(Ullah
BBS7	Exon 6	Homozygosity mapping followed by Sanger sequencing	Frameshift	c.580_582delGCA	p.Ala194del	RP, Polydactyly,obesity,hypogonadism, cognitive impairment, syndactyly, reproductive tract/organ anomalies	(Ullah
BBS7	Exon 6	Homozygosity mapping followed by Sanger sequencing	Frameshift	c.1592_1597delTTCCAG	p.Val531_Pro532del	RP, polydactyly, obesity, hypogonadism, cognitive impairment	(Ullah
BBS7	Exon 6	Whole exome sequencing (WES)	Frameshift	c.580_582delGCA	p.Ala194del	RP, Polydactyly, obesity, nystagmus	(Rao e
BBS7	Exon 6	Whole exome sequencing (WES)	Frameshift	c.580_582delGCA	p.Ala194del	RP, Polydactyly, intellectual disability, obesity, nystagmus	(Rao e
BBS8	Exon 1	Homozygosity mapping followed by Sanger sequencing	Missense	c.1347G>C	p.Gln449His	RP, polydactyly, obesity, hypogonadism, clinodactyly, cognitive impairment	(Ullah
BBS8	Exon 2	Whole exome sequencing (WES)	Splice site	-	p.?	RP, polydactyly, obesity, hypogonadism, clinodactyly, cognitive impairment	(Riazu
BBS9	Exon 3	Whole exome sequencing (WES)	Missense	c.1131G>A	p.38	intellectual disability along with vision loss, obesity, speech problems and learning disability.Hypogonadism	(Ain-u
BBS9	7–8 intron	Whole exome sequencing (WES)	Splice site	c.702 + 1del	p.?	developmental delay, postaxial polydactyly, overweight and microcephaly, nystagmus, brachydactyly, broad hands and feet, small penis and no pubertal changes	(Suáre

BBS9	Exon 3	Whole exome sequencing (WES)	Frameshift	c.252delA	p.Lys85SerTer39	RP, polydactyly, intellectual disability, obesity, nystagmus, hypogonadism	(Rao e
BBS9	Exon 7	Whole exome sequencing (WES)	Nonsense	c.223C>T	p.Arg75Ter	RP, Polydactyly, obesity, Nystagmus	(Rao e
BBS9	Exon 17	Targeted Exome sequencing	Nonsense	c.1789C > T	p.Q597*	RP, Polydactyly, Intellectual Disability, Hypogonadism, Obesity, Elevated liver enzymes, hypodontia, speech disability, gynaecomastia, cerebral atrophy	(Maria
BBS9	Exon 4	Whole exome sequencing (WES)	Frameshift	c.299delC	p.Ser100Leufs*24	RP, Liver Abnormalities, syn-hexa-dactyly, hexadactyly (central polydactyly) of both feet postaxial polydactyly of hands and feet, obesity and intellectual disability (ID)	(Muza
BBS9	Exon 4	Whole exome sequencing (WES)	Frameshift	c.299delC	p.Ser100Leufs*24	obesity, Gastro-intestinal complications,Digestion problem Speech disability Developmental delay mild hearing loss bilateral postaxial synpolydactyly of hands and feet, mild progressive retinal degeneration, intellectual disability, renal dysfunction, and	(Muza
BBS9	Exon 4	Whole exome sequencing (WES)	Frameshift	c.299delC	p.Ser100Leufs*24	RP, Nystagmus, Kidney and Liver Abnormalities, syn-hexa-dactyly, postaxial polydactyly, obesity and intellectual disability (ID)	(Muza
BBS10	Exon 2	Bidirectional sequencing	Frameshift	c.1958_1967del	p.Ser653Ilefsx4	abnormal liver functioning and bilateral basal ganglia calcification, Obesity and post axial polydactyly, d myopia, learning disabilities	(Agha
BBS10	Exon 2	Homozygosity mapping	Nonsense	c.1075C>T	p.Gln359*	polydactyly, cutaneous syndactyly, obesity, retinitis pigmentosa and mental delay	(Khan

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BBS10	Exon 2	Homozygosity mapping followed by Sanger sequencing	Frameshift	c.271_272insT	p.?	RP, polydactyly, obesity, hypogonadism, cognitive impairment, renal impairment	(Ullah
BBS12	Exon 2	Homozygosity mapping	Nonsense	c.2103C 1 A	p.S701X	bilateral polydactyly and mild vision impairment, hypodontia	(Ahma
BBS12	Exon 2	Homozygosity mapping	Nonsense	c.2103C 1 A	p.S701X	bilateral polydactyly and mild vision impairment, hypodontia	(Ahma
BBS12	Exon 2	Targeted Exome sequencing	Missense	c.2014G > A	p.A672T	RP, Intellectual Disability, Hypogonadism, Obesity, Irregular menstruation, Severe depression, Gynaecomastia, cerebral atrophy	(Maria
BBS12	Exon 2	Homozygosity mapping	Missense	c.1589T>C	p.L530P	RP, Polydactyly, hypogonadism, Renal anomalies, developmental delay, mental retardation, , situs inversus, bipolar disorder	(Harvi
BBS12	Exon 2	Homozygosity mapping	Missense	c.1589T>C	p.L530P	RP, Polydactyly, hypogonadism, Renal anomalies, developmental delay, mental retardation, , situs inversus, bipolar disorder	(Harvi
BBS12	Exon 2	Homozygosity mapping	Nonsense	c.2103C>A	p.S701X	postaxial polydactyly and late-onset retinal dysfunction ,atypical retinitis pigmentosa, myopia and astigmatism	(Pawli
BBS15/WDPCP	Exon 1	Whole exome sequencing (WES)	Nonsense	c.720C>A	p.Cys240Ter	Retinal degeneration, polydactyly, obesity, Hypogonadism, Renal abnormality, Speech disability, Mild spasticity, Hearing Loss	(Nawa
LZTFL1	Exon 6	Whole exome sequencing (WES)	Nonsense	c.505A>T	p.Lys169Ter	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism, Renal abnormality, Speech disability, Strabismus, cataract, astigmatism	(Nawa
BBIP1/BBS18	Exon 3	Whole exome sequencing (WES)	Nonsense	c.160A>T	p.Lys54Ter	Retinal degeneration, polydactyly, obesity, Hypogonadism, Renal abnormality, Speech disability, Strabismus, cataract, astigmatism	(Nawa

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						, Syndactyly	
IFT27/BBS19	Exon 2	Whole exome sequencing (WES)	Nonsense	c.94C>T	p.Gln32Ter	Retinal degeneration, polydactyly, obesity, Developmental delay, Renal abnormality, Speech disability, Strabismus, cataract, astigmatism, Hearing Loss	(Nawa
INPP5E	Exon 5	Whole exome sequencing (WES)	Nonsense	c.1879C>T	p.Gln627*	hypotonia, intellectual disability obesity, visual impairment, hyperactive behavior, speech impairment, and micropenis	(Khan
CEP164	Exon 5	Whole exome sequencing (WES)	Missense	c.277C > T	p.R93W	RP, Intellectual Disability, Hypogonadism, Obesity, Irregular menstruation, Severe depression, Gynaecomastia, cerebral atrophy	(Maria
BBS1	Exon 1	Whole exome sequencing (WES)	Splice site mutation	c.47+1G>T	p?	Retinitis pigmentosa, obesity, learning difficulties, polydactyly	(Ajma
BBS1	Exon 4	Whole exome sequencing (WES)	Missense	c.442G>A	p.Asp148Asn	Developmental delay, Retinitis pigmentosa, obesity, and learning difficulties, hypertensive	(Ajma
BBS1	Exon 12	Whole exome sequencing (WES)	Nonsense	c.1150 C>T	p.Glu384Ter	RP, Polydactyly, obesity, Hypogonadism, Renal failure, intellectual disability	(Rao e
BBS1	Exon 13	Whole exome sequencing (WES)	Missense	c.1339G>A	p.Ala447Thr	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism, Renal abnormality, Speech disability, Strabismus, cataract, astigmatism, Dental anomaly	(Nawa
BBS1	Exon 13	Whole exome sequencing (WES)	Missense	c.1339G>A	p.Ala447Thr	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism, Renal abnormality, Intellectual disability, Speech disability	(Nawa
BBS1	Exon 16	Whole exome sequencing (WES)	donor splice site	c.951+1G>A	p?	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism, Renal abnormality, Speech disability,	(Nawa

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						Strabismus, cataract, astigmatism	
BBS2	Exon 3	Whole exome sequencing (WES)	Missense	c.443A>T	p.Ala148Ile	obesity, renal problems, intellectual disability (ID), and postaxial polydactyly	(Ali et
BBS2	Exon 12	Linkage analysis and Sequencing	Nonsense	c.1658C>T	p.R413X	RP, Polydactyly, obesity, developmental delay, mental retardation, , situs inversus, bipolar disorder	(Kord
BBS2	Exon 12	SNP array	Nonsense	c.1438C>T	p.Arg480Ter	IRD and extra-ocular symptoms such obesity, hypogonadism, learning disabilities, post-axial polydactyly and renal abnormalities	(Ur R
BBS2	Exon 3	Whole exome sequencing (WES)	splice site	c.471G>A	no protein	RP, Polydactyly, obesity, Hypogonadism, Nystagmus	(Rao e
BBS2	Exon 12	Dideoxy Sequencing(DS)	Nonsense	c.1658C>T	p.R413X	Vision impairment, obesity, polydactyly, developmental delay	(Chen
BBS2	Exon 11	Homozygosity Mapping	Missense	c.1237C>T	p.R413X	RP, Polydactyly, obesity, developmental delay, mental retardation, situs inversus, bipolar disorder	(Harvi
BBS2	Exon 3	Whole exome sequencing (WES)	Missense	c.443A>T	p.Ala148Ile	obesity, renal problems, intellectual disability (ID), and postaxial polydactyly, diabetes mellitus, Speech delay	(Ali et
BBS3/ARL6	Intron 3	Dideoxy Sequencing(DS)	Frameshift	c.123+1118del53985†	p?	Congenital postaxial polydactyly, progressive night blindness, atypical retinitis pigmentosa (RP, rod-cone dystrophy), myopia and astigmatism	(Pawli
BBS3/ARL6	Exon 8	Targeted Exome sequencing	splice site	c.534A > G	p.Q178Q	RP, Polydactyly, Hypogonadism, Renal abnormalities, Elevated liver enzymes, abnormal ECG, gynaecomastia BBS like Syndrome	(Maria
BBS3/ARL6	Exon 1	Homozygosity mapping	Missense	c.281T>C	p.Ile94Thr	postaxial polydactyly, obesity and retinitis pigmentosa	(Khan
BBS3/ARL6	Exon 1	Whole exome	Frameshift	c.387_394delAAATAAAA	pAsn130GlyfsTer3	RP, polydactyly, obesity	(Rao e

		sequencing (WES)					
BBS5	Exon 1	Whole exome sequencing (WES)	Missense	c. 2T>A	p.Met1Lys	strabismus, bilateral clinodactyly of fifth and sixth fingers in hands and bilateral postaxial polydactyly, bulging eyes	(Ali et
BBS5	Exon 3	Whole exome sequencing (WES)	frameshift	c.196delA	p.Arg66Glufs*12	intellectual disability, visual impairment, truncal obesity, postaxial polydactyly, and renal anomalies, hypogonadism	(Khan
BBS5	Exon 3	Whole exome sequencing (WES)	Frameshift	c.196delA	p.Arg66Glufs*12	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism, Renal abnormality, Intellectual disability, Speech disability, Ataxia, imbalance	(Nawa
BBS5	Exon 1	Whole exome sequencing (WES)	Missense	c.2T > A	p. Met1Lys	strabismus, bilateral clinodactyly of fifth and sixth fingers in hands and bilateral postaxial polydactyly, bulging eyes, Ataxia, imbalance	(Ullah
BBS5	Exon 1	Homozygosity mapping	Missense	c.2T>A	p.Met1Lys	RP, Polydactyly, obesity, hypogonadism, developmental delay, mental retardation, , situs inversus, bipolar disorder	(Harvi
BBS5	Exon 1	Homozygosity mapping	Missense	c.2T>A	p.Met1Lys	RP, Polydactyly, hypogonadism, developmental delay, mental retardation, , situs inversus, bipolar disorder	(Harvi
BBS5	Exon 9	Sanger sequencing using dye-termination chemistry	Frameshift	c.734_744del	p.E245Gfs*18	RP, Polydactyly, Intellectual Disability, Hypogonadism, Bilateral renal calculi, Hypodontia, syndactyly, brachydactyly, ataxia, speech disability, gall bladder calculi, mild spleno- and hepatomegaly, elevated liver enzymes, abnormally high cholesterol level	(Maria
BBS5	Exon 9	Sanger sequencing using dye-termination chemistry	Frameshift	c.734_744del	p.E245Gfs*18	RP, Polydactyly, Hypogonadism, Developmental delay, irregular menstruation, diabetes, borderline hepatomegaly	(Maria

BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Frameshift	c.774delA	p.Thr259LeuTer21	RP, Polydactyly, obesity, Hypogonadism, Nystagmus	(Rao e
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Frameshift	c.774delA	p.Thr259LeuTer21	RP, Obesity	(Rao e
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Missense	c.748G>A	p.gly250Arg	RP, Polydactyly, obesity, Nystagmus	(Rao e
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	frameshift	c.774delA	p.Thr259LeuTer21	RP, polydactyly, intellectual disability, obesity, nystagmus	(Rao e
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Missense	1226G>A	p.Gly409Glu	RP, Polyudactyly,	(Rao e
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Nonsense	c.119C>G	p.Ser40*	RP, polydactyly, obesity, hypogonadism, cognitive impairment, renal impairment, intellectual disability, speech difficulties, mild hearing problems, and slight mental retardation	(Ullah
BBS6/MKKS	Exon 3	Microsatellite-based genotyping and whole exome sequencing.	Frameshift	c.775delA	p. Thr259Leufs*21	polydactyly, had obesity, incomplete syndactyly , mild intellectual disability, poor vision and hypogonadism, Ataxia, imbalance	(Ullah
BBS6/MKKS	Exon 3	Microsatellite-based genotyping and whole exome sequencing.	Nonsense	c.119 C > G	p.Ser40*	polydactyly, had obesity, incomplete syndactyly , mild intellectual disability, poor vision and hypogonadism, Ataxia, imbalance	(Ullah
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Frameshift	c.775 delA	p.Thr259Leufs*21	strabismus (exotropia), retinitis pigmentosa, obesity, weak vision, and intellectual disability, clinodactyly, postaxial polydactyly, Ataxia, imbalance	(Ullah
BBS6/MKKS	Exon 3	Homozygosity	Frameshift	c.775-775delA	p.Thr259Leufs*21	polydactyly, learning difficulties, retinitis	(Ullah

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		mapping+ Sanger sequencing				pigmentosa, truncal obesity, and hypogonadism, dental anomalie, sparse hairs on scalp	
BBS6/MKKS	Exon 3	Homozygosity mapping+ Sanger sequencing	variant	c.287C>T	p.Ala96Val	polydactyly, learning difficulties, retinitis pigmentosa, truncal obesity, and hypogonadism, clinodactyly of toes	(Ullah
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Frameshift	c.775delA	p.Thr259Leufs*21	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism, Renal abnormality, Intellectual disability, Speech disability, Strabismus, cataract, astigmatism, Diabetes mellitus	(Nawa
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Nonsense	c.119C>G	p.Ser40*	Retinal degeneration, polydactyly, obesity, Developmental delay, Hypogonadism, Intellectual disability, Speech disability, Strabismus, cataract, astigmatism	(Nawa
BBS6/MKKS	Exon 3	Microsatellite-based genotyping	Nonsense	c.775delA	p.Thr259Leufs*21	right foot polydactyly and 2/3digit incomplete syndactyly, strabismus,obesity, mild intellectual disability, poor vision and hypogonadism	(Ali, e
BBS6/MKKS	Exon 3	SNP array	Missense	c.280T>C	p.Phe94Leu	obesity, hypogonadism, learning/developmental disabilities, post-axial polydactyly of hands and/or feet, and renal abnormalities	(Ur R
BBS6/MKKS	Exon 3	Whole exome sequencing (WES)	Frameshift	c.775delA	p.Thr259Leufs*21	strabismus (exotropia), RP, obesity, weak vision, Intellectual Disability, Clinodactyly of 5th finger and postaxial polydactyly, bilateral brachydactyly	(Ur R
BBS6/MKKS	Exon 3	Microsatellite-based genotyping	Nonsense	c.119 C>G	p.Ser40*	right foot polydactyly and 2/3digit incomplete syndactyly, strabismus,obesity, mild intellectual disability, poor vision and hypogonadism	(Ali, e
BBS7	Exon 16	Whole exome sequencing	splice-site	c.1677-1G > A	p. Arg559ArgfsTer3	facial dysmorphology,scoliosis, polydactyly, speech impairment, and walking	(Shaul

		(WES)				difficulties	
BBS7	Exon 11	Homozygosity Mapping followed by Sanger sequencing	Missense	c.719G>T	p.Gly240Val	hypertelorism, deep-set eyes, a flat nasal bridge, a small mouth, hypogonadism, malar hypoplasia, obesity, mental retardation and poor analytical ability	(Hayat
BBS7	Exon 8	Whole exome sequencing (WES)	Missense	c.752G>T	p.Gly251Val	bulging eyes and misaligned teeth, bilateral clinodactyly ,hypertelorism	(Ali, e
BBS7	Exon 8	Whole exome sequencing (WES)	Missense	c.752G > T	p.Gly251Val	bulging eyes and misaligned teeth, facial anomalies including hypertelorism, postaxial polydactyly, obesity. Ataxia, imbalance	(Ullah
BBS7	Exon 6	Homozygosity mapping followed by Sanger sequencing	Frameshift	c.580_582delGCA	p.Ala194del	RP, Polydactyly, obesity, hypogonadism, cognitive impairment, syndactyly, reproductive tract/organ anomalies	(Ullah
BBS7	Exon 6	Homozygosity mapping followed by Sanger sequencing	Frameshift	c.1592_1597delTTCCAG	p.Val531_Pro532del	RP, polydactyly, obesity, hypogonadism, cognitive impairment	(Ullah
BBS7	Exon 6	Whole exome sequencing (WES)	Frameshift	c.580_582delGCA	p.Ala194del	RP, Polydactyly, obesity, nystagmus	(Rao e
BBS7	Exon 6	Whole exome sequencing (WES)	Frameshift	c.580_582delGCA	p.Ala194del	RP, Polydactyly, intellectual disability, obesity, nystagmus	(Rao e
BBS8	-	Homozygosity mapping	Splice site	N/A	N/A	RP, Polydactyly, obesity, hypogonadism, mental retardation, , hypotonia, developmental delay, brachycephaly,	(Ansle
BBS8	Exon 1	Homozygosity mapping followed by Sanger	Missense	c.1347G>C	p.Gln449His	RP, polydactyly, obesity, hypogonadism, clinodactyly, cognitive impairment	(Ullah

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		sequencing					
BBS8	Exon 2	Whole exome sequencing (WES)	Splice site	-	p.?	RP, polydactyly, obesity, hypogonadism, clinodactyly, cognitive impairment	(Riazu
BBS9	Exon 3	Whole exome sequencing (WES)	Missense	c.1131G>A	p.38	intellectual disability along with vision loss, obesity, speech problems and learning disability.Hypogonadism	(Ain-u
BBS9	7–8 intron	Whole exome sequencing (WES)	Splice site	c.702 + 1del	p.?	developmental delay, postaxial polydactyly, overweight and microcephaly, nystagmus, brachydactyly, broad hands and feet, small penis and no pubertal changes	(Suáre
BBS9	Exon 3	Whole exome sequencing (WES)	Frameshift	c.252delA	p.Lys85SerTer39	RP, polydactyly, intellectual disability, obesity, nystagmus, hypogonadism	(Rao e
BBS9	Exon 7	Whole exome sequencing (WES)	Nonsense	c.223C>T	p.Arg75Ter	RP, Polydactyly, obesity, Nystagmus	(Rao e
BBS9	Exon 17	Targeted Exome sequencing	Nonsense	c.1789C > T	p.Q597*	RP, Polydactyly, Intellectual Disability, Hypogonadism, Obesity, Elevated liver enzymes, hypodontia, speech disability, gynaecomastia, cerebral atrophy	(Maria
BBS9	Exon 4	Whole exome sequencing (WES)	Frameshift	c.299delC	p.Ser100Leufs*24	RP, Liver Abnormalities, syn-hexa-dactyly, hexadactyly, obesity and intellectual disability	(Muza
BBS9	Exon 4	Whole exome sequencing (WES)	Frameshift	c.299delC	p.Ser100Leufs*24	obesity, Gastro-intestinal complications, Speech disability, Developmental delay. hearing loss, bilateral postaxial synpolydactyly of hands and feet, mild progressive retinal degeneration, intellectual disability, renal dysfunction	(Muza
BBS9	Exon 4	Whole exome sequencing (WES)	Frameshift	c.299delC	p.Ser100Leufs*24	RP, Nystagmus, Kidney and Liver Abnormalities, syn-hexa-dactyly, obesity and intellectual disability (ID)	(Muza

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BBS10	Exon 2	Bidirectional sequencing	Frameshift	c.1958_1967del	p.Ser653Ilefsx4	abnormal liver functioning and bilateral basal ganglia calcification, Obesity and post axial polydactyly, myopia, learning disabilities	(Agha
BBS10	Exon 2	Homozygosity mapping	Nonsense	c.1075C>T	p.Gln359*	polydactyly, cutaneous syndactyly, obesity, retinitis pigmentosa and mental delay	(Khan
BBS10	Exon 2	Homozygosity mapping followed by Sanger sequencing	Frameshift	c.271_272insT	p.?	RP, polydactyly, obesity, hypogonadism, cognitive impairment, renal impairment	(Ullah
BBS12	Exon 2	Homozygosity mapping	Nonsense	c.2103C 1 A	p.S701X	bilateral polydactyly and mild vision impairment, hypodontia	(Ahma
BBS12	Exon 2	Homozygosity mapping	Nonsense	c.2103C 1 A	p.S701X	bilateral polydactyly and mild vision impairment, hypodontia	(Ahma
BBS12	Exon 2	Targeted Exome sequencing	Missense	c.2014G > A	p.A672T	RP, Intellectual Disability, Hypogonadism, Obesity, Irregular menstruation, Severe depression, Gynaecomastia, cerebral atrophy	(Maria
BBS12	Exon 2	Homozygosity mapping	Missense	c.1589T>C	p.L530P	RP, Polydactyly, hypogonadism, Renal anomalies, developmental delay, mental retardation, , situs inversus, bipolar disorder	(Harvi
BBS12	Exon 2	Homozygosity mapping	Missense	c.1589T>C	p.L530P	RP, Polydactyly, hypogonadism, Renal anomalies, developmental delay, mental retardation, , situs inversus, bipolar disorder	(Harvi
BBS12	Exon 2	Homozygosity mapping	Nonsense	c.2103C>A	p.S701X	postaxial polydactyly and late-onset retinal dysfunction ,atypical retinitis pigmentosa, myopia and astigmatism	(Pawli
BBS15/WDPCP	Exon 1	Whole exome sequencing (WES)	Nonsense	c.720C>A	p.Cys240Ter	Retinal degeneration, polydactyly, obesity, Hypogonadism, Renal abnormality, Speech disability, Mild spasticity, Hearing Loss	(Nawa
LZTFL1	Exon 6	Whole exome	Nonsense	c.505A>T	p.Lys169Ter	Retinal degeneration, polydactyly, obesity,	(Nawa

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		sequencing (WES)				Developmental delay, Hypogonadism, Renal abnormality, Speech disability, Strabismus, cataract, astigmatism	
BBIP1/BBS18	Exon 3	Whole exome sequencing (WES)	Nonsense	c.160A>T	p.Lys54Ter	Retinal degeneration, polydactyly, obesity, Hypogonadism, Renal abnormality, Speech disability, Strabismus, cataract, astigmatism , Syndactyly	(Nawa
IFT27/BBS19	Exon 2	Whole exome sequencing (WES)	Nonsense	c.94C>T	p.Gln32Ter	Retinal degeneration, polydactyly, obesity, Developmental delay, Renal abnormality, Speech disability, Strabismus, cataract, astigmatism, Hearing Loss	(Nawa
INPP5E	Exon 5	Whole exome sequencing (WES)	Nonsense	c.1879C>T	p.Gln627*	hypotonia, intellectual disability (mild/moderate and nonprogressive), obesity, visual impairment, aggressive and hyperactive behavior, delayed language acquisition, speech impairment, and micropenis	(Khan
CEP164	Exon 5	Whole exome sequencing (WES)	Missense	c.277C > T	p.R93W	RP, Intellectual Disability, Hypogonadism, Obesity, Irregular menstruation, Severe depression, Gynaecomastia, cerebral atrophy	(Maria

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The study sheds light on the frequency and distribution of mutations across several genes, offering insight into the genetic landscape of Bardet-Biedl Syndrome (BBS) in the Pakistani community. Interestingly, despite the fact that many genes are linked to BBS, a large number of them are still unknown because of gaps in molecular research. Nonetheless, the research illuminates the identified mutations responsible for BBS in the Pakistani population.

The results shown in Table 2 indicate that a number of genes are associated with BBS in the population of Pakistan. Of these, BBS6/MKKS stands out as a noteworthy contributor, accounting for 20% of BBS cases(Ali et al., 2023; M'hamdi et al., 2014).Figure 4. Other important genes after BBS6/MKKS are BBS5, BBS7, and BBS9, which together account for 11% of the disease burden. Furthermore, WDPCP/BBS15, BBIP1/BBS18, IFT27/BBS19, LZTFL1, CEP164, and INPP5E are among the genes that together account for 8% of BBS instances in the Pakistani population. The second largest group of BBS patients has mutations in the chaperonin gene (BBS6/MKKS, 10, 12), while the third most common group has mutations in the BBS3/ARL6 gene, which support BBSome function(Simičić Majce et al., 2023). Similar findings are documented in the present study in table 1.

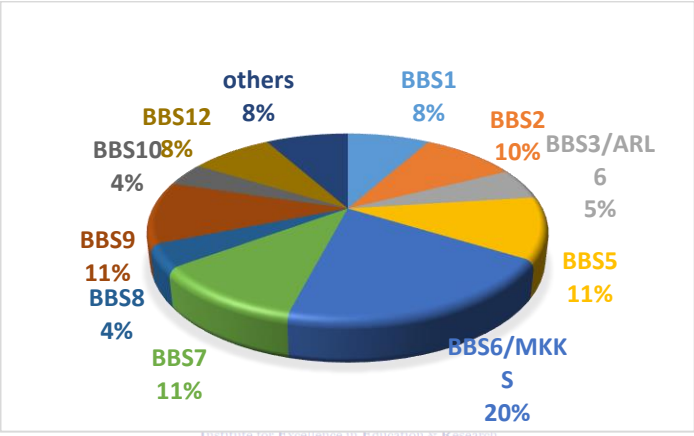


Figure 4 Frequency of reported genes in Pakistan

Potential genomic hotspots for pathogenic variations in these genes are suggested by the finding that all disease-causing mutations in BBS6/MKKS were located in exon 3, and that largely exon 2 was the site of mutations in BBS10 and BBS12 as evidenced by the studies of Nawaz et al., 2023 and Rao et al., 2023. Table 2. Multiple factors could impact this phenomenon, such as the functional importance of certain exons, the mechanisms underlying mutations, and the selection biases present in different research.

Following missense, nonsense, and splice-site mutations, frameshift mutations—which alter the gene's
reading frame—were found to be the primary cause of BBS as depicted in figure 5.

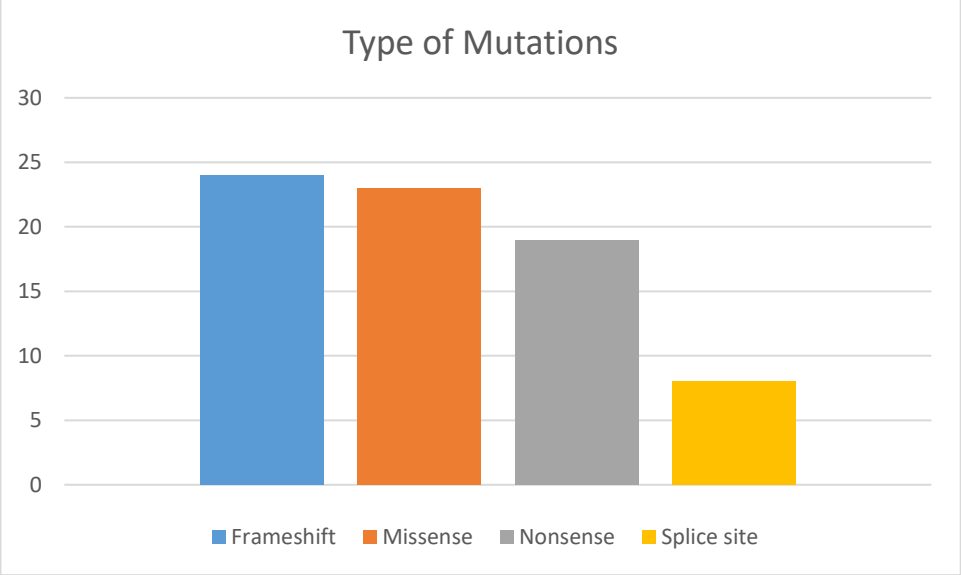


Figure 5 Histogram of different type of mutations in Pakistani population

The frameshift variant c.299delC in exon 4 of BBS9 and the missense variant c.2T>A in exon 1 of BBS5 have been frequently observed in the Pakistani community, which highlights their possible importance in the pathophysiology of Bardet-Biedl Syndrome (BBS) in this population. These variations might be common mutations or founder mutations that emerged and stayed within certain geographic or ethnic groupings.

Nevertheless, there is a significant degree of variance in clinical symptoms across BBS patients in the Pakistani population, even in the presence of these recurrent mutations. The variable nature of BBS, wherein affected individuals may display a wide variety of symptoms, such as retinal degeneration, polydactyly, obesity, renal abnormalities, intellectual disability, and developmental delays, is consistent with the variance in clinical presentation observed in this case.

Modifier genes, environmental factors, and genetic heterogeneity are some of the causes of the variety in clinical symptoms. Different phenotypic manifestations can result from distinct mutations in the same gene or from mutations in different genes. Variations in environmental factors can also affect the intensity and course of BBS-related symptoms. These factors include nutrition, lifestyle, and access to healthcare.

Moreover, the diagnostic criteria established by Beales et al. for BBS cover a wide range of clinical characteristics, making it possible to identify the illness in a variety of populations even when presentation varies. The intricacy of BBS is acknowledged, and the significance of thorough clinical examination and genetic testing for precise diagnosis and treatment is emphasized by this inclusive approach.

Discussion

Ciliopathies are caused by genetic abnormalities that impact the function of the primary cilium. Bardet-Biedl Syndrome (BBS) is a rare hereditary condition that represents a ciliopathy that affects several organs in different ways. Numerous clinical symptoms, such as polydactyly, obesity, retinal degeneration, and more, are associated with this autosomal recessive disorder. Genes linked to cilia are mutated, impairing development and sensory perception. The symptoms usually appear in early childhood, frequently accompanied by visual problems such as nystagmus and night blindness.

Because the symptoms of BBS develop gradually, the diagnosis is sometimes delayed until late childhood or early adulthood. Specific major and minor traits are part of the diagnostic criteria. Early detection is now possible thanks to developments in prenatal medicine and genetic testing, however some areas may not have easy access to sequencing because of cost.

Till now, 26 genes are linked to the condition(Forsyth & Gunay-Aygun, 2020). Mutations affecting BBS genes, including BBS1, BBS2, and

BBS10, are common worldwide and have differing distributions across various groups. A number of BBS proteins make up the BBSome complex, which is essential for preserving ciliary shape and function. Furthermore, there are genetic similarities across different ciliopathies, involving common mutations in genes such as MKKS, BBS2, BBS4, and BBS6. The complex link between ciliary malfunction and associated disorders is highlighted by this genetic intricacy.

In this review, we looked at Pakistani Bardet-Biedl Syndrome (BBS) mutations. To our knowledge, no thorough analysis of all the known mutations causing BBS in the Pakistani population has yet been published. We searched PubMed for papers published up until March 2024 and found 74 mutations (Table 2). The gene frequency in Pakistani BBS patients is shown in Figure 3.

This work sheds light on gene distribution and mutation patterns related to Bardet-Biedl Syndrome (BBS) mutations in the Pakistani population. Twenty percent of instances are BBS6/MKKS(Ali et al., 2023), with eleven percent coming from BBS5, BBS7, and BBS9. Furthermore, 8% is jointly contributed by mutations in WDPCP/BBS15, BBIP1/BBS18, IFT27/BBS19, LZTFL1, CEP164, and INPP5E. Figure Notably, exon 3, exon 2, and exon 2 are the primary locations of mutations in BBS6/MKKS, BBS10, and BBS12, respectively as evidenced by the studies of Nawaz et al., 2023 and Rao et al., 2023. Figure The most prevalent kind of mutations are frameshift mutations. The missense variant c.2T>A in exon 1 of BBS5, and the frameshift variant c.299delC in exon 4 of BBS9 was frequently observed in Pakistani population as shown in the table. Table 2. Beales et al. criteria show significant heterogeneity in clinical symptoms among Pakistani BBS patients.

Conclusion

Bardet-Biedl Syndrome (BBS) poses a challenging situation because of its rarity, clinical unpredictability, and multi-organ involvement. This review highlights the value of a multidisciplinary approach and the necessity of individualized therapy for patients with BBS. Future treatment strategies are hopeful due to recent progress in understanding the genetic intricacy of the disease and the roles of BBS proteins. Nonetheless, more investigation is necessary

to clarify the fundamental causes of BBS and to create specialized diagnostic and treatment plans. The results provided here clarify the genetics of BBS in the Pakistani population and emphasize the value of genetic screening and counselling, especially in areas where consanguineous marriages are common. In order to enhance the lives of those impacted by BBS, this review calls for more research, education, and focused interventions.

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