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Whole-Exome Sequencing Identifies Pathogenic Variants in *SMPD1*, *HIP1R*, and *POMC* Associated with Obesity in a Consanguineous Pakistani Population

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ABSTRACT

Background and Objective: Obesity, defined as a Body Mass Index (BMI) ≥30 kg/m^2, is a multifactorial metabolic disorder arising from an imbalance between energy intake and expenditure. This study aimed to identify pathogenic variants in consanguineous Pakistani families with early-onset obesity to elucidate the genetic basis of the disorder. **Materials and Methods:** Twenty affected families and twenty sporadic obese individuals from various regions of Balochistan were recruited. Genomic DNA was extracted from peripheral blood, followed by whole-exome sequencing and validation using Sanger sequencing. Identified variants were analyzed using bioinformatics tools to predict their pathogenicity. **Results:** A heterozygous missense variant in the *SMPD1* gene, segregating with autosomal dominant obesity, and previously reported variants in *HIP1R* and *POMC* genes associated with non-syndromic obesity phenotypes were identified. **Conclusion:** These findings broaden the mutational landscape of obesity-related genes, support genotype-phenotype correlations, and highlight the importance of genetic screening in consanguineous families for early diagnosis, counselling, and better understanding of hereditary obesity.

KEYWORDS

Obesity, *SMPD1*, *HIP1R*, *POMC*, whole exome sequencing, consanguinity, Balochistan, genetic variants

INTRODUCTION

Obesity is one of the most alarming global health problems and a major risk factor for metabolic disorders such as type II diabetes, cardiovascular diseases, and hypertension[1]. According to the World Health Organization, more than 1.9 billion adults worldwide are overweight, and over 650 million are obese[2].

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Obesity is defined as a body mass index (BMI) of 30 kg/m^2 or greater and results from a chronic imbalance between energy intake and expenditure, leading to the excessive accumulation of triglycerides in adipose tissue[3,4]. While environmental factors, such as a sedentary lifestyle and high-calorie diets, contribute significantly, genetic predisposition also plays a critical role in determining susceptibility to obesity[5]. Heritability estimates suggest that more than 40% of BMI variation can be attributed to genetic factors[6]. Genetic studies have revealed that obesity is a heterogeneous disorder involving complex interactions between multiple genes and environmental factors. Among the known genetic contributors, monogenic forms of obesity caused by rare variants in single genes provide key insights into the mechanisms of energy homeostasis. The *POMC* (proopiomelanocortin) gene encodes a precursor protein crucial in appetite regulation through the leptin-melanocortin pathway; mutations in *POMC* are associated with early-onset severe obesity due to impaired satiety signaling[7,8]. The *SMPD1* (sphingomyelin phosphodiesterase 1) gene encodes acid sphingomyelinase, an enzyme involved in sphingolipid metabolism; variants in *SMPD1* have been linked to lipid storage abnormalities and syndromic forms of obesity[9]. Similarly, *HIP1R* (huntingtin-interacting protein 1-related) plays a role in endocytosis and cytoskeletal organization; alterations in *HIP1R* are reported to disrupt neuronal signaling pathways associated with non-syndromic obesity[10]. Despite advances in genomic technologies, the genetic landscape of obesity remains incompletely characterized, particularly in populations with high rates of consanguinity, such as Pakistan. The Pakistani population provides a unique opportunity to identify novel homozygous variants underlying monogenic and syndromic obesity due to its genetic structure[11]. Therefore, this study aimed to identify pathogenic variants in the *SMPD1*, *HIP1R,* and *POMC* genes among consanguineous families from Balochistan presenting with early-onset obesity. These findings contribute to expanding the mutational spectrum of obesity-related genes and improving understanding of genotype-phenotype correlations in underrepresented populations.

MATERIALS AND METHODS

Study area: This study was conducted in Quetta, Balochistan, Pakistan, during the year 2022-2023.

Study subjects and ethical approval: Twenty consanguineous families with early-onset obesity and twenty sporadic obese individuals were recruited from various regions of Balochistan, Pakistan. Written informed consent was obtained from all participants or their legal guardians before sample collection. The study protocol was approved by the Institutional Ethics Review Committee of BUITEMS, Quetta, and all procedures adhered to the ethical standards outlined in the Helsinki Declaration.

Clinical evaluation and sample collection: Detailed clinical and anthropometric data, including age, sex, height, weight, and Body Mass Index (BMI), were recorded for each participant. Peripheral blood samples (5 mL) were collected in EDTA-coated tubes from all affected individuals and available family members. Samples were stored at -20°C until further processing.

This family was sampled from the Luni District, Sibi, Balochistan. Peripheral blood samples were taken in Vacutainer tubes containing EDTA from all affected individuals, their parents, and normal siblings. Clinical evaluations and family histories were obtained through detailed interviews with all family members as shown in Fig. 1. This family is segregating with an obesity phenotype, with clinical features (comorbidities) involving type 2 diabetes, hypertension, CVD, and an eating disorder. All affected individuals showed similar, frequent clinical features that appeared at an early stage or developed during early childhood shown in Table 1.

Table 1: Clinical description of affected individuals in Family 4, including age, age of obesity onset, and Body Mass Index (BMI) with percentiles

Clinical Phenotype	Patient # → Clinical observation↓	IV:2	V:1	V:2	V:3
Age	Age at the time of sampling	37	10	8	7
Obesity	Age of onset	2.5 years	1.5 year	2 years	1.8 year
	BMI (kg/m^2)/Percentile	39.5 kg/m^2	99th centile	95th centile	97th centile

Age is reported in years. BMI percentiles are based on age. BMI: Body Mass Index (kg/m^2). Roman numerals (IV, V) indicate generations, and Arabic numerals identify individuals within each generation (e.g., V:1 = first individual in the 5th generation)

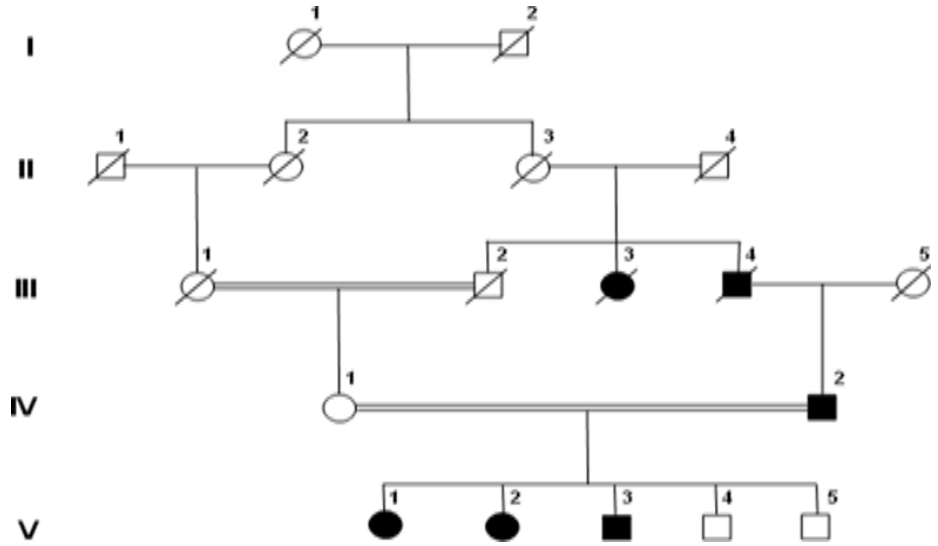

Fig. 1: Pedigree of a family with a syndromic disorder showing multiple affected individuals

Squares represent males and circles represent females. Filled (shaded) symbols indicate affected individuals, while unfilled (open) symbols denote unaffected individuals. The disorder is characterized by obesity, type 2 diabetes, and delayed motor development

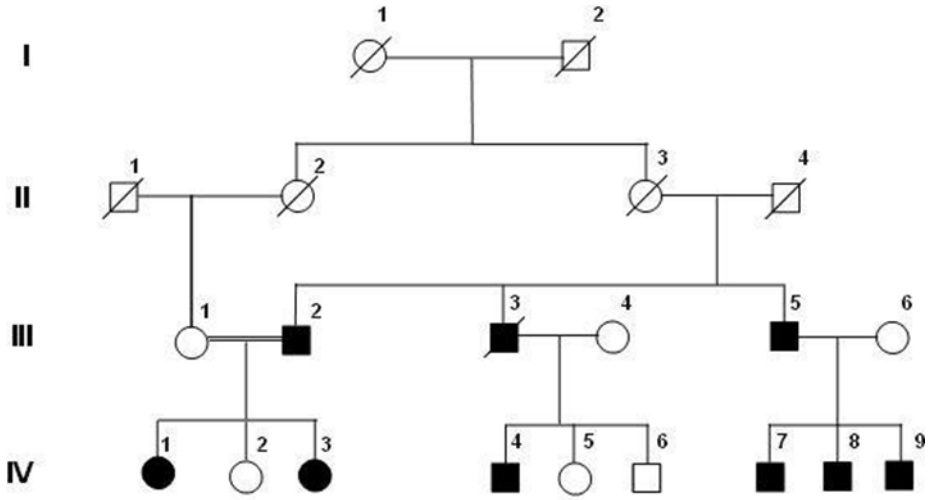

Fig. 2: Pedigree of a family with obesity showing multiple affected individuals

Squares represent males and circles represent females. Filled (shaded) symbols indicate affected individuals, while unfilled (open) symbols denote unaffected individuals. A diagonal line through a symbol indicates a deceased individual. Horizontal lines represent mating, and vertical lines indicate parent-offspring relationships. Roman numerals (I, II, III, IV, V) denote generations, and Arabic numerals identify individuals within each generation. Double horizontal lines indicate consanguineous marriages

A diagonal line through a symbol indicates a deceased individual. Horizontal lines represent mating, and vertical lines indicate parent-offspring relationships. Roman numerals (I, II, III, IV, V) denote generations, and Arabic numerals identify individuals within each generation. Double horizontal lines indicate consanguineous marriages.

This family was sampled from Khajak District, Sibi, Balochistan. Clinical evaluation and family history were obtained by all members of the family as shown in Fig. 2. This family is segregated with an obesity phenotype, with clinical features involving type 2 diabetes, hypertension, CVD, and an eating disorder, inherited in an autosomal dominant manner (Table 2).

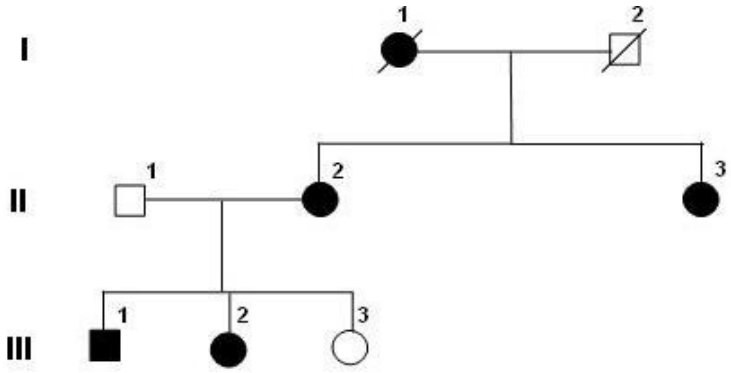

Fig. 3: Pedigree of a family with obesity showing multiple affected individuals

Squares represent males and circles represent females. Filled (shaded) symbols indicate affected individuals, while unfilled (open) symbols denote unaffected individuals. A diagonal line through a symbol indicates a deceased individual. Horizontal lines represent mating, and vertical lines indicate parent-offspring relationships. Roman numerals (I, II, III, IV, V) denote generations, and Arabic numerals identify individuals within each generation. Double horizontal lines indicate consanguineous marriages

Table 2: Clinical description of the affected individuals of the family

Clinical phenotype	Patient # → clinical observation↓	III:2	III:5	IV:1	IV:3	IV:4	IV:7	IV:8	IV:9
Age	Age at the time of sampling	45 years	32 years	21 years	20 years	17 years	5 years	4 years	2 years
Obesity	Age of onset	2 years	2.5 years	3 years	2 years	2.5 years	1.8 year	2.5 years	1.5 year
	BMI(kg/m^2)/	40 kg/m^2	39 kg/m^2	42 kg/m^2	35 kg/m^2	98th centile	96th centile	95th centile	97th centile
Type 2 diabetes	Age of onset	2.5 years	3.5 years	4 years	No	3 years	3 years	No	No
Hypertension	Yes/No	Yes	No	Yes	No	No	No	No	No
CVD	Yes/No	Yes	No	No	No	No	No	No	No
Eating disorder	Hyperphagia	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Depression	Yes/No	Yes	Yes	Yes	Yes	Yes	No	No	No

BMI: Body Mass Index (kg/m^2). Age is reported in years. A BMI percentiles are based on age- and sex-specific reference standards. "Yes/No" indicates the presence or absence of the clinical feature. Hyperphagia refers to excessive eating behavior. Roman numerals (III, IV) indicate generations, and Arabic numerals identify individuals within each generation (e.g., IV:1 = first individual in the 4th generation)

Table 3: Clinical description of the affected individuals of the family

Clinical Phenotype	Patient # →Clinical observation↓	II:2	III:1	III:2
Age	Age at the time of sampling	36	13	12
Obesity	Age of onset	2	3	2.5
	BMI (kg/m^2)/Percentile	39 kg/m^2	96th centile	95th centile
Type 2 diabetes	Age of onset	No	No	No
Hypertension	Yes/No	No	No	No
CVD	Yes/No	No	No	No
Eating disorder	Hyperphagia	Yes	Yes	Yes
Depression	Yes/No	Yes	Yes	No
Observations at birth	Delivery	Normal	Normal	Normal

BMI: Body Mass Index (kg/m^2) and CVD: cardiovascular disease. Age is reported in years. A BMI percentiles are based on age- and sex-specific reference standards. "Yes/No" indicates the presence or absence of the clinical feature. Hyperphagia refers to excessive eating behavior

This family was ascertained from Jaffarabad, Balochistan. A non-consanguineous family as show in Fig. 3. This family exhibits a segregated obesity phenotype; all affected individuals display similar, frequent clinical features (comorbidities) that typically appear at an early stage or develop during early childhood, inherited in an autosomal dominant manner (Table 3).

Genomic DNA extraction and quantification: Genomic DNA was extracted from peripheral blood leukocytes using the phenol-chloroform extraction method following standard protocols. DNA purity and concentration were assessed using a NanoDrop spectrophotometer (Thermo Fisher Scientific, USA), and integrity was confirmed by electrophoresis on a 1% agarose gel.

Whole exome sequencing (WES): High-quality genomic DNA from affected individuals was subjected to whole exome sequencing (WES) using the Illumina NovaSeq 6000 platform (Illumina, San Diego, USA). Exome capture was performed with the Agilent SureSelect Human All Exon V7 kit, and sequencing reads were aligned to the human reference genome (GRCh38/hg38) using the Burrows-Wheeler Aligner (BWA-MEM). Variant calling was carried out using GATK v4.0, and annotation was performed with ANNOVAR and Ensembl Variant Effect Predictor (VEP). Identified variants were filtered based on quality parameters, population frequency (gnomAD, 1000 Genomes), and predicted pathogenicity.

Sanger sequencing validation: Putative pathogenic variants identified by WES were validated using Sanger sequencing. PCR primers were designed using Primer3 software, and amplified products were purified and sequenced bidirectionally using the ABI 3730xl DNA Analyzer (Applied Biosystems, USA). Sequencing chromatograms were analyzed with Chromas and aligned using BioEdit software to confirm segregation within families.

Bioinformatics analysis: The detected variants in *SMPD1*, *HIP1R*, and *POMC* genes were also confirmed by using online databases. These variants were not reported previously in any of the online databases, i.e., Human Gene Mutation Database, gnomAD, ClinVar, and Exome Variant Server.

RESULTS

PCR amplification of the target exons of *SMPD1*, *POMC*, and *HIP1R* genes was successfully performed, producing fragments of the expected sizes: 299 bp for *SMPD1* (exon 3), 484 bp for *POMC* (exon 2), and 494 bp for *HIP1R* (exon 18), shown in Fig. 4-6. The PCR products were purified and sequenced bidirectionally using the ABI 3730xl DNA Analyzer (Applied Biosystems, USA). For *SMPD1*, primers AGCACAGGAGGACCAGGA (forward) and GAGGTGCTCCAGCTCAACA (reverse) with Tm values of 59.3°C and 60.1°C, respectively, were used. A *POMC* amplification utilized TGGTCACAGTTTACCCACCA (forward) and TGAATCACGCCTATCACTGG (reverse) primers with Tm values of 59.8°C and 59.7°C, respectively. A *HIP1R* fragments were amplified using GGCTACATGGGAGACAGGAC (forward) and GAAGAAGCCGGACACAAAAG (reverse) primers with Tm values of 59.5°C and 59.9°C.

Whole exome sequencing (WES) was performed, using the DNA of an affected and normal member of the family to identify the variant. Subsequently, Sanger sequence analysis was performed to confirm the identified variant; a heterozygous missense substitution [c.1135C>T (p.Leu379Phe)] in exon 3 of the

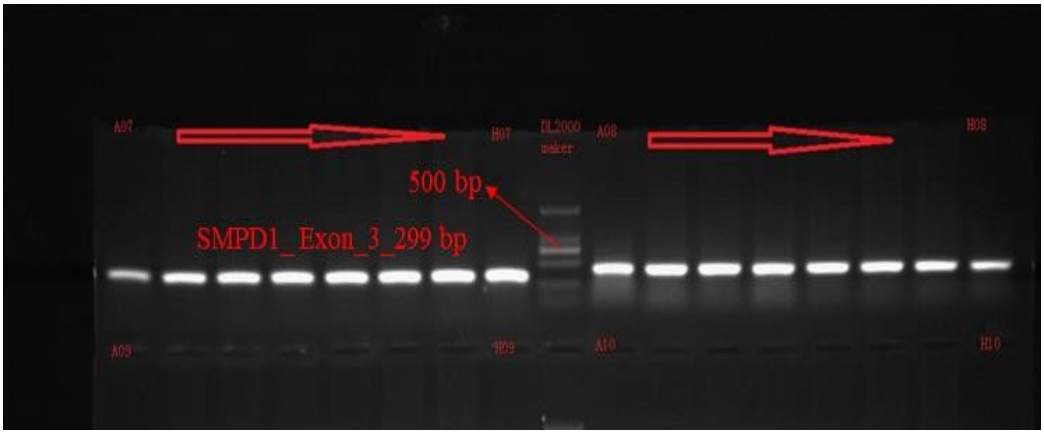

Fig. 4: Gel image of amplified PCR product of *SMPD1*

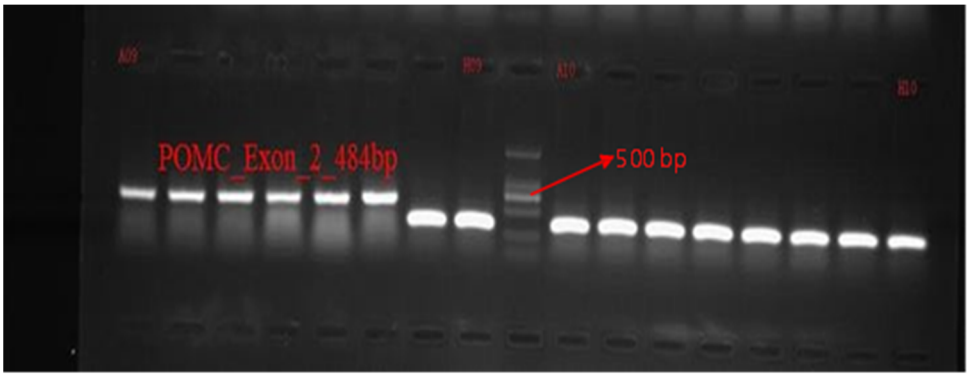

Fig. 5: Gel image of amplified PCR product of *POMC* gene

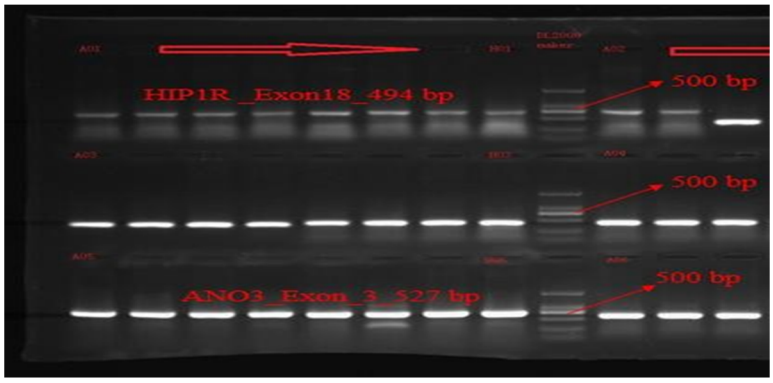

Fig. 6: Gel images of amplified PCR product of *HIP1R* gene

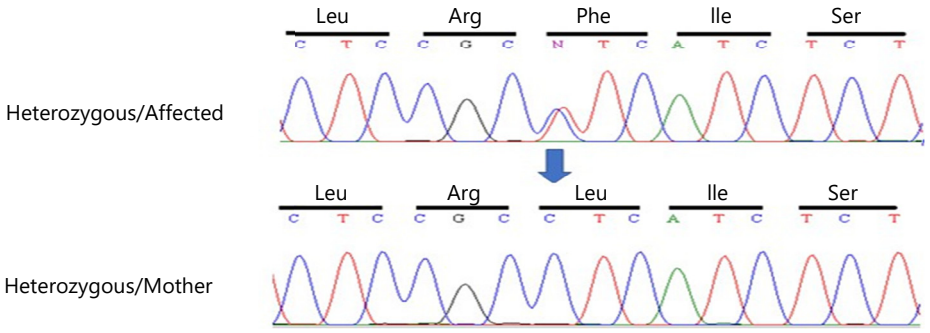

Fig. 7: Sequencing chromatogram showing heterozygous missense substitution [c.1135C>T (p.Leu379Phe)] in exon 3 of *SMPD1* gene
Arg: Arginine, Ile: Isoleucine, Leu: Leucine, Phe: Phenylalanine and Ser: Serine

SMPD1 gene, manifested a change "T" into "A" in the DNA sequence. The chromatogram depicts that affected individuals were heterozygous while unaffected parents and siblings were homozygous (Fig. 7). The identified novel variant revealed that this nucleotide change led to the loss of function of the ASM protein product shown in Fig. 8(a-b). The current variant is located within a domain, the mutated residue is situated near a highly conserved region, and it affects the normal function of the ASM protein product. Structural effects were studied through online bioinformatics software HOPE and UniProt. Confirmation of the identified variant was performed by online bioinformatics tools, including MutationTaster, PolyPhen-2, and SIFT, which predicted that the current substitution produces a pathogenic altered protein. The variant was not reported previously in any of the online databases, i.e., Human Gene Mutation Database, gnomAD, ClinVar, and Exome Variant Server.

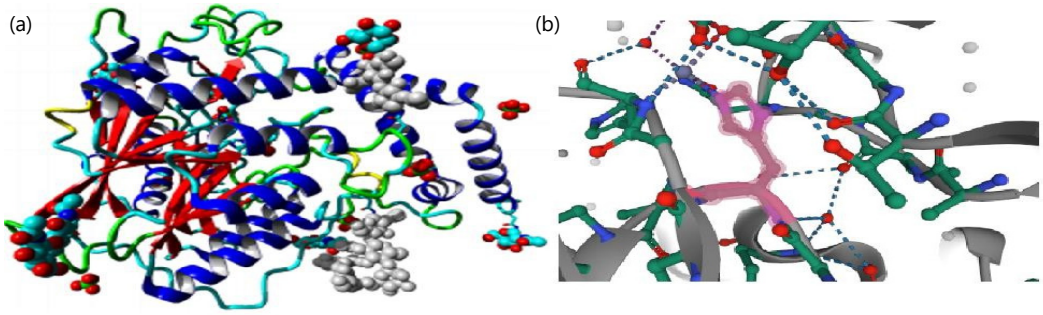

Fig. 8(a-b): (a) ASM structure of human gene *SMPD1*, (b) Purple highlighted is the residue that indicates the mutated position L379F

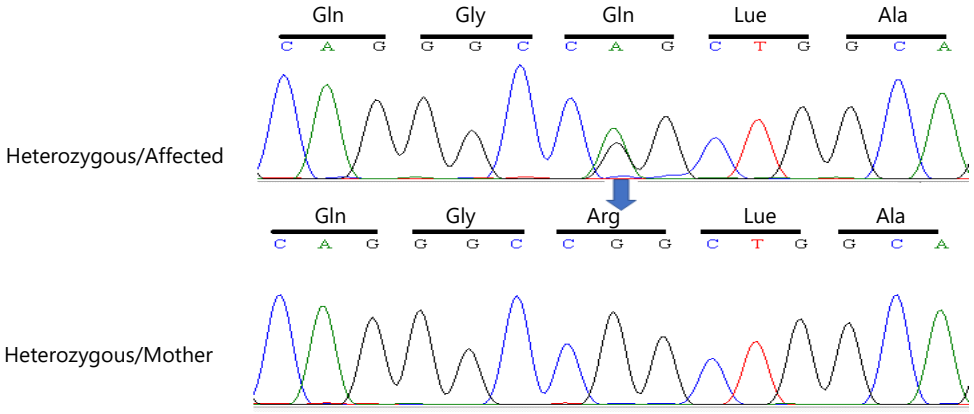

Fig. 9: Sequencing chromatogram of exon 18 of the *HIP1R* gene showing homozygous missense substitution c.1802G>A (p. Arg601Gln)
Ala: Alanine, Arg: Arginine, Gln: Glutamine, Gly: Glycine and Leu: Leucine

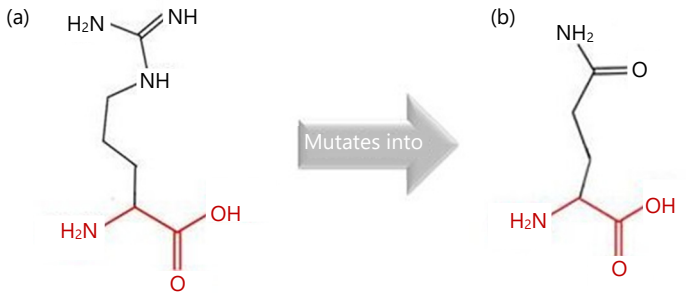

Fig. 10(a-b): *HIP1R* protein structure of human gene, (a) Wild type amino acid and (b) Mutated amino acid, at the mutated position (R601Q)

Whole exome sequencing (WES) was performed, using the DNA of an affected and a normal member of the family to identify the variant. Subsequently, Sanger sequence analysis was performed to confirm the identified variant [c.1802G>A (p. Arg601Gln)] in exon 18 of the *HIP1R* gene; the chromatogram depicts that unaffected parents and siblings were homozygous while affected individuals were heterozygous (Fig. 9). The identified variant [c.1802G>A (p.Arg601Gln)] revealed that this nucleotide change alters the function of the *HIP1R* protein product shown in Fig. 10(a-b), structural effects were studied through online bioinformatics software HOPE and UniProt. Confirmation of the identified variant was performed by online bioinformatics tools, including Mutation Taster, PolyPhen-2, and SIFT predicted that the current substitution produces a benign altered protein.

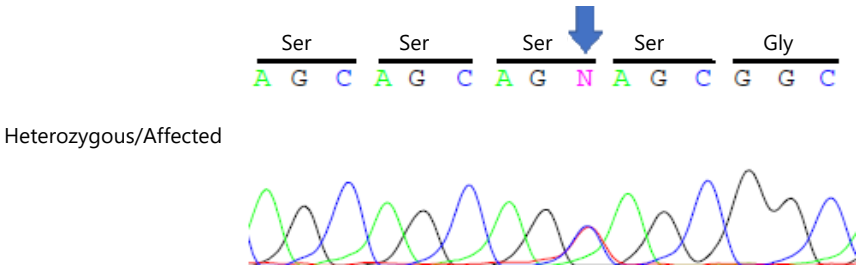

Fig. 11: Sequencing chromatogram of exon 2 of *POMC* showing heterozygous silent substitution c.282C>T (p.Ser94 Ser)

Whole exome sequencing (WES) was performed. Subsequently, Sanger sequence analysis was performed to confirm the identified heterozygous silent variant [c.282C>T (p. Ser94 Ser)] in exon 2 of the *POMC* gene, a change in nucleotide 'C' into 'T', but no amino acid change Fig. 11. The identified variant [c.282C>T (p. Ser94 Ser)] revealed no change in amino acid. This variant (rs28930368) was previously reported in online databases, i.e., Human Gene Mutation Database, gnomAD, ClinVar, and Exome Variant Server.

DISCUSSION

In this study, three major obesity-associated genes-*SMPD1*, *HIP1R*, and *POMC* were identified to segregate with obesity phenotypes in consanguineous families from Balochistan. These findings support the role of rare and inherited pathogenic variants in the development of monogenic obesity in populations with high consanguinity rates.

A heterozygous novel variant in *SMPD1* was identified segregating with obesity and related clinical features, including type 2 diabetes, hypertension, and hyperphagia. A *SMPD1* encodes acid sphingomyelinase, an enzyme responsible for sphingolipid metabolism. Dysregulation of sphingolipid pathways has previously been associated with metabolic disease and obesity, where high-fat diet exposure increases ceramide accumulation and leads to obesity, insulin resistance, and altered leptin signaling[12]. Pharmacological inhibition of *SMPD1* activity has been shown to reverse diet-induced metabolic effects, highlighting its key role in obesity physiology[13]. Additionally, elevated secretory acid sphingomyelinase levels have been reported in obese children, reinforcing its clinical relevance to adiposity and metabolic dysfunction[14]. These findings collectively support the hypothesis that the *SMPD1* variant identified in the present study may contribute to obesity susceptibility through disruption of lipid homeostasis.

The *HIP1R* missense variant detected in this study was also found to segregate in an autosomal dominant manner with obesity, hypertension, cardiovascular conditions, and diabetes. A *HIP1R* plays a role in clathrin-mediated endocytosis and interacts with metabolic pathways influencing lipid and glucose regulation[15]. Genome-wide association studies have linked *HIP1R* variants with increased BMI and altered metabolic signaling, suggesting its involvement in energy expenditure and adipocyte function[16]. Prior studies also report altered *HIP1R* gene expression patterns in diabetes, further supporting its pathogenic association with metabolic disorders[17]. The presence of this previously reported variant in the current cohort strengthens existing evidence linking *HIP1R* genetic variation with obesity pathogenesis.

Finally, a previously reported synonymous variant in *POMC* (p. Ser94Ser) was identified in a highly obese family. Although synonymous, prior studies have reported this variant among severely obese patients and implicated *POMC* dysfunction in neuroendocrine regulation of appetite and satiety[18]. A *POMC* plays a crucial role in hypothalamic melanocortin pathways controlling energy balance, and previously documented obesity-associated loci near *POMC* further support its importance in monogenic and polygenic obesity[19]. While no novel *POMC* variants have been reported previously in Pakistani cohorts, the presence of this variant in the current study confirms its relevance in this population[20].

CONCLUSION

This study identified both novel and previously reported pathogenic variants in *SMPD1*, *HIP1R*, and *POMC* segregating with obesity in consanguineous families from Balochistan, expanding the mutational spectrum of obesity-related genes in underrepresented populations. The findings highlight the importance of population-specific genetic screening for early diagnosis, counseling, and management of hereditary obesity. Families without identified variants are candidates for whole-genome sequencing to uncover deep intronic or regulatory mutations. Future functional analyses of these candidate genes will provide deeper insight into the molecular mechanisms underlying obesity, informing targeted interventions and improving genotype-phenotype correlations in high-consanguinity communities.

SIGNIFICANCE STATEMENT

This study reports the identification of novel and known pathogenic variants in the *SMPD1*, *HIP1R*, and *POMC* genes among consanguineous families from Balochistan with early-onset obesity. The findings contribute to understanding the genetic architecture of obesity in underrepresented populations and emphasize the need for population-specific genetic screening programs. This work provides valuable insight for future diagnostic strategies, genetic counselling, and targeted management of obesity in Pakistan's high-consanguinity communities.

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