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REVIEW ARTICLE - PUBLIC HEALTH

# Two novel SNPs, rs1545 and rs1547, in the *BBS6/MKKS* gene of Bardet Biedl syndrome have been linked to metabolic syndrome: Review

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Abstract

**BACKGROUND AND AIMS:** The metabolic syndrome is a multifactorial disorder, and the urban Indian population is at high risk for diabetes mellitus and cardiovascular disorders, with numbers consistently rising. Hence, we aim to scrutinize the frequent mutations, predominantly single-nucleotide polymorphisms (SNPs), of complex disorders like Bardet-Biedl syndrome (BBS).

**METHOD AND DESIGN:** A greater knowledge of the metabolic syndrome is needed to determine the inheritability of complex disorders. Multiple genome-wide association studies with case-control, meta-analysis, haplotype, and genotype analysis and investigations on mutation screening in obese, metabolic syndrome, and BBS subjects demonstrated that including disease-associated polymorphisms (or) SNPs (or) common mutations might suffice as an efficacious tool in disease prognostication. In a wide range of populations, mutational profiling and analysis of *BBS* genes revealed that certain disease-correlated SNPs of these genes were linked to metabolic syndrome. Hence, we have inspected multiple research and review articles about genetic mutations, particularly SNPs in the *BBS* genes and their association with metabolic syndrome.

**RESULTS :** The two reported SNPs, rs1545 and rs1547, which are present in the exonic region of the *BBS6/MKKS* gene, have been integrated to be related to obesity and metabolic syndrome in a substantially diverse population.

**CONCLUSION :** The roles of the varied genotypes observed in Bardet-Biedl syndrome and diabetic retinopathy, which falls under metabolic syndrome, are much needed to understand their interconnection and etiology. The recurrent SNPs rs1545 and rs1547 of the *BBS6/MKKS* gene might perform as a candidate diagnostic tool to envisage obesity.

**KEYWORDS :** rs1545, rs1547, Single-nucleotide polymorphisms, Bardet-Biedl syndrome, *BBS6/MKKS* gene, metabolic syndrome

## INTRODUCTION

### INTRODUCTION TO METABOLIC SYNDROME:

Metabolic syndrome is a compendium of risk factors possibly influenced by central obesity and insulin resistance.[1] The International Diabetes Federation (IDF) elucidated that "metabolic syndrome" is significantly associated with high-normal urinary albumin excretion (UAE), polyneuropathy, and retinopathy.[1, 2] Also, there are multiple definitions stated by other bodies like the World Health Organization (WHO), the National Cholesterol Education Program—Third Adult Treatment Panel (NCEP ATP III), and the European Group for the Study of Insulin Resistance (EGIR).[1] During the years 1998[3] and 1999[4], WHO put forth that diabetes or insulin resistance, or impaired glucose tolerance (IGT) were the benefactors of the metabolic syndrome. Later additional criteria like obesity (waist-hip ratio for women > 0.85, men > 0.90 (or) body mass index > 30 kg/m$^2$), blood pressure (≥

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140/90 mmHg), high-density lipoprotein (HDL) cholesterol (women – 39 mg/dl (or) < 1.0 mmol/l, men 35 mg/dl (or) < 0.9 mmol/l), and microalbuminuria (creatinine: albumin ≥ 30mg/g or ≥ 20 µg/min of excretion rate of urinary albumin) have been considered as supplementary risk factors.[1,3,4] In the same year 1999, EGIR propounded the criteria for euglycemic subjects with varied cut-points for obesity (waist circumference of women ≥ 80 cm and men ≥ 94 cm), HDL cholesterol (39 mg/dl (or) < 1.0 mmol/l), hypertension (≥ 140/90 mmHg), triglycerides (178 mg/dl (or) > 2.0 mmol/l) and the utilization of fasting insulin (110 mg/dl (or) ≥ 6.1 mmol/l) as an alternative for IGT.[1, 5] In the year 2001, NCEP ATP III postulated metabolic syndrome as a combination of more than three medical criteria like obesity (waist circumference of women > 88 cm and men > 102 cm), declined levels of HDL cholesterol (women 50 mg/dl (or) < 1.29 mmol/l and men 40 mg/dl (or) < 1.03 mmol/l), escalated blood pressure (≥ 130/ ≥ 85 mmHg), fasting glucose (100 mg/dl (or) ≥ 5.6 mmol/l) and triglycerides (150 mg/dl (or) ≥ 1.7 mmol/l).[1, 6] Also, the interpretation of the metabolic syndrome by NCEP ATP III was not glucose-centric.[6] On a whole, the universally recognized vital and distinguishable aspects of metabolic syndrome include obesity, hypertension, dyslipidemia, and insulin resistance.[1, 7] Globally, the threat of non-communicable diseases like diabetes, obesity, and coronary heart disease is aggravating, and it is reported that about 25% of the US population[8] and 19.52% of the Indian urban population, have the prevalence of metabolic syndrome.[9, 10] According to different bodies, the percentage of metabolic syndrome differs.[11, 12] As in the USA Texas (WHO – 25%, NCEP ATP III - 25%),[13] USA National (IDF - 39%, NCEP ATP III - 35%),[14] Australia (WHO - 21%, IDF - 16%, NCEP ATP III - 19%),[11, 12] Mainland China (NCEP ATP III - 14%),[15] France (WHO - 18%, IDF - 13%, NCEP ATP III - 9%),[11, 12] Italy (WHO - 34%, NCEP ATP III - 18%),[11, 12] South Asia (WHO - 23%, IDF - 18%, NCEP ATP III - 26%).[11, 12] The Indian urban population (age-adjusted analysis) has been promulgated to have 25% ubiquity in metabolic syndrome rate with women (31%) affected more than men (18.5%) population. Also, the frequency of incidence of metabolic syndrome in India is relentlessly escalating in adolescents and adults (20% – 25%) and aggravates with higher age.[7, 16]

## PATHOPHYSIOLOGY OF METABOLIC SYNDROME:

Metabolic disorders originate when a group of risk factors like obesity, hyperglycemia, etc., co-occur, which increases the occurrence of cardiovascular disorders, type 2 diabetes, and hepatic fibrosis. Other characteristics comprise obesity with expanded waist circumference, hypertension, escalated C-reactive protein (CRP), and elevated triglyceride levels.[17, 18] The prime risk factors for metabolic syndrome may include insulin resistance and obesity, which often account for the etiology and pathogenesis.[19] The foremost physiologic features include insulin resistance, which enhances atherosclerotic cardiovascular disease, hyperglycemia, hypertension, which occurs routinely in people with insulin resistance, fatty liver (produced due to obesity) and stress-metabolic syndrome, disorganizing the hormonal equilibrium of the hypothalamic-pituitary-adrenal axis (HPA-axis), causing prolonged stress.[20, 21] Obesity being a predominant attribute of metabolic syndrome, which is defined by adiposity with increased waist-to-hip circumference and accumulated adipocytes. Sometimes, patients may be insulin-resistant and have a complex disorder with normal weight.[20, 21, 22] Other risk liability involves hyperadiponectinemia, which plays a crucial role in the emergence of insulin resistance and chronic inflammation, hyperuricemia, lipodystrophy, atherogenic dyslipidemia denoted by elevation in triglycerides level and small dense low-density lipoprotein (sdLDL) particles, decreased high-density lipoprotein (HDL) cholesterol; a proinflammatory state with an increase in C-reactive protein (CRP) ; and a prothrombotic state, with an increase in plasminogen activator inhibitor (PAI-1) and fibrinogen levels.[22, 23] Also, monocyte/macrophage and adipocyte-derived factors induce atherothrombotic effects, which progress into cardiovascular disorders. Genetic variants and environmental factors may contribute to atherosclerosis and influence central obesity, dysfunction in innate immunity, glucose and lipoprotein metabolism, and vascular function.[23, 24] Multiple diseases, like diabetic retinopathy and Bardet-Biedl syndrome (BBS), are classified under the metabolic syndrome. Diabetic retinopathy is effected due to the complications of diabetes, microvascular retinal alterations, and hyperglycemia, which can eventually lead to blindness. Diabetic retinopathy might have precedence over proliferative diabetic retinopathy (PDR) or non-proliferative diabetic retinopathy (NPDR).[25] BBS is a complex pleiotropic and ciliopathy disorder with divergent effects.[26, 2, 27, 28] Approximately 26 *BBS* genes have been identified and cloned to date. [27, 29, 30, 31]

## DIABETIC RETINOPATHY:

Diabetic retinopathy occurs due to complications caused by diabetes, microvascular retinal abnormalities, hyperglycemia, and affects people who have had diabetes for a prolonged time and can eventually reverberate into blindness. It is caused by sustained excessive blood glucose levels, which affect the small blood vessels within the retina,

causing damage to the retina. This current condition may lead to hemorrhage and swelling of the retina, such that the retina starves for oxygen, and abnormal vessels may grow, and are termed proliferative diabetic retinopathy (PDR).[32, 33] Diabetic retinopathy can be proliferative when the retina becomes blocked, causing the dilation of abnormal blood vessels that bleed into the eyes, then causing the retina to detach, and seriously damaging vision. It can flourish and evolve in anyone who has either type-1 diabetes or type-2 diabetes and may be distinct in origin.[33] Hyperglycemia causes intramural pericyte death by activating p38 mitogen-activated protein kinase (MAPK) and protein kinase to amplify the expression of a target Src homology-2 domain–containing phosphatase-1 (SHP-1), PKC-δ signaling, which genesis dephosphorylation of the signaling protein and induces pericyte apoptosis.[34, 35, 36] Patients with diabetic retinopathy are more susceptible to complex disorders since excessive sugar and blood pressure levels upsurge the blood flow and thicken the retina, often leading to visual impairment and the prevalence of other metabolic disorders. But patients without retinopathy have a flourishing retina, and when appropriate control of diabetes is achieved, it can be prevented from other complex disorders.[34]

## HERITABILITY OF OCULAR TRAITS:

Genetic factors play a significant part in numerous kinds of eye diseases. Hereditary ophthalmic disorders emerge due to defects in more than 800 different genes and can either arise as an isolated condition or be correlated with a syndrome. Like other hereditary diseases, ocular diseases are inherited as single gene, chromosomal, complex, and mitochondrial diseases.[8, 37] Some examples of inherited ocular disorders are as follows: Retinitis Pigmentosa - Autosomal recessive, Color blindness - X-linked disorder, Diabetic Retinopathy - Metabolic disorder, Stargardt's disease - Single gene disorder, Leber's Hereditary Optic Neuropathy (LHON) - caused by mutation in mitochondrial DNA. Eye abnormalities are contemporary in one-third of inherited systemic diseases.[37] These autoinflammatory syndromes (AIS) are rarely inherited disorders, whose expression stimulates ocular diseases.[38] In diabetic retinopathy, it's reported that patients with BBS and photoreceptor degeneration are commonly blind in their 3rd decade of life. According to the WHO, the predominant causes of blindness are glaucoma, age-related macular dystrophy (AMD), optic atrophy, eye malformations, and diabetic retinopathy.[37, 39] The molecular basis of an ocular disease is studied diligently using techniques of gene mapping and isolation to excel in understanding the ocular pathophysiology and to classify the eye disease.[21, 40] About 60% of the studies deployed variance component methods and structural equation modelling (SEM) to study the heritability of the ocular traits, which evaluated heritability better than the family data to derive heritability values. And these ocular disorders are often inherited as complex disorders. Knowledge of the genotype of an ocular disorder can help in classifying its apparent phenotype and can help to cure ocular disorders. [22, 37, 39]

## BARDET-BIEDL SYNDROME:

Bardet-Biedl syndrome is a pleiotropic ciliopathy disorder with a composite autosomal recessive inheritance trait having heterogeneous effects.[25, 40, 41] It has the following primary characteristics: obesity, postaxial polydactyly, hypogonadism, retinal pigmentary dystrophy, and renal dysplasia. The distinctive secondary characteristics include: cardiovascular disorder, type-2 diabetes, polyuria, hearing loss, speech impairment, hypertension, cognitive impairment, anosmia, hypertonia, ataxia, dysfunctional thyroid and hypodontia.[41] Earlier in 1866, BBS was communicated as "Laurence–Moon syndrome" from an ophthalmic hospital situated in South London by Laurence and Moon .[42] It is an autosomal dominant disorder. Laurence-Moon-Biedl-Bardet syndrome was not anymore considered an appropriate terminology for patients suffering from Laurence and Moon syndrome, because they had paraplegia and no polydactyly or obesity, which are predominant features of the Bardet–Biedl syndrome.[43, 44, 45] Being classified as an unusual disorder, BBS prevails in the ratio of 1:140,000 – 160,000 in the European and North American populations,[44, 46, 47] 1: 160,000 in Switzerland,[48] 1:156,000 in Tunisia,[49] 1:59,000 in Denmark,[50] 1:18,000 in Newfoundland, and 1:17,000 in Kuwait. The consanguinity in births may be the vindication of elevated cases of BBS in Newfoundland and Kuwait.[44, 46, 47]

## *BBS* GENES:

Bardet-Biedl syndrome is an uncommon developmental defect disorder that is inherited due to mutations in diverse genes that cause "Bardet-Biedl syndrome". Till date, 26 *BBS* genes (Table 1) have been identified.[27, 29, 30, 31, 51]

## FUNCTION OF BBS PROTEINS:

*BBS* genes play a significant role in the genesis of cell structures called cilia.[44, 47] The BBS proteins are segments of primary cilia emerging from the basal body and assist in the maintenance of homeostasis in diverse tissues and BBSome protein assembly. This BBSome is formed by a complex group of *BBS* genes, comprising *BBS1, BBS2, BBS3, BBS5, BBS7, BBS8, BBS9,* and *BBS18*. The fundamental responsibility of the BBSome involves ciliary membrane biogenesis and interacts to facilitate the pathways consisting

of intraflagellar transportation to modulate sonic hedgehog signal transduction.[27, 29, 41, 45] *BBS1, BBS2, BBS7*, and *BBS9* incorporate β propeller domains; whereas *BBS4* and *BBS8* accommodate numerous tetratricopeptide domains; and *BBS5* carries around two pleckstrin homology domains and configures a complex (Figure 1). *BBS3/ARL6* is mandatory for localization of cilia of the BBSome and a Ras superfamily member.[52, 53] About three genes of *BBS - BBS6, BBS10*, and *BBS12* - have a systemic homology to type II chaperonin and intercommunicate with proteins like chaperonin containing tailless complex polypeptide 1/ tailless complex polypeptide 1 ring complex *(CCT/TRiC)* and *BBS7* to construct a complex, entitled the "BBS chaperonin complex", which configures as a prerequisite fundamental component for the gene formation assemblage and accumulation of BBSome complex clusters.[29, 51, 53] Other *BBS* genes like *BBS16/SDCCAG8, BBS17/LZTFL1, BBS19/IFT27, BBS20/ IFT172, BBS21/C8orf37, BBS22/ IFT74,* and *BBS23/CEP19* were a necessitate constituent of intraflagellar trafficking (IFT), especially IFT-B and pathways comprising Sonic Hedgehog signaling. For degradation by *BBS11/TRIM32*, an E3 ubiquitin ligase is utilized in process of ubiquitination to catalyze the targets.

*Table 1: BBS genes with their corresponding locus*

| Locus Name | Gene | Locus of Chromosome | Protein Name |
|---|---|---|---|
| *BBS1* | *BBS1* | 11q13.2 | Bardet-Biedl syndrome1 protein |
| *BBS2* | *BBS2* | 16q12.2 | Bardet-Biedl syndrome 2 protein |
| *BBS3* | *ARL6* | 3q11.2 | ADP-ribosylation factor-like protein 6 |
| *BBS4* | *BBS4* | 15q24.1 | Bardet-Biedl syndrome 4 protein |
| *BBS5* | *BBS5* | 2q31.1 | Bardet-Biedl syndrome 5 protein |
| *BBS6* | *MKKS* | 20p12.2 | McKusick-Kaufman syndrome (or) Bardet-Biedl syndrome putative chaperonin |
| *BBS7* | *BBS7* | 4q27 | Bardet-Biedl syndrome 7 protein |
| *BBS8* | *TTC8* | 14q31.3 | Tetratricopeptide repeat protein 8 |
| *BBS9* | *PTHB1* | 7p14.3 | Protein PTHB1/ PTH-Responsive Osteosarcoma B1 Protein/ Parathyroid Hormone Responsive B1 Gene |
| *BBS10* | *BBS10* | 12q21.2 | Bardet-Biedl syndrome 10 protein |
| *BBS11* | *TRIM32* | 9q33.1 | E3 ubiquitin-protein ligase TRIM32 |
| *BBS12* | *BBS12* | 4q27 | Bardet-Biedl syndrome 12 protein |
| *BBS13* | *MKS1* | 17q22 | Meckel syndrome type 1 protein |
| *BBS14* | *CEP290* | 12q21.32 | Centrosomal protein of 290 kDa |
| *BBS15* | *WDPCP* | 2p15 | WD repeat containing Planar cell Polarity effector protein |
| *BBS16* | *SDCCAG8* | 1q43 | Serologically Defined Colon Cancer Antigen 8 protein |
| *BBS17* | *LZTFL1* | 3p21.31 | Leucine zipper transcription factor like 1 |
| *BBS18* | *BBIP1* | 10q25.2 | BBSome-Interacting Protein 1 |
| *BBS19* | *IFT27* | 22q12.3 | Intraflagellar transport protein 27 Homolog |
| *BBS20* | *IFT172* | 2p23.3 | Intraflagellar transport protein 172 Homolog |
| *BBS21* | *C8ORF37* | 8q22.1 | Chromosome 8 Open Reading Frame 37 |
| *BBS22* | *IFT74* | 9p21.2 | Intraflagellar transport protein 74 Homolog |
| *BBS23* | *CEP19* | 3q29 | Centrosomal protein 19 |
| *BBS24* | *NPHP1* | 2q13 | Nephrocystin 1 |
| *BBS25* | *SCAPER* | 15q24.3 | S-phase cyclin A associated protein in the endoplasmic reticulum |
| *BBS26* | *SCLT1* | 4q28.2 | Sodium channel and clathrin linker 1 |

During ciliogenesis, cell-cell adhesions and cell-matrix signaling were assisted by *BBS24/NPHP1, BBS25/SCAPER*, and *BBS26/SCLT1*.[51, 53] *BBS6/MKKS, BBS10,* and *BBS12* genes were non-specific to invertebrates and specific to vertebrates, as there were no traces of their gene homologs in invertebrates.[54, 55]

## MUTATIONS IN THE BBS PROTEINS:

One of the crucial features of Bardet-Biedl syndrome is obesity (72% - 92%).[44, 47, 49, 51] Multiple complications of obesity can comprise type-2 diabetes, high blood pressure (hypertension), and unusually high cholesterol levels (hypercholesterolemia).[29, 41, 56] Important abnormal trafficking of leptin receptor mediators was aggregated due to BBS proteins.[41] Also, the loss or reduction of the *BBS* gene intensifies leptin resistance, which leads to non-syndromic customary obesity in patients. Defects in BBS proteins can reorganize the morphology and function of motile cilia,[57] hence the name "ciliopathy disorders". This defective and faulty cilia emerge into primary ciliary dyskinesia, which manifests into infertility and bronchiectasis.[58] Deformities originated in immotile cilia were indicated by polydactyly, learning difficulties, retinitis pigmentosa, and cystic liver, pancreas, and kidneys.[59] The obesity noticed in BBS is multifactorial in nature[25] and has aggravated the risk and proliferation of cardiovascular diseases.[25, 24, 60, 61] Multitudinous disease oriented gene mutations and their interconnection have expedited the characterization of unique polymorphisms and SNPs in *BBS* gene and their association with metabolic syndrome. These enactments via high-throughput sequencing, employing SNPs arrays for homozygosity mapping.[62] Divergent populations have discrete *BBS* gene mutations. For instance, in Meckel syndrome *(BBS13, BBS15, BBS16 (SDCCAG8)* have been communicated,[63, 64] Tunisian population (*BBS1, BBS2* - p.R189, *BBS8* - c.459 + 1G>A),[49, 65] Saudi Arabia population (*BBS1* – 33%, *BBS3* – 17%, *BBS4* – 17%),[66, 67] North European population (*BBS1* - p.M390R (causative of 50% cases in *BBS1*), *BBS10* - p.C91Lfs),[68] Caucasian and European population (*BBS1* and *BBS10* – 21-30%),[69, 70] Hutterite population (*BBS2* - c.472 – 2A>G),[71] Faroe Islands population (*BBS1* - c.1091 + 3G>C),[72] Chinese population (*BBS6/MKKS* gene with 2 disease causing pathogenic variants - c.635C>T and c.1664C>G, and *TMEM67* gene with 1 pathogenic variant) [73]. In some cases of BBS, during the year 2001, triallelic inheritance (lower frequency) was detected in a child with a 3rd mutation observed in *BBS1* (or) *BBS6/MKKS* (added heterozygous missense mutation) gene. These patients had a drastic phenotype with mental retardation and obesity in an

earlier outbreak.[62, 74] *BBS6/MKKS, BBS10* and *BBS12* genes effectuate genetic heterogeneity, and the absence of ATPase enzyme activity adds up to the genesis of around 30% of BBS mutations.[30, 51, 74] Several chaperonopathies like McKusick-Kaufman Syndrome, X-linked retinitis pigmentosa, motor neuropathies, and multifarious neurological disorders were all linked with the *BBS6/MKKS* gene, with mostly interpreting for nonsense and missense mutations, which accounts for nearly 50 predisposition deleterious variants. Multinucleated cells and multi-centrosomal clustering cells emerged and transpired upon disruption of *BBS6/MKKS* gene.[51, 54, 62, 74, 75]

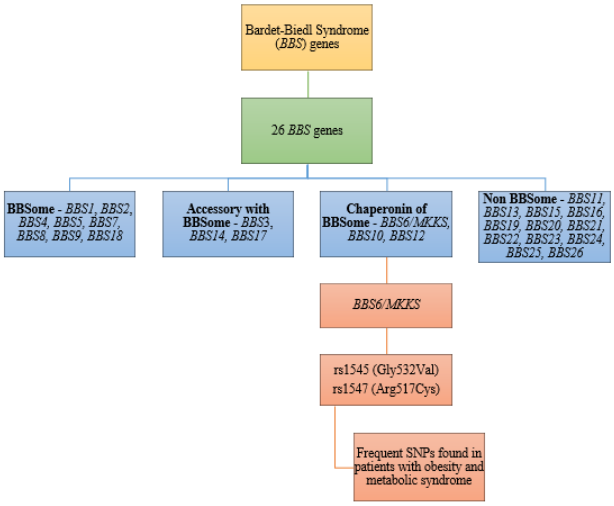


*Figure 1: Schematic representation of the entire BBS gene family with their integral functional profile and role in the formation of the "BBSome protein complex" as well as the prevalence of non-synonymous SNPs rs1545 and rs1547 of the BBS6/MKKS gene in obese and metabolic syndrome sufferers*

## *BBS6/MKKS* GENE:

*BBS6/MKKS* encodes a 570-amino acid protein and comprises six exons, which are located at the 20p12.2 arm.[35, 76, 77] It is a chaperonin-like protein with a resemblance to the type II class of chaperonins like eukaryotic T-complex-related proteins (TCPs) and plays a prime role in cytokinesis. This BBS6/MKKS protein has a predominant function in the processing of proteins in limb, cardiac, and reproductive system development. It is often confined within a proteinaceous tube that surrounds centrioles called the Pericentriolar Material (PCM), but it is also found at intercellular bridges during mitosis.[78, 79, 80] *BBS6/MKKS* gene swiftly transports across cytoplasm and nucleus and is primarily expressed in olfactory epithelia, renal tubule, retina ciliated epithelial cells and regulates *SMARCC1* gene subcellular localization.[30, 54, 81] Multiple genetic variations located in this gene might initiate an extensive role in contributing to the emergence of metabolic syndrome and obesity.[28, 51] The SNPs associated with this gene are considerable for common adult morbid obesity, and *BBS6/MKKS* variants show evidence for the metabolic syndrome components (e.g., obesity, dyslipidemia, hyperglycemia, and hyperuricemia), a previously disclosed complication in BBS patients (Figure 1).[28, 51, 82]

## SNPs rs1545 AND rs1547 OF *BBS6/ MKKS*:

SNPs emerge due to the swapping of single or lone nucleotides, and it has been communicated that these SNPs technologies have a wider perspective in recognizing disease-incorporated genes and the onset or evolution of a disorder [83] and may be utilized in developing a biomarker for metabolic syndrome.[84] It was outlined that around 30% of multitudinous BBS mutations were caused by these three *BBS* genes - *BBS6/MKKS*, *BBS10*, and *BBS12*. Among this *BBS6/MKKS*, which is a chaperonin protein, have been reported with heterozygous mutation (locus heterogeneity), triallelic inheritance, obesity, and have been integrated with several chaperonopathies of BBS in different populations.[30, 51, 74, 75, 85] Disparate and divergent populations have been analyzed for common *BBS* gene mutations, whereas in the year 2000, Slavotinek *et al.,* published that numerous mutations in *BBS6/MKKS* gene were accountable for the development of BBS. They investigated 34 probands (predominantly from Hispanic and Newfoundland populations), which were completely unrelated, and had familiar symptoms of BBS like, polydactyly, retinitis pigmentosa, mental retardation, either hydrometrocolpos (or) vaginal atresia, diabetes, obesity, and congenital heart disease. Among these, four probands carried mutations in the *BBS6/MKKS* genes, with the first proband having a heterozygous nonsense mutation (1679TA, Y264stop), missense mutation (1042GA, G52D) and obesity (with BMI > 40 kg/m$^2$) in a Hispanic girl (13 years old). The second proband had a homozygous, frameshift mutation (two deletions - 1324-1326delGTA and 1316delC), obesity (with BMI > 50 kg/m$^2$) in a Newfoundland female (33 years old). The maternal grandfather and parents of the second proband had heterozygous deletions, and her brother, who had the same BBS symptoms with a homozygous deletion. The third proband (4 years old, male from Newfoundland) was born to a consanguineous marriage whose parents had a heterozygous mutation, and the fourth proband (5 years old, female from Newfoundland) had a heterozygous mutation detected in her mother. Both the third and fourth families have an apportionment of 5 SNPs, 5 short tandem repeat polymorphisms (STRPs), and a frameshift homozygous

mutation (1167 delT) in the *BBS6/MKKS* genes (with a frequency of 11.8%). They hypothesized that the emergence of all the typical traits and BBS features, might be due to the loss of chaperonin protein integrity of *BBS6/MKKS* genes [85]. Another study in the Newfoundland population by Katsanis *et al.*, in the year 2000, speculated that the *BBS6/MKKS* gene might play a drastic role in BBS pathogenesis, as they suggest that, the mutated gene reverberates in the multimeric chaperone, causing retinal dystrophy, kidney malfunction, and obesity. This *BBS6/MKKS* gene mutation (heterozygous Y37C, delGG (exon 5), BBS$^{6H84Y;\ A242S,}$ T57A, L277P) is the second most widespread after *BBS1* (6/17 with 35%) on that island, with 5/17 cases accounting for 34% frequency.[47] In a Chinese proband, two heterozygous pathogenic variants, c.1664C>G and c.635C>T, have been detected apart from the usual polymorphisms of the *BBS6/MKKS* gene, constituting to the disease and obesity.[73] The *BBS6/MKKS* gene as a secondary deformity causes cardiovascular diseases, obesity, and polydactyly, which have been associated with metabolic syndrome since two reported SNPs, rs1545 and rs1547, were investigated in a few populations. According to Hotta (2009),[76] about 336 SNPs in 85 obesity-related genes were chosen for the investigation from the Japanese Single Nucleotide Polymorphism (JSNP) database. They performed an association study with a case-control analysis utilizing patient samples with metabolic syndrome (control – 528, metabolic syndrome patients – 1080) from the Japanese population and found that three SNPs, rs1545 (P = 0.000043, odds ratio (OR) age, gender adjusted 1.45 and confidence interval (95% CI) = 1.21-1.74), rs1547 (P = 0.000041, odds ratio (OR) age, gender adjusted 1.45 and confidence interval (95% CI) = 1.21-1.74) and rs2294901 (P = 0.000033, odds ratio (OR) age, gender adjusted 1.46 and confidence interval (95% CI) = 1.22-1.75) are related to metabolic syndrome, hence stating the fact that variation in this gene influences the risk of obesity and complex disorder manifestations.[76] In French Caucasian populations, they demonstrated the interconnection between the *BBS6/MKKS* gene and the metabolic syndrome (obesity, hyperglycemia, dyslipidemia) by scrutinizing four genes, *BBS1, BBS2, BBS4, BBS6/MKKS* in 12 genotyped variants (from 36 recognized variants in 48 individuals). By analyzing 1,299 French Caucasian normal control subjects (non-diabetic, non-obese) with 1,943 French Caucasian affected subjects, heterogeneous frequency of SNPs were detected in an age dependent manner. As in the case of *BBS6/MKKS* SNPs, rs221667 (P = 0.01, odds ratio (OR) 1.23 and confidence interval (95% CI) = 1.05–1.44) was observed in adult morbid obesity. And in the case of childhood obesity, especially early-onset, two SNPs were related, rs221667 (P = 0.0007, odds ratio (OR) 1.33 and confidence interval (95% CI) = 1.13–1.56) and rs6108572 (P = 0.007, odds ratio (OR) 1.21 and confidence interval (95% CI) = 1.05–1.39). The children assigned under childhood obesity had both of the SNPs (rs6108572 and rs221667) variants in homozygous conditions, which manifested into constrained BBS characteristics like dyslipidemia (atherogenic), elevated fasting triglycerides, and apolipoprotein B and had excessive postprandial glycaemia (P = 0.006) in children with homozygous rs221667 variant. Also, people with a heterozygous *BBS* gene mutation are extremely obese. Other recurrent polymorphisms of *BBS6/MKKS* genes, SNPs in the exonic region, rs1545 (Gly532Val), rs1547 (Arg517Cys), were present in the obese subjects (24 number) and non-diabetic non-obese subjects (24 number), and might render in the progression of common obesity. These SNPs were fewer in frequency compared to other variants and were not pervasive in obese subjects in contrast to lean individuals.[77] In the Danish population, an intense investigation was conducted on juvenile obese subjects (60 white Danish men) to validate the connection of *BBS6/MKKS* gene mutations (or) variations in correlation with typical polygenic obesity forms. There were three non-synonymous variants, Arg517Cys (rs1547), Gly532Val (rs1545) and Ala242Ser, two synonymous variants, Ile178Ile and Pro39Pro and one rare variant, Ala242Ser. During the analysis of the *BBS6/MKKS* coding region in those 60 white Danish men, Arg517Cys (16 out of 60 obese cases) was the most highly expressed variant, followed by Ala242Ser (2 out of 60 obese cases) and Gly532Val (1 out of 60 obese cases). Other variants prevalence probing was analyzed to be in linkage disequilibrium. The non-synonymous haplotype variant Arg517Cys (rs1547) was also found to be in complete linkage disequilibrium. In a case-control association study, there was an 11.4% prevalence of the allele polymorphism of Arg517Cys in the early childhood onset obesity group, which examined 744 men (confidence interval (95% CI) = 9.7–13.0) and a control group with a 9.5% prevalence of allele, which examined 867 subjects (confidence interval (95% CI) = 7.9–10.7) with P = 0.048. Another case-control study in middle-aged men, perceived a 9.7% prevalence of the allele, in the obese group, which examined 523 obese men (confidence interval (95% CI) = 7.9–11.4) and a control group with a 12.2% prevalence of the allele, which examined 1051 lean men (confidence interval (95% CI) = 10.8–13.6) with P = 0.037. They concluded that *BBS6/MKKS* mutation variants might take part an important function in the development of

juvenile onset obesity and non-syndromic obesity pathogenesis.[86] In the Greek population, an investigation of haplotype and genotype interpretation was performed in 220 cases (obese subjects with body mass index ≥ 30 kg/m$^2$) compared with 330 controls (non-obese subjects). Familiar polymorphisms like 986-29A>T (P = 0.0196), 985+33C>G, 985+16T>G (P = 0.0016), 1161+58A>G, 534C>T (or) I178I, 1595G>T (P = 0.0069) (or) G532V (rs1545 of the coding region) were exacerbated in diabetes mellitus type-2, arterial hypertension, and metabolic syndrome subjects. In French Caucasians and Danish, two SNPs of the exonic region, rs1545 (Gly532Val) and rs1547 (Arg517Cys), were communicated in obese cases, but due to their unfavorable frequency and linkage disequilibrium in the obesity affected and control groups, the association analysis was unattainable. In the 1595G>T polymorphism, the carriers (90.9%) of the T allele had increased arterial hypertension than non-carriers (67%, P = 0.007), and the obese subjects furthermore had magnified T allele polymorphism than non-obese controls (odds ratio (OR) = 1.63, P = 0.0127) and have outrageous risks of obesity and metabolic syndrome. In the Greek population, SNPs G532V (rs1545) were remarkably at elevated frequencies in the obese cases than at lower occurrences in non-obese subjects.[87] It was also communicated for the first time in Indian cohorts that were reported for a divergent ciliopathy gene mutation having *BBS6/MKKS* associated SNPs rs1545 and rs1547 in patients (pedigree with an autosomal recessive clinical aspect) suffering from BBS disorder. In an investigation conducted amidst 30 families (23 non-consanguineous and 7 consanguineous), chosen as the study observation group under distinct diagnostic criteria for BBS, almost 80% constituted the known *BBS* gene alterations along with metabolic syndrome integrated with SNPs of the *BBS6/MKKS* gene, rs1547 (p.R517C) and rs1545 (p.G532V). Another work conducted in North India, to analyze the *MKKS/BBS6* gene novel mutation connected with polydactyly and autosomal recessive retinitis pigmentosa, postulated that amidst the 300 outlined missense variants of the *MKKS/BBS6* gene, only three frequent homozygous variants exist in South Asians. The allele frequencies of these three homozygous variants in South Asian populations are p.Gly532Val (0.2473), p.Ile339Val (0.005852), and p.Arg517Cys (0.2471) subsequently.[88, 89]

To culminate the fact that the *BBS6/MKKS* gene is one of the prominent chaperonin proteins necessitated for BBSome assembly and various investigations suggest the fact that mutations in this gene causes numerous chaperonopathies and have been linked with diabetes and obesity. Nearly, *BBS6/MKKS, BBS10,* and *BBS12* genes alone comprise 30% of BBS mutations. Among these many disease-associated mutations, frameshift mutations, polymorphisms, and SNPs of the *BBS6/MKKS* genes were mostly affixed with obesity and metabolic syndrome. In multiple population-inspected studies, a few recurrent SNPs rs1547 and rs1545 were observed. They exist in the coding or exonic region, and these two SNPs, rs1545 (Gly532Val) and rs1547 (Arg517Cys), can hinder with the functional activities, developmental processes, and primarily in the burgeoning and progression of obesity with metabolic syndrome.[76, 88, 89] These SNPs were substantially in triallelic inheritance, missense mutations, both in heterozygous (locus) and homozygous conditions in diverse populations. It is confined to either juvenile or childhood obesity, non-syndromic obesity, and adult morbid obesity in contrasting probands and sometimes with linkage disequilibrium and inappropriate frequency. The subjects with heterozygous conditions of these *BBS6/MKKS* genes and SNPs were exceedingly diabetic and obese. Even though Hotta *et al.,* (2009), Sathya Priya *et al.,* (2015), and Goyal *et al.,* (2020) enunciated the significance of these two SNPs, our review has specific limitations. First and foremost, all the populations that reported the SNPs rs1547 and rs1545 insisted on their occurrence in most of the subjects, but they might be in linkage disequilibrium, in certain cases these SNPs were found both in control and cases. Secondly, immensely few populations and a very small but sizeable number of cohorts were included in the research and have carried out the *BBS* gene (especially *BBS6/MKKS*) mutational analyses studies, hence, with this relatively little data, it's not suffice to commence only rs1547 and rs1545 as the impetus, objective cause, or linkage of metabolic syndrome. We conclude that the two SNPs of the *BBS6/MKKS* gene, rs1547 and rs1545, have been disclosed in most of the studied populations and are certainly associated with chaperonopathies, obesity, and metabolic syndrome, but are assuredly not the only polymorphisms responsible for the disease pathogenesis. Further additional inclusion of a wide population group and by enlarging the study number might add more precedence and reliability to these SNPs and improve our cognizance about metabolic syndrome.

## OBJECTIVE AND METHODOLOGY

The origination of the metabolic syndrome still needs better elucidation. Multiple complex disorders like obesity, diabetes, diabetic retinopathy, Bardet-Biedl syndrome (BBS), and polycystic ovary syndrome (PCOS) are categorized

under the metabolic syndrome. Several bodies, like WHO, IDF, EGIR, etc., have different evaluation criteria for the disease, but there is no deciphering idea of the disease's pathogenesis. Innumerable pathways were investigated to recognize an early onset, common progenitor gene, or frequent disorder interrelationship or occurrence, yet there is a gap in the perception of metabolic syndrome. In 2009, Hotta *et al.,* published that in a case-control association study of nearly 85 genes from the Japanese Single Nucleotide Polymorphism (JSNP) database, from around 336 genotyped SNPs, three SNPs rs1547, rs1545, and rs2294901 in the *BBS6/MKKS* gene were interconnected with metabolic syndrome (referenced in the text). This article served as the starting point of our paper. Hence, our prime objective was to execute a review search to ascertain whether the same SNPs were analyzed and disclosed in other populations. The method of intervention and data sourcing were completely from online resources like Google Scholar, SCOPUS, MEDLINE, PubMed, SCINDEX, Embase, Wiley, and EBSCO. We scrutinized multiple case studies, population reports, meta-analysis, research, and review articles about the SNPs of *BBS* genes and their connection with metabolic syndrome. The online search strategy keywords included, metabolic syndrome, obesity, BBS, diabetes, diabetic retinopathy, SNPs of BBS, *BBS6/MKKS* gene, rs1547, rs1545, rs2294901, and relevant articles with coverage till date or the latest evaluations were selected for our work. Divergent eligibility criteria were stipulated by various study groups in their reports, which incorporated obesity cases (varied BMI and computing gene polymorphisms and SNPs), cohort observational studies of BBS subjects (SNPs inspected), case-control association studies (SNPs examined), and the subjects had morphological changes in both genders, and mixed age groups. The investigations and outcomes of our review article were further narrated and discussed

## CONCLUSION

Bardet-Biedl syndrome and diabetic retinopathy are metabolic syndrome since they have common characteristics and hallmarks like obesity, hyperglycemia, cardiovascular disorders, etc. These SNPs and polymorphisms of the *BBS6/MKKS* gene were reported in the Japanese, French Caucasian, Hispanic, Newfoundland, Chinese, Danish, Greek, and Indian populations to be analogous with obesity and metabolic syndrome. Due to the exorbitant prevalence of this disorder in the world population, further additional population-based studies may be carried out for better insight. SNPs are also so unique with respect to a single individual, and they happen due to a genetic variation in a single nucleotide of a genome when it is altered or transmuted in a DNA sequence. It falls within the coding sequence of genes or intermittently in the non-coding regions of genes, or sometimes in the intergenic regions. Most of these SNPs are present within a gene, in the regulatory region situated near a gene. Therefore, they can contribute directly to disease development. Also, we can speculate about how humans progress and respond to diseases, chemicals, pathogens, vaccines, drugs, and other factors by screening the variations in their DNA sequences. So, these SNPs may act as markers for lifestyle diseases like heart disease, diabetes, and cancer in the near future. Hence, these two reported SNPs, rs1545 and rs1547, which are present in the exonic region of the *BBS6/MKKS* gene, must be chosen for screening in patients with obesity and metabolic syndrome in disparate and heterogeneous communities. The frequency distribution of rs1545 and rs1547 in the world population might contribute to the interpretation of metabolic syndrome pathogenesis.

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