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Review

Molecular variants of Bardet-Biedl Syndrome

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Bardet-Biedl Syndrome (BBS) is a genetically and clinically heterogeneous disorder clinically characterized by obesity, mental retardation, dysphormic extremities (syndactyly, brachydactyly or polydactyly), retinal dystrophy or pigmentary retinopathy, hypogonadism and kidney structural abnormalities or functional impairment. Till now, 14 *genes* have been identified for BBS on different chromosomes, that is, 11q13 (BBS1), 16q21 (BBS2), 3p12 (BBS3), 15q22 (BBS4), 2q31 (BBS5), 20p12 (BBS6), 4q27 (BBS7), 14q32.11 (BBS8), 7p14 (BBS9), 12q21.2 (BBS10), 9q33.1 (BBS11), 4q27 (BBS12), 17q23 (BBS13), and 12q21.3 (BBS14). Genetic and mutational analysis has indicated that a combination of 3 mutant alleles at two loci is necessary for pathogenesity of BBS. Mutations in BBS *genes* have impact on different pathways. This study is helpful in generating the databank of disease related mutations and in controlling the disease by understanding the pathogenesis of disease.

Key words: Bardet-Biedl Syndrome (BBS), BBS *genes*, allelic variants.

INTRODUCTION

The increasing importance of the genetic contribution to the overall disease profile in both developed and developing countries has highlighted potential problems associated with detrimental recessive *gene* expression in consanguineous progeny (Bittles, 2001). Genetic disorders like mental retardation, Bardet-Biedl syndrome, retinitis pigmentosa, cone dystrophy, deafness, muscular dystrophy etc., are common worldwide.

In 1866, four siblings with obesity, retinal degeneration and mental retardation were reported (Laurence and Moon, 1866). Over 50 years later, Bardet and Biedl found individuals who, in addition to the Laurence-Moon symptoms, presented with polydactyly. It is now generally accepted that Laurence-Moon syndrome and Bardet-Biedl syndrome are not distinct disorders, but rather are allelic (Blacque and Leroux, 2006). Farag and Teebi (1988) concluded that the frequency of both the Bardet-Biedl and the Laurence-Moon syndromes is increased in in the Arab population of Kuwait and in 1989 Farag and Teebi pointed to a high frequency of the Bardet-Biedl syndrome among the Bedouin; the estimated minimum frequency was 1/13,500 (Farag and Teebi, 1988).

Bardet–Biedl Syndrome (BBS) [MIM#209900] is a genetic autosomal-recessive ciliopathy phenotypically characterized by obesity, mental retardation, dysphormic extremities such as syndactyly, brachydactyly or polydactyly, retinal dystrophy or pigmentary retinopathy, hypogonadism, and kidney structural abnormalities or functional impairment (Forti et al., 2007; Iannello et al., 2002). Phenotypes of BBS are extremely variable. Different scientist reported different symptoms at different times. Therefore, Beales et al., 1999 suggested clinical diagnostic criteria for BBS. Beales et al. (1999) proposed that clinical diagnosis of BBS requires four of six primary symptoms (obesity, rod – cone dystrophy, renal abnormalities, polydactyly, male hypogonadism and learning disabilities), or three primary symptoms and at least two secondary symptoms, which include diabetes mellitus, hepatic fibrosis, ataxia/poor coordination/ imbalance, speech disorder / delay, polyuria / polydipsia (nephrogenic diabetes insipidus), mild spasticity (especially lower limbs), dental crowding/ hypodontia/ small roots/ high arched palate, left ventricular hypertrophy/ congenital heart disease, hearing loss, anosmia, and situs inversus (Beales et al., 1999; Blacque and Leroux, 2006).

Clinical evaluation for infants is difficult because of late onset of some manifestations. Beales modified criteria for the diagnosis of BBS is mentioned in Table 1. One of our studies suggested the use of less strict diagnostic

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Table 1. Modified BBS diagnostic criteria proposed by Beales et al., 1999.

Four features required	
Primary features	Rod-cone dystrophy
	Polydactyly
	Obesity
	Learning disabilities
	Hypogonadism in males
	Renal anomalies
Three primary + two secondary features required	
Secondary features	Speech disorder/delay
	Strabismus/cataracts/astigmatism
	Brachydactyly/syndactyly
	Developmental delay
	Polyuria/polydipsia (nephrogenic diabetes insipidus)
	Ataxia/poor coordination/imbalance
	Mild spasticity (especially lower limbs)
	Diabetes mellitus
	Dental crowding/ hypodontia/small roots/high arched palate
	Left ventricular hypertrophy/congenital heart disease
	Hepatic fibrosis

criteria in familial cases of BBS (Pawlink et al., 2010).

BBS *genes* and their variants

So far, fourteen *genes* for BBS have been mapped and cloned: BBS1 (11q13) [MIM#209901], BBS2 (16q21) [MIM#606151], BBS3 (ARL6) (3p12-q13) [MIM#608845], BBS4 (15q22.3) [MIM#600374], BBS5 (2q31) [MIM#603650], BBS6 (MKKS) (20p12) [MIM#604896], BBS7 (4q27) [MIM#607590], BBS8 (14q32.11) [MIM#608132], BBS9 (7p14) [MIM#607968], BBS10 (12q21.2) [MIM#610148], BBS11 (9q33.1) [MIM#602290], BBS12 (4q27) [MIM#610683], BBS13 (MKS1) (17q23) [MIM#609883], and BBS14 (CEP290) (12q21.3) [MIM#610142] (Zhenglin et al., 2008).

Mutations in BBS1 constitute the most mutations in the known BBS families (about 23.3%). Mutations in BBS10, BBS2, and BBS12 account for 20, 8.1, and 5% of all mutations, respectively. Other known BBS genes are rarely mutated in the known BBS families (Zhenglin et al., 2008). The total mutational load of BBS genes is summarized in Figure 1 (Zaghloul and Katsanis, 2009). BBS is a rare development disorder, and 14 genes that cause BBS have been identified. However, because of the significant clinical and genetic heterogeneity of BBS, there are still unknown *genes* involving at least 25 – 50% of BBS families (Zhenglin et al., 2008; Chiang et al., 2006; Stoetzel et al., 2007; Stoetzel et al., 2006a and 2006b). Reported mutations of all these known BBS *genes* are summarized in Table 2.

BBS1

It is located on 11q13, and expressed in fetal tissue, testes, retina and adipose tissue. Mykytyn et al. (2002) found that the BBS1 *gene* contains 17 exons and spans Approximately 23 kb. This *gene* encodes the protein of 593 amino acids. Allelic variants of BBS1 have different impact on different stages or pathways e.g., BBS1 is considered as an important component of BBSome, a complex of BBS proteins, having an importance in promoting the ciliary membrane biogenesis by increasing the level of Rab8- GTP (Nachury et al., 2007). Similarly BBS1 is important for leptin receptor signaling pathway. Allelic variant of BBS1 are as follows:

MET390ARG

Mykytyn et al. (2002) identified a met390-to-arg (M390R) missense mutation in the BBS1 gene in affected members of a consanguineous Puerto Rican family with Bardet-Biedl syndrome. The substitution results from a T to G transversion at nucleotide 1169 (1169 T → G) in exon 12 (Mykytyn et al., 2002). Beales et al. (2003) identified homozygous M390R alleles in 2 separate families. They interpreted this as consistent with an oligogenic rather than a recessive model of disease transmission, as seen in triallelic inheritance (Beales et

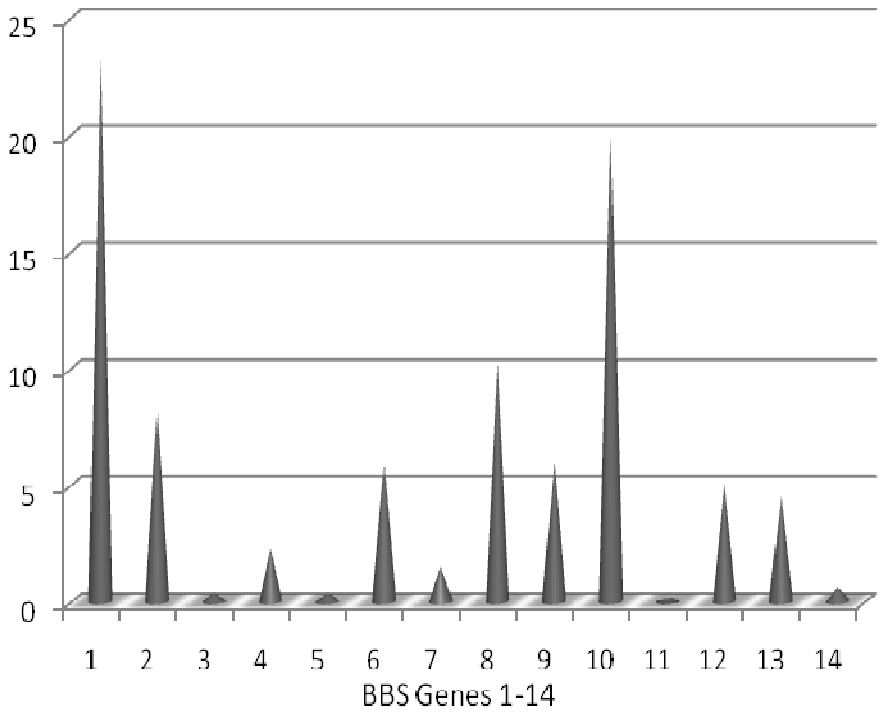

Figure 1. Mutational load of BBS genes.

al., 2003). Fan et al. (2004) reported the cases of 2 sisters homozygous for the M390R mutation.

GLU549TER

Mykytyn et al. (2002) found a homozygous G-to-T transversion at nucleotide 1655 (1655G-T) in exon 16 of the BBS1 gene that resulted in a glu549-to-ter (E549X) nonsense mutation.

IVS4, +1, G-A

Mykytyn et al., 2002 found a heterozygous G-to-A transition at the +1 position of the splice donor site in exon 4 of the BBS1 *gene.*

1-BP DEL, 851A

Mykytyn et al., 2002 found a homozygous deletion of 1 bp in exon 10 of the BBS1 *gene* (851delA), resulting in premature termination at codon 288 (tyr284fsX288).

LEU518PRO

One of 10 novel mutations in the BBS1 *gene* reported was a 1553T-C transition in exon 15 of the cDNA, resulting in a leu518-to-pro (L518P) change. It was detected in 3 patients with Bardet-Biedl syndrome, all in combination with the M390R mutation, and in none of 96 control subjects (Mykytyn et al., 2003).

GLU234LYS

Badano et al. (2003) found a heterozygous glu234-to-lys (E234K) mutation in the BBS1 *gene* in all 3 affected members. These individuals were also homozygous for a thr211-to-ile (T211I) amino acid substitution in the BBS7 *gene*, raising the possibility that the BBS1 and BBS7 loci interact.

1-BP DEL, 1650C

Badano et al. (2003) identified compound heterozygosity for mutations in the BBS1 *gene*: a 1-bp deletion in exon 16, 1650delC, resulting in a frameshift at codon 548 and a premature stop at codon 579 and met390-to-arg (M390R). The more severely affected sister was heterozygous for a thr 325-to-pro substitution in the MKKS gene (T325P).

BBS 2

Chromosomal location of BBS2 is 16q21. It displays a wide pattern of tissue expression, including brain, kidney, adrenal gland, and thyroid gland. Nishimura et al. (2004) found that the BBS2 *gene* contains 17 exons which encode a protein of 721 amino acids (Nishimura et al.,

Table 2. Summary of reported mutations of BBS genes.

Gene	Mutations	References
BBS1	MET390ARG GLU549TER IVS4, +1, G-A 1-BP DEL, 851A LEU518PRO	Mykytyn et al.
	GLU234LYS 1-BP DEL, 1650C	Badano et al.
	1-BP DEL, 940A VAL75GLY	Nishimura et al.
BBS2	TYR24TER GLN59TER ARG275TER ARG315TRP ASP170FS, TER171 CYS210FS TER246 ASP104ALA ARG634PRO IVS1, G-C, -1 VAL158FS, TER200 ASN70SER LEU168FS, TER170 THR560ILE ARG216TER	Katsanis et al.
	GLY139VAL	Stoetzel et al. and Laurier et al.
	ARG122TER	Chiang et al.
BBS3	859G-C, GLY169ALA THR31MET LEU170TRP THR31ARG	Fan et al.
BBS4	ARG295PRO EX3-4 DEL	Mykytyn et al.
	IVS3, A-G, -2 ALA364GLU	Katsanis et al
BBS5	IVS6DS, A-G, +3 LEU142TER 8-BP DEL/7-BP INS, NT263 TRP59TER	Li et al.
	GLY72SER THR183ALA	Hjortshoj et al

Table 2 Contd.

	HIS84TYR ALA242SER	
BBS6	TYR37CYS 2-BP DEL, 2111GG	Stone et al.
	GLY52ASP TYR264TER	Slavotinek et al.
BBS7	HIS323ARG THR211ILE 4-BP DEL	Badano et al.
BBS8	3-BP DEL 6-BP DEL	Ansley et al.
	THR153THR IVS6DS, G-A, +1	Stoetzel et al.
BBS9	IVS17DS, G-A, +1 ARG598TER 1-BP INS, 2046C GLY141ARG GLN355TER IVS5DS, G-C, +1 4-BP DEL, 1887AACA.	Nishimura et al.
BBS10	1-BP INS, CYS91 ARG34PRO SER303 FS+M390R (BBS1)+E549X SER311ALA	Stoetzel et al.
	VAL11GLY	Laurier et al.
	ASP487ASN	Frosk et al.
BBS11	PRO130SER	Chiang et al.
	1-BP DEL ARG394HIS	Saccone et al.
BBS12	ARG355TER 3-BP DEL 2-BP DEL ALA289PRO 2-BP DEL S701TER	Stoetzel et al. Pawlik et al.
BBS13 BBS14	Any mutations in MKS1, MKS3 and CEP290→ BBS	Leitch et al.

2001). It is also a part of BBSome complex so we can say that it also promotes the ciliary membrane biogenesis. Nishimura et al. (2004) showed that the mutation in BBS2 results in obesity and retinopathy (due to defective BBSome comples), and they also showed defective social function. Berbari et al. (2008) reported

that neurons deficient in BBS2 or BBS4 lacked ciliary localization of SSTR3 (182453) and MCHR1 where as MCHR1 is responsible for the regulation of feeding behavior. Some of the allelic variants of BBS 2 are as follows:

1-BP DEL, 940A

Nishimura et al., 2001 identified a homozygous 1-bp deletion in exon 8 (940delA) of the BBS2 *gene*, predicting a truncated protein 10 amino acids downstream from codon 324.

VAL75GLY

Nishimura et al., 2001 revealed a T-to-G transversion at position 224 of the BBS2 *gene*, resulting in a val75-to-gly substitution in exon 2.

TYR24TER

Katsanis et al., 2001 identified homozygosity for a tyrosine-to-termination substitution at codon 24 (Y24X) of the BBS2 *gene* in 2 unrelated patients with Bardet-Biedl syndrome. One of those patients carried an additional mutation in the BBS6 *gene* (ala242-to-ser). The Y24X mutation was also found in compound heterozygosity with the gln59-to-ter mutation in a patient who carried a third mutation in the MKKS *gene* (Q147X).

GLN59TER

Katsanis et al., 2001 also identified compound heterozygosity for a glutamine-to-termination substitution at codon 59 in the BBS2 *gene*. This mutation was found with the Y24X mutation and also the gln147-to-ter mutation in MKKS.

ARG275TER

Katsanis et al. (2001) identified an arg-to-ter substitution at codon 275 of the BBS2 gene in homozygosity. Katsanis et al., 2001 also identified some other mutations which are ARG315TRP; ASP170FS, TER171; CYS210*FS* TER246; ASP104ALA; ARG634PRO; IVS1, G-C, -1; VAL158FS, TER200; ASN70SER; LEU168FS, TER170; THR560ILE and ARG216TER.

Stoetzel et al., 2006b and Laurier et al., 2006 also contributed in identifying a homozygous gly139-to-val (G139V) substitution in the BBS2 *gene.*

BBS3

BBS3 *gene* name is ARL6 and is located on 3p12-q13. The protein encoded by this gene is 186-amino acid long and it is a cytosolic protein. ARL6 contains conserved features of the ARF family that is a part of RAS superfamily, including an N-terminal myristoylation site followed by a hydrophobic alpha helix and a GTP-binding site (Ingley et al., 1999). It regulates diverse cellular functions including regulation of intracellular traffic. Allelic variants of BBS 3 are as follows:

ARG122TER

Chiang et al., 2004 identified a homozygous C-to-T transition in exon 7 of the ARL6 *gene*, resulting in an arg122-to-ter (R122X) mutation with a premature truncation of the protein from 186 to 121 amino acids.

859G-C, GLY169ALA

Fan et al., 2004 found a homozygous 859G-C transversion in exon 8 of the ARL6 *gene*, resulting in a gly-to-ala substitution at residue 169 (G169A). Fan et al., 2004 also found the G169A mutation in heterozygous state in 1 of 2 sisters homozygous for the met390-to-arg (M390R) mutation of the BBS1 *gene,* and also identified some other mutations which are THR31MET (exon 3); LEU170TRP (exon 8) and THR31ARG (exon 3).

BBS4

Chromosomal location for BBS4 is 15q22.3-q23. It has homology to acetyl-glucosamine transferase from several species, including archaebacteria and plants. Mykytyn et al., 2001 found that the BBS4 *gene* contains 16 exons and spans approximately 52 kb. The protein encoded by BBS4 is 519 amino acids long (Mykytyn et al. 2001). The protein of BBS4 is the part of BBSome complex. Kim et al. (2004) explained that BBS4 protein localizes to the centriolar satellites of centrosomes and basal bodies of primary cilia, where it functions as an adaptor of the p150 subunit of the dynein transport machinery (DCTN1) to recruit pericentriolar material-1 protein (PCM1) and its associated cargo to the satellites (Kim et al., 2004; Nachury et al., 2007). Mykytyn et al. (2004) observed the obesity and retinal degeneration as phenotypes of BBS4 allelic variations. Berbari et al. (2008) reported that neurons deficient in BBS2 or BBS4 lacked ciliary localization of SSTR3 (182453) and MCHR1 where as MCHR1 is responsible for the regulation of feeding behavior. Allelic variants of BBS 4 are as follows:

1. Mykytyn et al., 2001 found some mutations in BBS4 genes. These are ARG295PRO (exon 12) and EX3-4

DEL (Exon3 and 4 del).
2. Katsanis et al. (2002) also contributed in identification of BBS4 *gene* mutations. These mutations are IVS3, A-G, -2 (exon 4) and ALA364GLU.

BBS5

BBS5 *gene* is located on 2q31 and encodes a protein involved in the generation of cilia and flagella, where as BBS5 gene contains 12 coding exons and the protein encoded by this *gene* is the part of BBSome complex. BBS5 contains two pleckstrin homology (PH)-like domains and binds to phosphoinositides; inhibition of phosphoinositide production prevents ciliogenesis (Nachury et al., 2007), which provides a possible mechanism for tethering the IFT machinery to the cilium membrane (Hao and Scholey, 2009).

Li. et al., 2004 contributes alot in identifying the allelic variants of BBS5. He identified IVS6DS, A-G, +3; LEU142TER in exon 6 of BBS5 *gene*; 8-BP DEL/7-BP INS, NT263, that is, an insertion-deletion mutation at nucleotide 263 of the BBS5 *gene* that had the net effect of removing a single base, resulting in a premature termination codon and TRP59TER. Hjortshoj et al., 2008 also chip in some information related to some mutations. These mutations are a homozygous 214G-A transition in exon 4 of the BBS5 *gene*, resulting in a gly72-to-ser (G72S) substitution (GLY72SER) and homozygous 547A-G transition in exon 7 of the BBS5 *gene*, resulting in a thr173-to-ala (T183A) substitution (THR183ALA).

BBS6

BBS6 *gene* name is MKKS which is located on 20p12. It encodes a protein having similarity with members of chaperonin family suggesting a role for protein processing in limb, cardiac and reproductive system development. BBS6 is a centrosomal protein that is also found at the midbody during cytokinesis. In 2000 two groups of scientists, Slavotinek et al. (2000) and Katsanis et al. (2000) identified a sixth form of Bardet-Biedl syndrome (BBS6) due to mutations in the MKKS gene. However, the mutation in this gene can also cause McKusick-Kaufman syndrome.

For allelic variation studies, Stone et al., 2000 put their effort first and identified homozygosity for 2 mutations on the same allele in the MKKS *gene*. One was 1137C-T transition, resulting in a his84-to-tyr (H84Y) substitution (HIS84TYR) and the other resulted in an ala242-to-ser (A242S) substitution (ALA242SER). This group also identifies some other mutations, these are TYR37CYS; 2-BP DEL, 2111GG. Then Slavotinek et al. (2000) found compound heterozygosity for a missense (1042G-A, gly52 to asp; G52D) and a nonsense (1679T-A, tyr264 to ter; Y264X) mutation in exon 3 of the MKKS gene in the same year. Similarly some other scientists also contribute well in identifying the genetics of BBS6 gene.

BBS7

BBS7 *gene* is located on *gene* 4q27. Badano et al. (2003) established the presence of 19 exons in the BBS7 *gene* encoding 672 amino acid long protein. This group of scientists searched for genes with moderate similarity to BBS2 by performing phylogenetic and genomic studies using the human and zebrafish BBS2 peptide. BBS7 exhibits similarity with a 252-amino acid region of BBS2, between residues 147 and 398. They identified a domain that lies in the conserved area between residues 171 to 315 that is predicted to encode a 6-bladed beta-propeller structure. Local alignment of BBS1, BBS2 and BBS7 specified that both BBS1 and BBS7 contain partially overlapping portions of this domain. Finally, Badano group of scientist concluded that this potential structural link between BBS1, BBS2 and BBS7 may indicate that these *genes* belong to a distinct subfamily of proteins, mutations in any of them may lead to the same clinical entity (Badano et al. 2003).

BBS7 is the component of BBSome complex. In C. elegans, the loss of BBSome components, such as BBS7 or BBS8, leads to the dissociation of the IFT-A and IFT-B subcomplexes (Ou et al., 2005).

Badano et al. (2003) studied three mutations in BBS7 *gene* which are (1) HIS323ARG: homozygous for a his323-to-arg (H323R) alteration in exon 10 of the BBS7 gene. (2) THR211ILE: homozygous for a thr211-to-ile (T211I) alteration in the BBS7 *gene* along with glu234-to-lys (E234K) alteration in exon 8 of BBS1. (3) 4-BP DEL: homozygous 4-bp deletion in the BBS7 *gene* that abolished the lysine at position 237 in exon 7 and which, by conceptual translation, resulted in premature termination in exon 9, at residue 296 (K237fsX296).

BBS8

Gene name of BBS8 is TTC8 (tetratricopeptide repeat protein having 8 domains) and is located on 14q32.1. BBS8 is also the component of BBSome complex. In C. elegans, the loss of BBSome components, such as BBS7 or BBS8, results in the separation of the IFT-A and IFT-B subcomplexes (Ou et al., 2005). It is involved in pilus formation and twitching mobility. TTC8 colocalized with gamma-tubulin, BBS4, and PCM1 in the centrosome. Ansley group of scientists found that all C. elegans BBS homologs studied are expressed exclusively in ciliated neurons and contain regulatory elements for RFX, a transcription factor that modulates expression of *genes* associated with ciliogenesis and intraflagellar transport (Ansley et al. 2003).

Ansley and group identified a 6bp deletion in exon 6 of

TTC8 and also identified 3 bp deletion in exon 10. Where as Stoetzel et al. (2006b) identified a homozygous 459G-A transition affecting the last G of exon 4 of the TTC8 *gene* and predicted to abolish the splice site of exon 4 but they concluded that mutation is not pathogenic in nature and other mutation they identified is a homozygous G-to-A splice site mutation in intron 6 of the TTC8 *gene*.

BBS9

BBS9 *gene* named PTHB1 is located on 7p14. Expression of this *gene* was detected in adult heart, skeletal muscle, lung, liver, kidney, placenta, brain and fetal kidney. Its *gene* structure was determined by Vernon et al. (2003). This gene contains 24 exons and spans, more than 700 kb producing a protein of 802 amino acids. This protein also takes part in the BBSome complex formation.

Using homozygosity mapping of small consanguineous families with Bardet-Biedl syndrome (BBS) followed by comparative genomic analysis, expression studies, and sequencing, Nishimura et al. (2005) identified mutations in this BBS *gene*. These mutations are IVS17DS, G-A, +1 ; ARG598TER (exon 18); 1-BP INS, 2046C (exon 19); GLY141ARG (exon 5); GLN355TER (exon 10); IVS5DS, G-C, +1 and 4-BP DEL, 1887AACA.

BBS10

BBS 10 *gene* name is C12ORF58. It is located on 12q21 .2 chromosomal location. The C12ORF58 gene is composed of 2 exons (Stoetzel et al., 2006b). It encodes a 723-amino acid protein that defines a novel type II chaperonin subfamily. Gerth et al., 2008 identified phenotypes of clinodactyly or polydactyly, obesity, polycystic kidneys, learning disability and retinopathy in patients with mutation in this *gene.*

Stoetzel et al. (2006b) identified different allelic variants of this *gene* at different locations. Those variants are 1-BP INS, CYS91; ARG34PRO; SER303 FS along with M390R (BBS1) and E549X and SER311ALA, whereas Laurier et al. (2006) identified a mutation VAL11GLY.

BBS11

It is located on chromosomal location 9q33.1. This *gene* expresses in adipose tissue and encodes a protein of 653 amino acids. Kudryashova et al. (2009) identified muscular dystrophy phenotypes as result of mutation in this *gene*.

Frosk et al. (2002) identified homozygosity for an asp487-to-asn (D487N) missense mutation in the TRIM32 gene as a causative mutation in the mild autosomal recessive myopathy. Chiang et al. 2004 identified the TRIM32 *gene* as the site of mutations causing Bardet-Biedl syndrome.

The specific mutation was a change of codon 130 from CCT (pro) to TCT (ser). Saccone et al. (2008) identified a homozygous 1-bp deletion (1559delC) in the TRIM32 *gene* resulting in frameshift and premature truncation. They also identified a homozygous 1180G-A transition in the TRIM32 *gene*, resulting in an arg394-to-his (R394H) substitution.

BBS12

It is located on 4q27. With BBS6 and BBS10, encodes to a novel branch of the type II chaperonin superfamily. For this *gene* again, Stoetzel et al. (2007) contributed well. This group identified different mutations which are 1062C-T that resulted in an arg355-to-stop (R355X) substitution in the gene product; 3-bp deletion (335delTAG, val113del); frameshift mutation in the BBS12 gene, (1483delGA); a missense mutation: 865G-C, ala289 to pro (A289P) and 2-bp deletion in the BBS12 *gene* that resulted in frameshift and premature termination of the protein. Pawlik et al. (2010) identified a missense mutation Serine 701 to termination codon. They clinically diagnosed the affected individuals with postaxial polydactyly and late-onset retinal dysfunction and also proposed the use of less strict diagnostic criteria in familial BBS cases.

BBS13

BBS13 *gene* is located at chromosomal location 17q23. Leitch et al. (2008) demonstrated that mutations in MKS1, MKS3 and CEP290 either can cause Bardet-Biedl syndrome or may have a potential epistatic effect on mutations in known BBS-associated loci.

BBS14

Its *gene* name is CEP290 and it is located at chromosomal location 12q21.3. Valente et al., 2006 detected CEP290 expression mostly in proliferating cerebellar granule neuron populations and showed centrosome and ciliary localization, whereas Leitch et al. (2008) demonstrated that mutations in MKS1, MKS3 and CEP290 can either cause Bardet-Biedl syndrome or may have a potential epistatic effect on mutations in known BBS-associated loci.

BBS genes and pathways

Many pathways like Planar cell polarity (PCP) pathway (2006), intraflagellar transport (IFT) pathway (Bittles,

2001; Chiang et al., 2006) etc. which on mutation get disturbed as BBS *genes* function within them. And BBS proteins interact with some receptors like leptin receptors (2009) to function properly but on mutation in these BBS genes, they cause disorder like obesity.

Centrioles and BBS6

The presence of BBS6 in the pericentriolar material (PCM) of centrosomes and basal bodies suggests that it probably plays a role in association with centrioles whereas disruption of this role results to cytokinesis and produces multi-nucleate, multi-centrosomal cells, but BBS6 may also have more subtle effects on other centrosome/basal body-based functions, including ciliogenesis and cytoskeletal organization (Kim et al. 2005).

PCP pathway and BBS proteins

The planar cell polarity (PCP) pathway is conserved throughout evolution, but it mediates distinct developmental processes. PCP Pathway drives several important cellular processes, including epithelial cell polarization, cell migration and mitotic spindle orientation (Ross et al., 2005). They also identified genetic interactions between BBS *genes* and a PCP gene in both mouse (Ltap, also called Vangl2) and zebrafish (vangl2).

Leptin receptor signalling and BBS proteins

Seo et al. (2009) determined that BBS proteins are required for leptin receptor (LepR) signaling in the hypothalamus. They found out that BBS1 protein physically interacts with the LepR and that loss of BBS proteins perturbs LepR trafficking.

SUMMARY AND CONCLUSION

In this review, studies on Bardet-Biedl syndrome, a previously understudied rare genetic disorder, have provided significant insights into a multigene family of proteins implicated in a surprising range of human ailments, including obesity, retinal degeneration and cystic kidneys. As discussed above, the research findings of different research groups have led us to conclude that BBS prote ins function together, possibly as an oligomeric complex or BBSome complex, in intracellular transport processes that are relevant to cilia function, microtubule organisation, cell division, PCP pathways and leptin receptor signalling pathway and even a single mutation could be responsible for the disturbance of more than one pathway. Further identification of genes involved in BBS and their allelic variants will help to provide the detail insight into genetically and clinically heterogeneous disorder and also in generating the mutation databank to help the clinicians. However, the protein structural studies might help in understanding the effect of mutations on 3-D structure of proteins and the complexes form for different pathways. Furthermore it can also help in developing the drugs for the treatment of this disorder.

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