

- Supplementary Material -

List of diagnostic and candidate genes

Table S1. Diagnostic genes sequenced in the present study. Gene, OMIM ID, associated pathology and reference as from OMIM or literature are reported.

Gene	OMIM ID	Gene-phenotype relationship	Reference
ADRA2	104210	Atypical familial partial lipodystrophy	[42]
AGPAT2	*603100	Lipodystrophy, congenital generalized, type 1	608594
AKT2	164731	AKT2-linked lipodystrophy	[43]
ALDH18A1	138250	Cutis laxa, autosomal recessive, type IIIA	219150
ALMS1	606844	Alström syndrome	203800
ARL6	608845	Bardet-Biedl syndrome 3	600151
BBIP1	613605	Bardet-Biedl syndrome 18	615995
BBS1	209901	Bardet-Biedl syndrome 1	2099009
BBS10	610148	Bardet-Biedl syndrome 10	615987
BBS12	610683	Bardet-Biedl syndrome 12	615989
BBS2	606151	Bardet-Biedl syndrome 2	615981
BBS4	600374	Bardet-Biedl syndrome 4	615982
BBS5	603650	Bardet-Biedl syndrome 5	615983
BBS7	607590	Bardet-Biedl syndrome 7	615984
BBS9	607968	Bardet-Biedl syndrome 9	615986

BSCL2	*606158	Lipodystrophy, congenital generalized, type 2	269700
C8orf37	614477	Bardet-Biedl syndrome 21	617406
CARTPT	602606	Obesity	[44]
CAV1	*601047	Lipodystrophy, familial partial, type 7	606721
CAVIN1	*603198	Lipodystrophy, congenital generalized, type 4	613327
CEP19	615586	CEP19 deficiency obesity	615703
CEP290	610142	Bardet-Biedl syndrome 14	615991
CIDEC	612120	Lipodystrophy, familial partial, type 5	615238
DYRK1B	604556	Abdominal Obesity-Metabolic Syndrome	615812
FTO	*610966	Obesity	612460
GHR	*600946	Hypercholesterolemia	143890
GNAS	139320	McCune-Albright syndrome	174800
HDAC8	300269	Cornelia de Lange syndrome	300882
IFT172	607386	Bardet-Biedl syndrome	615630
IFT27	615870	Bardet-Biedl syndrome 19	615996
INPP5E	613037	MORM syndrome	610156
INSR	147670	INSR deficiency hyperinsulinism	610549
KSR2	610737	Obesity and insulin resistance	[45]
LEP	164160	Obesity from congenital leptin deficiency	614962
LEPR	601007	Obesity from leptin receptor deficiency	614963
LIPE	151750	Lipodystrophy, familial partial, type 6	615980
LMNA	150330	Lipodystrophy, familial partial, type 2	151660
LZTFL1	606568	Bardet-Biedl syndrome 17	615994
MC3R	155540	Susceptibility to severe obesity	602025
MC4R	155541	Obesity from melanocortin receptor deficiency 4	618406
MCHR1	601751	Obesity	601751
MEGF8	604267	Carpenter syndrome 2	614976
MFN2	608507	Obesity	[46]
MKKS	604896	Bardet-Biedl syndrome	605231

MKS1	609883	Bardet-Biedl syndrome 13	615990
NCOA2	*601993	Obesity phenotype	601993
NPC1	*607623	Niemann-Pick disease, type C1	257220
NR0B2	604630	Obesity	601665
NSD1	606681	Sotos syndrome 1	117550
PALB2	*610355	Accumulation of adipose tissue	[47]
PCSK1	162150	Prohormone convertase 1 deficiency obesity	600955
PDX1	*600733	MODY, type IV	606392
PHF6	300414	Borjeson-Forssman-Lehmann syndrome	301900
PLIN1	170290	Lipodystrophy, familial partial, type 4	613877
PNPLA2	*609059	Neutral lipid storage disease with myopathy	610717
POMC	176830	Obesity from pro-opiomelanocortin deficiency	609734
POU1F1	173110	Lipedema	[48]
PPARG	601487	Severe obesity	601665
PPP1R3A	600917	Severe insulin resistance, digenic	125853
RAB23	606144	Carpenter's syndrome	201000
RYR1	*180901	Central core disease	117000
SDC3	*186357	Obesity, association with	601665
SDCCAG8	613524	Bardet-Biedl syndrome 16	615993
SH2B1	608937	Obesity	[49]
SIM1	603128	Obesity	[50]
TBL1XR1	608628	Pierpont syndrome	602342
TRIM32	602290	Bardet-Biedl syndrome 11	615988
TTC8	608132	Bardet-Biedl syndrome 8	615985
UCP3	602044	Severe obesity and insulin resistance	601665
VPS13B	607817	Cohen's syndrome	216550
WDPCP	613580	Bardet-Biedl syndrome	615992
ZMPSTE24	*606480	Mandibuloacral dysplasia with type B lipodystrophy	608612

Table S2. Candidate genes sequenced in the present study. Gene, description and OMIM ID are reported.

Gene	Description	OMIM ID
<i>A2M</i>	ALPHA-2-MACROGLOBULIN	*103950
<i>A2ML1</i>	ALPHA-2-MACROGLOBULIN-LIKE	*610627
<i>ABCC6</i>	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 6	*603234
<i>ABCG4</i>	ATP-BINDING CASSETTE, SUBFAMILY G, MEMBER 4; ABCG4	*607784
<i>ABCG1</i>	ATP-BINDING CASSETTE, SUBFAMILY G, MEMBER 1	*603076
<i>ACBD7</i>	ACYL-CoA BINDING DOMAIN CONTAINING	-
<i>ACSL1</i>	ACYL-CoA SYNTHETASE LONG CHAIN FAMILY, MEMBER 1	*152425
<i>ACVR1C</i>	ACTIVIN A RECEPTOR, TYPE IC	*608981
<i>ADCY3</i>	ADENYLATE CYCLASE	*600291
<i>ADIG</i>	ADIPOGENIN	*611396
<i>ADIPOQ</i>	ADIPOCYTE-, C1q-, AND COLLAGEN DOMAIN-CONTAINING	*605441
<i>ADRB2</i>	BETA-2-ADRENERGIC RECEPTOR	109690
<i>ADRB3</i>	BETA-3-ADRENERGIC RECEPTOR;	*109691
<i>AEBP1</i>	AE-BINDING PROTEIN 1	*602981
<i>AGRP</i>	AGOUTI-RELATED NEUROPEPTID	*602311
<i>AKR1B1</i>	ALDO-KETO REDUCTASE FAMILY 1, MEMBER B1	*103880
<i>AKR1B10</i>	ALDO-KETO REDUCTASE FAMILY 1, MEMBER B10	*604707
<i>AKR1B15</i>	ALDO-KETO REDUCTASE FAMILY 1, MEMBER B15	*616336
<i>AKR1C1</i>	ALDO-KETO REDUCTASE FAMILY 1, MEMBER 1	*600449
<i>AKR1C2</i>	ALDO-KETO REDUCTASE FAMILY 1, MEMBER C2	*600450
<i>AKR1C3</i>	ALDO-KETO REDUCTASE FAMILY 1, MEMBER C3	*603966
<i>AKR1C4</i>	ALDO-KETO REDUCTASE FAMILY 1, MEMBER C4	*600451
<i>AKR1E2</i>	ALDO-KETO REDUCTASE FAMILY 1, MEMBER E2	*617451
<i>AKT2</i>	AKT SERINE/THREONINE KINASE 2	*164731
<i>ANGPTL4</i>	ANGIOPOIETIN-LIKE 4	*605910
<i>ANK2</i>	ANKYRIN	*06410
<i>ANKRD26</i>	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 26	*610855
<i>ANXA1</i>	ANNEXIN A1	*151690

<i>APOA1</i>	APOLIPOPROTEIN A-I	*107680
<i>APOE</i>	APOLIPOPROTEIN E	*107741
<i>ARNTL</i>	ARYL HYDROCARBON RECEPTOR NUCLEAR TRANSLOCATOR-LIKE PROTEIN	*602550
<i>ARRDC3</i>	ARRESTIN DOMAIN-CONTAINING 3	*612464
<i>ATG12</i>	AUTOPHAGY-RELATED 12	*609608
<i>ATXN1</i>	ATAXIN 1	*601556
<i>BAIAP3</i>	BAI1-ASSOCIATED PROTEIN 3	*604009
<i>BDNF</i>	BRAIN-DERIVED NEUROTROPHIC FACTOR	*113505
<i>BECN2</i>	BECLIN 2	*615687
<i>BRD2</i>	BROMODOMAIN-CONTAINING PROTEIN 2	*601540
<i>BRS3</i>	BOMBESIN-LIKE RECEPTOR 3	*300107
<i>BSCL2</i>	BSCL2 GENE	*606158
<i>CADM2</i>	CELL ADHESION MOLECULE 2	*609938
<i>CAMKK2</i>	CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE KINASE 2, BETA	*615002
<i>CAV1</i>	CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE KINASE 2, BETA; CAMKK2	*601047
<i>CAVIN1</i>	CAVEOLAE-ASSOCIATED PROTEIN 1	*603198
<i>CCBE1</i>	COLLAGEN AND CALCIUM-BINDING EGF DOMAIN-CONTAINING PROTEIN 1	*612753
<i>CD300E</i>	CD300E ANTIGEN	*609801
<i>CDKN1A</i>	CYCLIN-DEPENDENT KINASE INHIBITOR 1A	*116899
<i>CDKN1B</i>	CYCLIN-DEPENDENT KINASE INHIBITOR 1B	*600778
<i>CIDEA</i>	CELL DEATH-INDUCING DFFA-LIKE EFFECTOR	*604440
<i>CLOCK</i>	CIRCADIAN LOCOMOTOR OUTPUT CYCLES KAPUT	*601851
<i>CNR1</i>	CANNABINOID RECEPTOR 1	*114610
<i>CNTNAP2</i>	CONTACTIN-ASSOCIATED PROTEIN-LIKE 2	*604569
<i>COL3A1</i>	COLLAGEN, TYPE III, ALPHA-1	*120180
<i>CPE</i>	CARBOXYPEPTIDASE E	*114855
<i>CPEB4</i>	CYTOPLASMIC POLYADENYLATION ELEMENT-BINDING PROTEIN 4	
<i>CRY2</i>	CRYPTOCHROME 2	*603732
<i>CYP19A1</i>	CYTOCHROME P450, FAMILY 19, SUBFAMILY A, POLYPEPTIDE	*107910
<i>DNAAF1</i>	DYNEIN, AXONEMAL, ASSEMBLY FACTOR 1	*613190
<i>DYRK1A</i>	DUAL-SPECIFICITY TYROSINE PHOSPHORYLATION-REGULATED KINASE 1A	*600855

<i>EBF1</i>	EARLY B-CELL FACTOR 1	*164343
<i>ELN</i>	ELASTIN	*130160
<i>ENPP1</i>	ECTONUCLEOTIDE PYROPHOSPHATASE/PHOSPHODIESTERASE 1	*173335
<i>EPAS1</i>	ENDOTHELIAL PAS DOMAIN PROTEIN 1	*603349
<i>ESR1</i>	ESTROGEN RECEPTOR 1	*133430
<i>ESRRA</i>	ESTROGEN-RELATED RECEPTOR, ALPHA	*601998
<i>FABP2</i>	FATTY ACID-BINDING PROTEIN 2	*134640
<i>FABP4</i>	FATTY ACID-BINDING PROTEIN 4	*600434
<i>FFAR4</i>	FREE FATTY ACID RECEPTOR 4	*609044
<i>FGF21</i>	FIBROBLAST GROWTH FACTOR 21	*609436
<i>FLT4</i>	FMS-LIKE TYROSINE KINASE 4	*136352
<i>FOXC2</i>	FORKHEAD BOX C2	*602402
<i>FOXO1</i>	FORKHEAD BOX O1	*136533
<i>GATA2</i>	GATA-BINDING PROTEIN 2	*137295
<i>GCKR</i>	GLUCOKINASE REGULATORY PROTEIN	*600842
<i>GDF15</i>	GROWTH/DIFFERENTIATION FACTOR 15	*605312
<i>GDF3</i>	GROWTH/DIFFERENTIATION FACTOR 3	*606522
<i>GFRAL</i>	GDNF FAMILY RECEPTOR ALPHA-LIKE PROTEIN	*617837
<i>GHRL</i>	GROWTH HORMONE SECRETAGOGUE RECEPTOR LIGANDMOTILIN-RELATED PEPTIDE	*605353
<i>GHSR</i>	GROWTH HORMONE SECRETAGOGUE RECEPTOR	*601898
<i>GJA1</i>	GAP JUNCTION PROTEIN, ALPHA-1	*121014
<i>GPD1</i>	GLYCEROL-3-PHOSPHATE DEHYDROGENASE 1	*138420
<i>GPR26</i>	G PROTEIN-COUPLED RECEPTOR 26	*604847
<i>GPR82</i>	G PROTEIN-COUPLED RECEPTOR 82	*300748
<i>GPRC6A</i>	G PROTEIN-COUPLED RECEPTOR, FAMILY C, GROUP 6, MEMBER A	*613572
<i>GRAMD2B</i>	GRAM Domain Containing 2B	-
<i>GRB14</i>	GROWTH FACTOR RECEPTOR-BOUND PROTEIN 14	*601524
<i>GRIK1</i>	GLUTAMATE RECEPTOR, IONOTROPIC, KAINATE 1	*138245
<i>GRPR</i>	GASTRIN-RELEASING PEPTIDE RECEPTOR	*305670
<i>GSDMB</i>	GASDERMIN B	*611221
<i>GSK3A</i>	GLYCOGEN SYNTHASE KINASE 3-ALPHA	*606784

<i>GSK3B</i>	GLYCOGEN SYNTHASE KINASE 3-BETA	*605004
<i>GUCY2C</i>	GUANYLATE CYCLASE 2C	*601330
<i>H6PD</i>	HEXOSE-6-PHOSPHATE DEHYDROGENASE	*138090
<i>HDAC4</i>	HISTONE DEACETYLASE 4	*605314
<i>HGF</i>	HEPATOCYTE GROWTH FACTOR	*142409
<i>HIF1A</i>	HYPOXIA-INDUCIBLE FACTOR 1, ALPHA SUBUNIT	*603348
<i>HIPK2</i>	HOMEODOMAIN-INTERACTING PROTEIN KINASE 2	*606868
<i>HMGA2</i>	HIGH MOBILITY GROUP AT-HOOK 2	*600698
<i>HOXA1</i>	HOMEODOMAIN A1	*142955
<i>HOXA10</i>	HOMEODOMAIN A10	*142957
<i>HOXA2</i>	HOMEODOMAIN A2	*604685
<i>HOXA4</i>	HOMEODOMAIN A4	*142953
<i>HOXA5</i>	HOMEODOMAIN A5	*142952
<i>HOXA7</i>	HOMEODOMAIN A7	*142950
<i>HOXB4</i>	HOMEODOMAIN B4	*142965
<i>HOXB8</i>	HOMEODOMAIN B8	*142963
<i>HOXC13</i>	HOMEODOMAIN C13	*142976
<i>HOXC4</i>	HOMEODOMAIN C4	*142974
<i>HOXC8</i>	HOMEODOMAIN C8	*142970
<i>HOXD4</i>	HOMEODOMAIN D4	*142981
<i>IFI35</i>	INTERFERON-INDUCED PROTEIN 3	*600735
<i>IFT74</i>	INTRAFLAGELLAR TRANSPORT 74	*608040
<i>IL18</i>	INTERLEUKIN 18	*600953
<i>IL6</i>	INTERLEUKIN 6	*147620
<i>IL6R</i>	INTERLEUKIN 6 RECEPTOR	*147880
<i>INSIG2</i>	INSULIN-INDUCED GENE 2	*608660
<i>IRS1</i>	INSULIN RECEPTOR SUBSTRATE	147545
<i>IRX3</i>	IRROQUOIS HOMEODOMAIN PROTEIN 3	*612985
<i>ITGA9</i>	INTEGRIN, ALPHA-9	*603963
<i>KAT5</i>	LYSINE ACETYLTRANSFERASE 5	*601409
<i>KDM3A</i>	LYSINE DEMETHYLASE 3A	*611512

<i>KIRREL3</i>	KIRRE-LIKE NEPHRIN FAMILY ADHESION MOLECULE 3	*607761
<i>KLF16</i>	KRUPPEL-LIKE FACTOR 16	*606139
<i>KRAS</i>	KRAS PROTOONCOGENE	*190070
<i>LPIN1</i>	LIPIN 1	*605518
<i>LRP2</i>	LOW DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 2	*600073
<i>LRRC8A</i>	LEUCINE-RICH REPEAT-CONTAINING PROTEIN 8	*608360
<i>LYPLAL1</i>	LYSOPHOSPHOLIPASE-LIKE 1	*616548
<i>MAPK11</i>	MITOGEN-ACTIVATED PROTEIN KINASE 11	*602898
<i>MAPK12</i>	MITOGEN-ACTIVATED PROTEIN KINASE 12	*602399
<i>MAPK13</i>	MITOGEN-ACTIVATED PROTEIN KINASE 13	*602899
<i>MAPK14</i>	MITOGEN-ACTIVATED PROTEIN KINASE 14	*600289
<i>MC1R</i>	MELANOCORTIN 1 RECEPTOR	*155555
<i>MED13</i>	MEDIATOR COMPLEX SUBUNIT 13	*603808
<i>MEIS1</i>	MEIS HOMEODOMAIN 1	*601739
<i>MLXIPL</i>	MLX-INTERACTING PROTEIN-LIKE	*605678
<i>MMP19</i>	MATRIX METALLOPROTEINASE 19	*601807
<i>MRAP2</i>	MELANOCORTIN 2 RECEPTOR ACCESSORY PROTEIN 2	*615410
<i>MSX2</i>	MSH HOMEODOMAIN 2	*123101
<i>NBEA</i>	NEUROBEACHIN	*604889
<i>NCOA1</i>	NUCLEAR RECEPTOR COACTIVATOR 1	*602691
<i>NCOA3</i>	NUCLEAR RECEPTOR COACTIVATOR 3	*601937
<i>NDN</i>	NECDIN	*602117
<i>NEGR1</i>	NEURONAL GROWTH REGULATOR 1	*613173
<i>NEIL1</i>	ENDONUCLEASE VIII-LIKE 1	*608844
<i>NF1</i>	NEUROFIBROMIN 1	*613113
<i>NGEF</i>	NEURONAL GUANINE NUCLEOTIDE EXCHANGE FACTOR	*605991
<i>NMU</i>	NEUROMEDIN U	*605103
<i>NPY</i>	NEUROPEPTIDE Y	*162640
<i>NPY4R</i>	PANCREATIC POLYPEPTIDE RECEPTOR 1	*601790
<i>NR1D1</i>	NUCLEAR RECEPTOR SUBFAMILY 1, GROUP D, MEMBER	*602408
<i>NR2F2</i>	NUCLEAR RECEPTOR SUBFAMILY 2, GROUP F, MEMBER 2	*107773

<i>NR2F6</i>	NUCLEAR RECEPTOR SUBFAMILY 2, GROUP F, MEMBER 6	*132880
<i>NR3C1</i>	NUCLEAR RECEPTOR SUBFAMILY 3, GROUP C, MEMBER 1	*138040
<i>NTRK2</i>	NEUROTROPHIC TYROSINE KINASE, RECEPTOR, TYPE 2	*600456
<i>OGG1</i>	8-OXOGUANINE DNA GLYCOSYLASE	*601982
<i>OMA1</i>	OMA1 ZINC METALLOPEPTIDASE	*617081
<i>OSBPL8</i>	OXYSTEROL-BINDING PROTEIN-LIKE PROTEIN 8	*606736
<i>PANX1</i>	PANNEXIN 1	*608420
<i>PAX6</i>	PAIRED BOX GENE 6	*607108
<i>PBX1</i>	PRE-B-CELL LEUKEMIA TRANSCRIPTION FACTOR 1	*176310
<i>PDE11A</i>	PHOSPHODIESTERASE 11A	*604961
<i>PDE3B</i>	PHOSPHODIESTERASE 3B	*602047
<i>PER1</i>	PERIOD CIRCADIAN REGULATOR 1	*602260
<i>PIGC</i>	PHOSPHATIDYLINOSITOL GLYCAN ANCHOR BIOSYNTHESIS CLASS C PROTEIN	*601730
<i>PIK3CA</i>	PHOSPHATIDYLINOSITOL 3-KINASE, CATALYTIC, ALPHA	*171834
<i>PITPNM1</i>	PHOSPHATIDYLINOSITOL TRANSFER PROTEIN, MEMBRANE-ASSOCIATED, 1	*608794
<i>PNPLA2</i>	PATATIN-LIKE PHOSPHOLIPASE DOMAIN-CONTAINING PROTEIN 2	*609059
<i>PPARGC1A</i>	PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-GAMMA, COACTIVATOR 1, ALPHA	*604517
<i>PPARGC1B</i>	PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-GAMMA, COACTIVATOR 1, BETA	*608886
<i>PRDM16</i>	PR DOMAIN-CONTAINING PROTEIN 16	*605557
<i>PRDM2</i>	PR DOMAIN-CONTAINING PROTEIN 2	*601196
<i>PRKAA1</i>	PROTEIN KINASE, AMP-ACTIVATED, CATALYTIC, ALPHA-1	*602739
<i>PRKAA2</i>	PROTEIN KINASE, AMP-ACTIVATED, CATALYTIC, ALPHA-2	*600497
<i>PRKAB1</i>	PROTEIN KINASE, AMP-ACTIVATED, NONCATALYTIC, BETA-1	*602740
<i>PRKAB2</i>	PROTEIN KINASE, AMP-ACTIVATED, NONCATALYTIC, BETA-2	*602741
<i>PRKACA</i>	PROTEIN KINASE, cAMP-DEPENDENT, CATALYTIC, ALPHA	*601639
<i>PRKACB</i>	PROTEIN KINASE, cAMP-DEPENDENT, CATALYTIC, BETA	*176892
<i>PRKAG1</i>	PROTEIN KINASE, AMP-ACTIVATED, NONCATALYTIC, GAMMA-1	*602742
<i>PRKAG2</i>	PROTEIN KINASE, AMP-ACTIVATED, NONCATALYTIC, GAMMA-2	*602743
<i>PRKAG3</i>	PROTEIN KINASE, AMP-ACTIVATED, NONCATALYTIC, GAMMA-3	*604976
<i>PRKAR1A</i>	PROTEIN KINASE, cAMP-DEPENDENT, REGULATORY, TYPE I, ALPHA	*188830
<i>PRKAR2A</i>	PROTEIN KINASE, cAMP-DEPENDENT, REGULATORY, TYPE II, ALPHA	*176910

<i>PRKAR2B</i>	PROTEIN KINASE, cAMP-DEPENDENT, REGULATORY, TYPE II, BETA	*176912
<i>PROX1</i>	PROSPERO-RELATED HOMEODOMAIN 1	*601546
<i>PRRC2A</i>	PROLINE-RICH COILED-COIL PROTEIN 2A	*142580
<i>PTN</i>	PLEIOTROPHIN	*162095
<i>PYY</i>	PEPTIDE YY	*600781
<i>RARB</i>	RETINOIC ACID RECEPTOR, BETA	*180220
<i>RB1</i>	RB TRANSCRIPTIONAL COREPRESSOR 1	*614041
<i>RBP4</i>	RETINOL-BINDING PROTEIN 4	*180250
<i>RETN</i>	RESISTIN	*605565
<i>RGS2</i>	REGULATOR OF G PROTEIN SIGNALING 2	*600861
<i>RREB1</i>	RAS-RESPONSIVE ELEMENT BINDING PROTEIN	*602209
<i>RSC1A1</i>	REGULATORY SOLUTE CARRIER PROTEIN, FAMILY 1, MEMBER 1	*601966
<i>RSPO3</i>	R-SPONDIN 3	*610574
<i>SCD</i>	STEAROYL-CoA DESATURASE	*604031
<i>SCPEP1</i>	SERINE CARBOXYPEPTIDASE I	-
<i>SFRP1</i>	SECRETED FRIZZLED-RELATED PROTEIN 1	*604156
<i>SFRP5</i>	SECRETED FRIZZLED-RELATED PROTEIN 5	*604158
<i>SIRT1</i>	SIRTUIN 1	*604479
<i>SIRT6</i>	SIRTUIN 6	*606211
<i>SKP2</i>	S-PHASE KINASE-ASSOCIATED PROTEIN 2	*601436
<i>SLC13A5</i>	SOLUTE CARRIER FAMILY 13 (SODIUM-DEPENDENT CITRATE TRANSPORTER), MEMBER 5	*608305
<i>SLC2A4</i>	SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 4	*138190
<i>SLC35D3</i>	SOLUTE CARRIER FAMILY 35, MEMBER D3	*612519
<i>SLCO4C1</i>	SOLUTE CARRIER ORGANIC ANION TRANSPORTER FAMILY, MEMBER 4C1	*609013
<i>SNAP25</i>	SYNAPTOSOMAL-ASSOCIATED PROTEIN, 25-K	*600322
<i>SNRPN</i>	SMALL NUCLEAR RIBONUCLEOPROTEIN POLYPEPTIDE	*182279
<i>SREBF1</i>	STEROL REGULATORY ELEMENT-BINDING TRANSCRIPTION FACTOR 1	*184756
<i>STAB1</i>	STABILIN 1	*608560
<i>STAT3</i>	SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3	*102582
<i>STAT5A</i>	SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 5A	*601511
<i>STAT5B</i>	SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 5B	*604260

<i>STRA6</i>	STIMULATED BY RETINOIC ACID 6	*610745
<i>SYPL2</i>	SYNAPTOPHSIN LIKE	-
<i>TAF7L</i>	TATA BOX-BINDING PROTEIN-ASSOCIATED FACTOR 7-LIKE	*300314
<i>TBC1D1</i>	TBC1 DOMAIN FAMILY, MEMBER 1	*609850
<i>TBC1D4</i>	TBC1 DOMAIN FAMILY, MEMBER 4	*612465
<i>TBX15</i>	T-BOX TRANSCRIPTON FACTOR 15	*604127
<i>TGFB1</i>	TRANSFORMING GROWTH FACTOR, BETA-1	*190180
<i>TGM2</i>	TRANSGLUTAMINASE 2	*190196
<i>TMEM18</i>	TRANSMEMBRANE PROTEIN 18	*613220
<i>TNXB</i>	TENASCIN XB	*600985
<i>TRH</i>	THYROTROPIN-RELEASING HORMONE	*613879
<i>TRIM72</i>	TRIPARTITE MOTIF-CONTAINING PROTEIN 72	*613288
<i>TTR</i>	TRANSTHYRETIN	*176300
<i>TUB</i>	TUB BIPARTITE TRANSCRIPTION FACTOR	*601197
<i>TYK2</i>	TYROSINE KINASE 2	*176941
<i>UBE2E2</i>	UBIQUITIN-CONJUGATING ENZYME E2E 2	*602163
<i>UCP1</i>	UNCOUPLING PROTEIN 1	*113730
<i>UCP2</i>	UNCOUPLING PROTEIN 2	*601693
<i>VEGFA</i>	VASCULAR ENDOTHELIAL GROWTH FACTOR A	*192240
<i>VEGFC</i>	VASCULAR ENDOTHELIAL GROWTH FACTOR	*601528
<i>WDR13</i>	WD REPEAT-CONTAINING PROTEIN 13	*300512
<i>WNT10B</i>	WINGLESS-TYPE MMTV INTEGRATION SITE FAMILY, MEMBER 10B	*601906
<i>WNT11</i>	WINGLESS-TYPE MMTV INTEGRATION SITE FAMILY, MEMBER 1	*603699
<i>WNT4</i>	WINGLESS-TYPE MMTV INTEGRATION SITE FAMILY, MEMBER 4	*603490
<i>YWHAZ</i>	TYROSINE 3-MONOOXYGENASE/TRYPHTOPHAN 5-MONOOXYGENASE ACTIVATION PROTEIN, ZETA ISOFORM	*601288
<i>ZEB1</i>	ZINC FINGER E BOX-BINDING HOMEBOX 1	*189909
<i>ZMPSTE24</i>	ZINC METALLOPROTEINASE STE2	*606480
<i>ZNF423</i>	ZINC FINGER PROTEIN 423	*604557
<i>ZNRF3</i>	ZINC FINGER AND RING FINGER PROTEIN	*612062

Table S3. Genetic variants identified in the diagnostic gene panel. MAF = Minor allele frequency in gnomAD. Transcript isoforms: *BBS1*, NM_024649.5; *BBS2*, NM_031885.4; *BBS5*, NM_152384.3; *BBS9*, NM_001033604.1; *C8orf37*, NM_001363260.1; *CEP290*, NM_025114.4; *MC4R*, NM_005912.3; *MKS1*, NM_017777.4. VarSome: P (Pathogenic), LP (Likely pathogenic).

Patient	Gene	Nucleotide change	Amino acid change	SNP ID	MAF (%)	VarSome
1	<i>BBS1</i>	c.1169T>G	p.Met390Arg	rs113624356	0.1	LP
2	<i>BBS1</i>					
3	<i>BBS2</i>	c.1928G>A	p.Arg643His	rs532361142	0.004	LP
4	<i>BBS5</i>	c.551A>G	p.Asn184Ser	rs137853921	0.4	LP
5	<i>BBS9</i>	c.263C>T	p.Ser88Leu	rs749974697	0.002	LP
6	<i>C8orf37</i>	c.374+1G>C	-	rs974031657	0.0004	P
7	<i>CEP290</i>	c.3894dup	p.Lys1299*	rs761907569	0.0004	LP
8	<i>MC4R</i>	c.281G>A	p.Ser94Asn	rs772213710	0.0008	LP
9	<i>MCHR1</i>	c.86C>G	p.Pro29Arg	rs150937708	0.006	LP
10	<i>MKS1</i>	c.1298C>T	p.Thr433Met	rs755841031	0.009	LP
11	<i>MKS1</i>	c.827A>G	p.Asp276Gly	rs151023718	0.05	LP
12	<i>MKS1</i>	c.1349T>C	p.Ile450Thr	rs200865108	0.04	LP

Table S4. Genetic variants identified in candidate genes. MAF = Minor allele frequency in gnomAD. Transcript isoforms: *APOE*, NM_000041.4; *DNAAF1*, NM_178452.6; *ESR1*, NM_000125.3; *GHR*, NM_000163.5; *GUCY2C*, NM_004963.4; *NCOA2*, NM_001321703.2; *NPC1*, NM_000271.5; *PDX1*, NM_000209.4; *RYR1*, NM_000540.3; *STRA6*, NM_001199042.2; *ZNF423*, NM_001271620.2. VarSome: P (Pathogenic), LP (Likely pathogenic).

Patient	Gene	Nucleotide change	Amino acid change	SNP ID	MAF (%)	VarSome
13	<i>APOE</i>	c.305C>G	p.Pro102Arg	rs11083750	0.003	LP
14	<i>DNAAF1</i>	c.715del	p.Ser239AlafsTer12	rs758650222	-	P
15	<i>ESR1</i>	c.805C>T	p.Arg269Cys	rs142712646	0.09	LP
16						
17						
18	<i>GHR</i>	c.686G>A	p.Arg229His	rs6177	0.1	LP
19						
20	<i>GHR</i>	c.718T>C	p.Tyr240His	rs143814221	0.03	LP
21	<i>GUCY2C</i>	c.2662del	p.Arg888GlyfsTer4	rs764325331	0.001	LP
22						
23	<i>NCOA2</i>	c.4366G>T	p.Glu1456Ter	rs1161802201	0.0004	P
24	<i>NPC1</i>	c.665A>G	p.Asn222Ser	rs55680026	0.3	P
25						
26	<i>NPC1</i>	c.3742_3745del	p.Leu1248ValfsTer3	rs774943545	0.003	P

26	<i>NPC1</i>	c.2974G>T	p.Gly992Trp	rs80358254	-	P
27	<i>PDX1</i>	c.97C>A	p.Pro33Thr	rs192902098	0.3	LP
28	<i>RYR1</i>	c.14524G>A	p.Val4842Met	rs193922879	0.008	LP
23	<i>RYR1</i>	c.5602C>G	p.Pro1868Ala	rs780420316	0.001	LP
29	<i>RYR1</i>	c.1807T>C	p.Cys603Arg	rs769492466	0.0008	LP
30	<i>RYR1</i>	c.7025A>G	p.Asn2342Ser	rs147213895	0.1	P
31	<i>RYR1</i>	c.2697C>A	p.Asn899Lys	rs201401814	0.004	P
32	<i>STRA6</i>	c.1684G>A	p.Gly562Ser	rs910950973	-	LP
33	<i>ZNF423</i>	c.172A>G	p.Met58Val	rs150427822	0.006	LP

Table S5. List of diagnostic and candidate genes for which genetic variants were identified in obese patients. OMIM number, gene-phenotype relationship as from OMIM, OMIM reference, and protein localization as from UniProt are reported for each gene.

Gene	OMIM	Gene-phenotype relationship	Reference	Protein localization
<i>APOE</i>	107741	Obesity phenotype	107741	Extracellular region
<i>BBS1</i>	209901	Bardet-Biedl syndrome 1	257220	BBSome complex
<i>BBS2</i>	615981	Bardet-Biedl syndrome 2	606151	BBSome complex
<i>BBS5</i>	615983	Bardet-Biedl syndrome 5	603650	BBSome complex
<i>BBS9</i>	615986	Bardet-Biedl syndrome 9	607968	BBSome complex
<i>C8orf37</i>	614477	Bardet-Biedl syndrome 21	617406	Base of the primary cilium, cytoplasm
<i>CEP290</i>	610142	Bardet-Biedl syndrome 14	615991	Centriole
<i>DNAAF1</i>	613190	Ciliary dyskinesia, primary, 13	613193	Cilium, cytoplasm, cytoskeleton
<i>ESR1</i>	133430	Estrogen resistance	615363	Plasma membrane, nucleus, and cytoplasm
<i>GHR</i>	600946	Laron dwarfism	262500	Plasma membrane
<i>GUCY2C</i>	601330	Obesity phenotype	601330	Plasma membrane and endoplasmic reticulum
<i>MC4R</i>	618406	Obesity (BMIQ20)	155541	Plasma membrane
<i>MCHR1</i>	601751	Obesity phenotype	601751	Cell membrane
<i>MKS1</i>	609883	Bardet-Biedl syndrome 13	615990	Basal body
<i>NCOA2</i>	601993	Obesity phenotype	601993	Nucleus
<i>NPC1</i>	607623	Niemann-Pick disease, type C1	257220	Endosome and lysosome
<i>PDX1</i>	600733	MODY, type IV	606392	Cytoplasm and nucleus
<i>RYR1</i>	180901	Central core disease	117000	Sarcoplasmic reticulum
<i>STRA6</i>	610745	Microphthalmia, syndromic 9	601186	Plasma membrane
<i>ZNF423</i>	604557	Impaired adipogenesis	604557	Nucleus

Table S6. Deleterious genetic variants identified in clinically followed patients. MAF = Minor allele frequency in gnomAD. Transcript isoforms: *BBS9*, NM_001033604.1; *APOE*, NM_000041.4; *GHR*, NM_000163.5; *PDX1*, NM_000209.4; *ZNF423*, NM_001271620.2. VarSome: LP (Likely pathogenic).

Patient	Gene	Nucleotide change	Amino acid change	SNP ID	MAF (%)	VarSome
5	<i>BBS9</i>	c.263C>T	p.Ser88Leu	rs749974697	0.002	LP
13	<i>APOE</i>	c.305C>G	p.Pro102Arg	rs11083750	0.003	LP
20	<i>GHR</i>	c.718T>C	p.Tyr240His	rs143814221	0.03	LP
27	<i>PDX1</i>	c.97C>A	p.Pro33Thr	rs192902098	0.3	LP
33	<i>ZNF423</i>	c.172A>G	p.Met58Val	rs150427822	0.006	LP

Materials and Methods

While the molecular structures of the regions of interest in *BBS9*, *GHR*, and *APOE* proteins were solved experimentally, we used their respective high-confidence alphafold models [57,58] to make up for the missing residues in the solved structures. The alphafold models were super imposed to the solved structures in PyMOL v2.4.1 [62], and the regions out of our interest were trimmed out from the model. In silico mutagenesis of each variant was performed using the highest-ranked rotamer provided by the “mutagenesis” function of PyMOL [62].

Molecular dynamics simulations were carried out on both wildtype and mutant *BBS9*, *GHR*, *APOE* using Gromacs v2019.3 package [56]. Each protein molecule was placed in a triclinic box with a minimum 1.2 nm spacing on each face. The system was then solvated using TIP3P water molecules, neutralized with Na⁺/Cl⁻ and energy minimized via gradient descent ($F_{\max} = 100 \text{ kJ mol}^{-1} \text{ nm}^{-1}$, $n_{\text{steps}} = 50'000$, $\text{step_size} = 0.001$). The minimized systems were subjected to two subsequential equilibration steps position-restrained molecular dynamics in the NVT and NPT ensembles, 100 ps each. Reference temperature of 300 K and pressure of 1 bar were imposed, respectively. Finally, a molecular dynamics production run was performed for 100ns with a 2 fs integration step size in both wildtype and mutants.

The molecular dynamics analysis was performed by first computing the Root Mean Squared Deviation (RMSD) of the backbone atoms, relative to the structure in the minimized and equilibrated system. Highly flexible interdomain loops and termini were excluded from the RMSD due to their large movements during the simulation. The RMSD computation was then followed by Root Mean Squared Fluctuations (RMSF) to compute the fluctuations of the C- α atoms on a per residue basis. To estimate the compactness of the structure during the simulation, the radius of gyration, the number of hydrogen bonds, and the extent of secondary structures were computed.

Results

APOE

The variant is located in the single β -strand connecting H2 to H3 (the loop’s backbone conformations fall into the β region of the Ramachandran plot of the N-terminal domain [59]), and replaces proline with a large charged amino acid – arginine (Figure S1). The mutation causes the region nearby the mutation (the loop comprising residues 98-104) to exhibit larger fluctuations than the wildtype (Figure S2). On the other hand, the other peak that is apparent in the RMSF plot comprises residues 140-150 (which connect H3 to H4 and are responsible for heparin binding), and shows a smaller fluctuation in the mutant [60]. The difference in RMSF concerning the first peak (residues 98-104) is $\sim 0.17 \text{ nm}_2$ and may in part be linked to a

disruption of the *apoE* N-terminal domain activity. The RMSD scores (Figure S3) and the molecular dynamics movies provide evidence on the stability of both structures throughout the 100ns simulation. For APOE, the alphafold model was superposed to the structure provided by PDB entry 1BZ4, and the regions out of interest were trimmed out.

GHR

RMSD for both structures, oscillated between ~0.1-0.2nm throughout the simulation, providing evidence on the stability of the folded structure (Figure S4).

The p.Tyr240His variant replaces tyrosine (polar non-charged) with histidine (polar charged), introducing a positive charge into a positively charged region (R231, K233) (Figure S5). By using comparative molecular dynamic simulations between the wildtype and mutant, we were able to observe a movement of the loop comprising residues 234-238, in the mutant. In the wildtype, Y240 – which acts as a H-bond acceptor - is part of a hydrogen bonding network (Figure S5), involving E193, R231, and K233, making it stable throughout the 100ns simulation. On the other hand, in the mutant, histidine was not able to form stable hydrogen bonds with the neighboring residues due to the repulsive forces between the positively charged groups of R231, K233 and H240 (Figure S6). The fluctuations observed in residues 234-238 (in proximity to the hGH:receptor interface (PDB entry 1AXI), and including another positively charged residue - R235) (Figure S7) may be a consequence of this variant and may affect the hGH:receptor interface (PDB entry 1AXI). Overall, the introduction of histidine in place of tyrosine 240, despite having similar side chains in terms of size, is able to disrupt the neighboring region due to its positively charged side chain and can alter the ability of the receptor to bind the hGH.

For GHR, the alphafold model was superposed to the structure provided by PDB entry 1AXI, and the regions out of interest were trimmed out.

BBS9

The p.Ser88Leu variant replaces serine (polar) with leucine (hydrophobic), and is located in the loop connecting the A and B strands in blade $\beta 2$ of BBS9 propeller domain, which is in the opposite end of the interface binding to the rest of BBSome complex [61,63]. In the wildtype GLN166 prefers hydrogen bonding with ASP165 and SER88, where the latter acts as a H-bond donor, instead of ARG149 (Figure S8), while in the mutant, the introduction of the hydrophobic LEU88, causes GLN166 to change conformation, and to form two hydrogen bonds with ARG149 (Figure S9). Despite the mutation doesn't seem to affect the overall folding of the structure, the H-bond network appears to be at least in part disrupted by the introduction of the hydrophobic leucine. The RMSD score of both wildtype and mutant (Figure S10) adheres to an invariant behavior, with fluctuations in the range of ~0.1nm. From the RSMF (Figure S11) plot, two large peaks are observed, corresponding to the loop region connecting the C and D strands of blade $\beta 1$ and the helix structure to the D strand of blade $\beta 4$. In the second peak, a difference of ~0.1nm is also observed between the wildtype and mutant (the mutant possessing the larger fluctuations). However, more work is needed to correctly address the pathogenicity of the BBS9 S88L variant at the structural level.

For BBS9, the alphafold model was superposed to the structure provided by PDB entry 4YD8, and the regions out of interest were trimmed out.

Figure S1. The superposed structures of wildtype and mutant APOE. The mutant arginine at position 102 is highlighted in orange, and the wildtype proline is highlighted in purple.

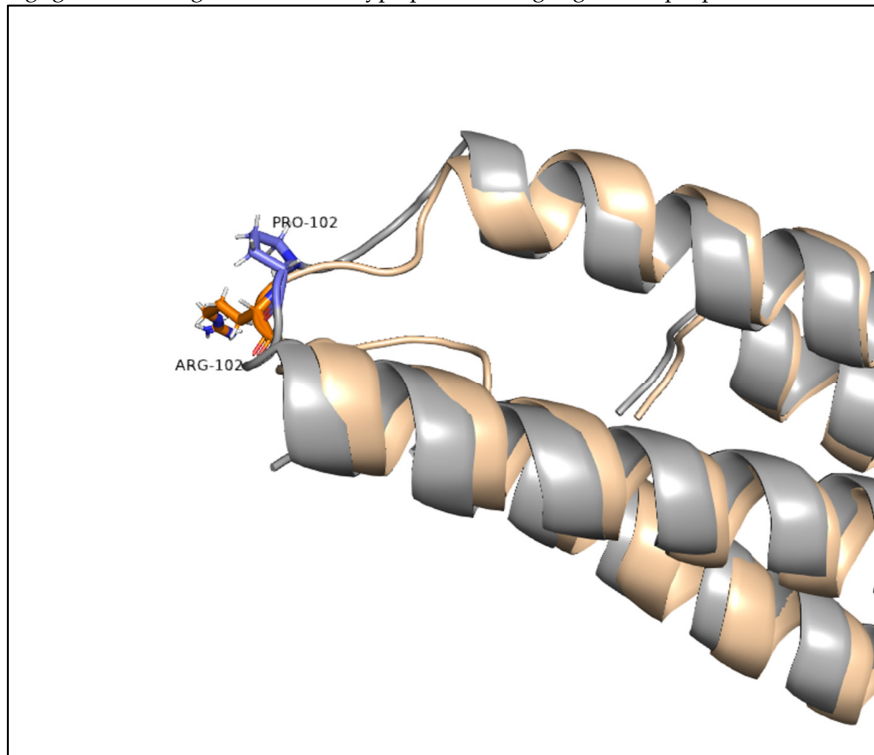


Figure S2. RMSF plots of wildtype and mutant APOE.

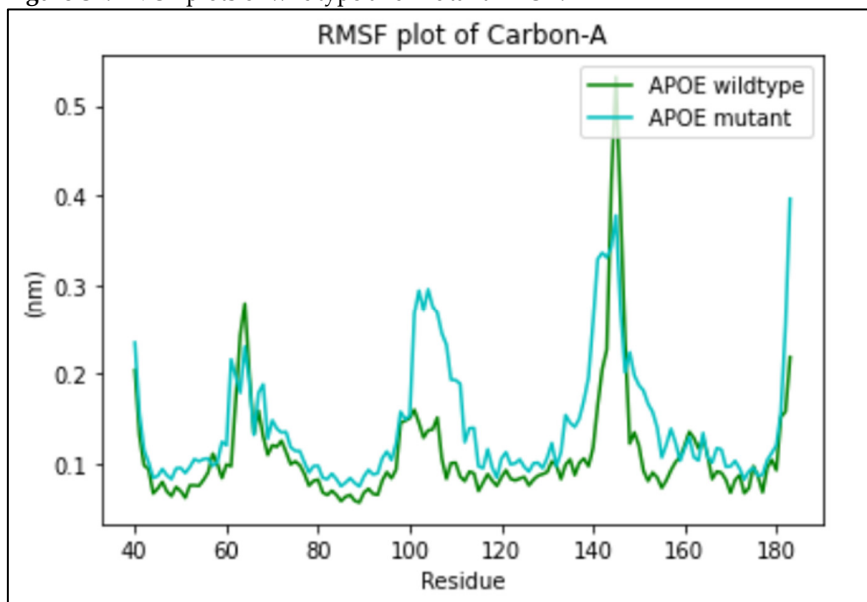


Figure S3. RMSD plots of wildtype and mutant APOE.

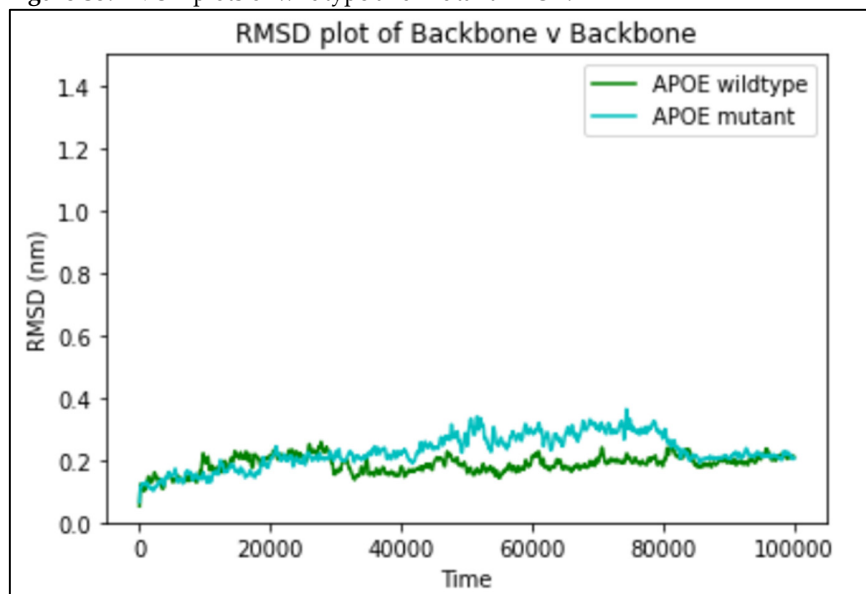


Figure S4. RMSD plots of wildtype and mutant GHR.

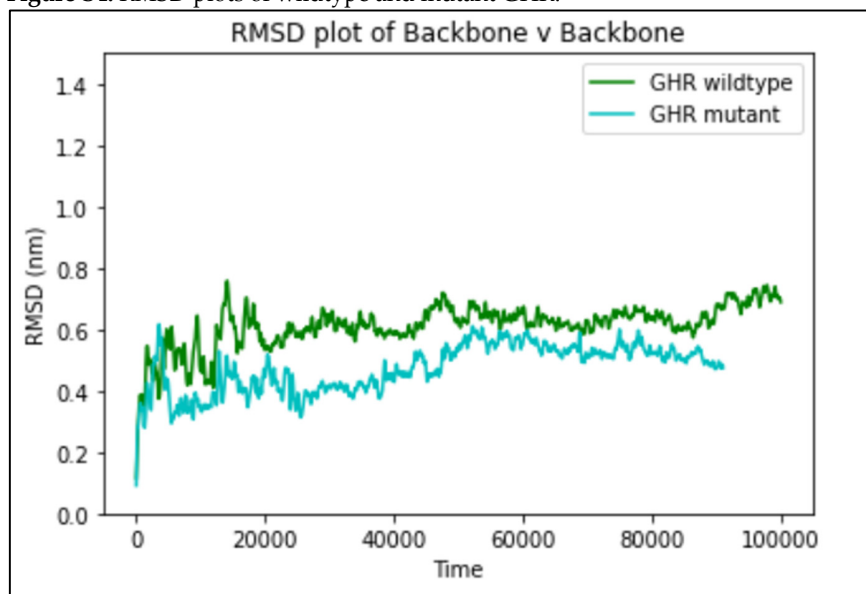


Figure S5. Wildtype GHR hydrogen bond network neighboring the mutation site.

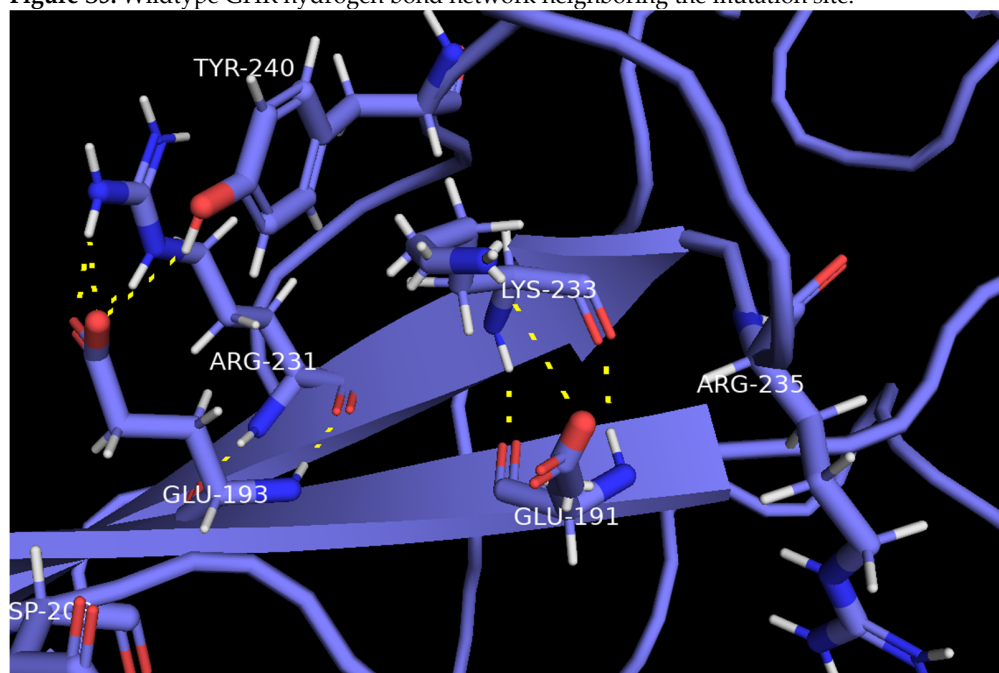


Figure S6. Mutant GHR hydrogen bond network disruption by the mutant.

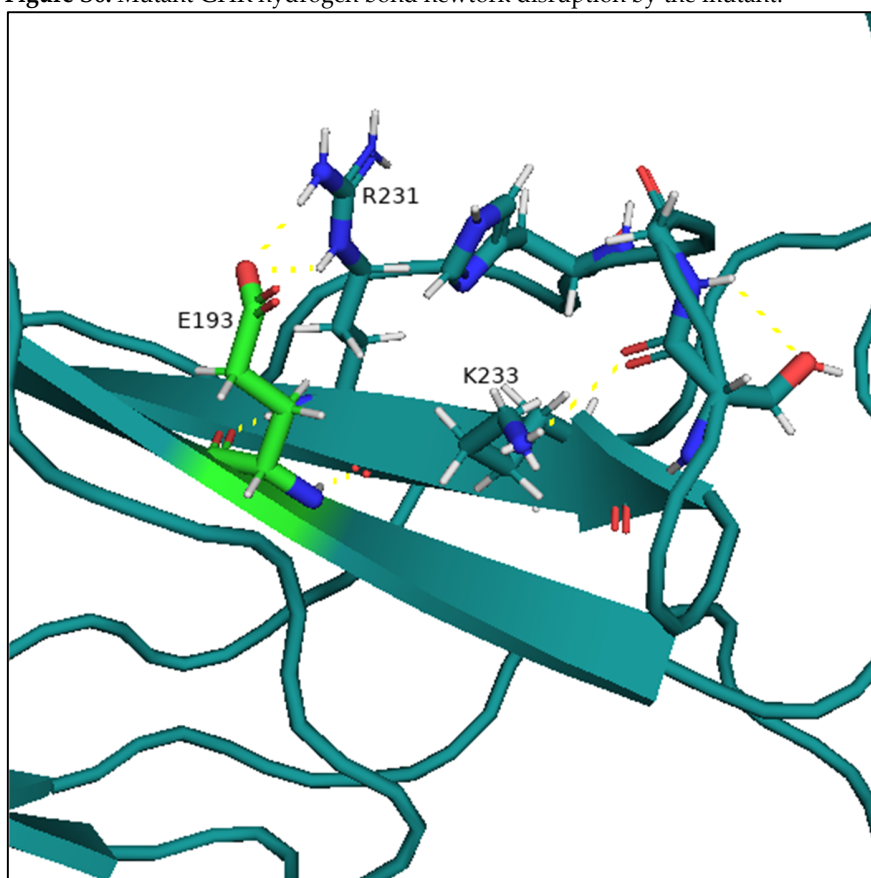


Figure S7. RMSF plots of wildtype and mutant GHR.

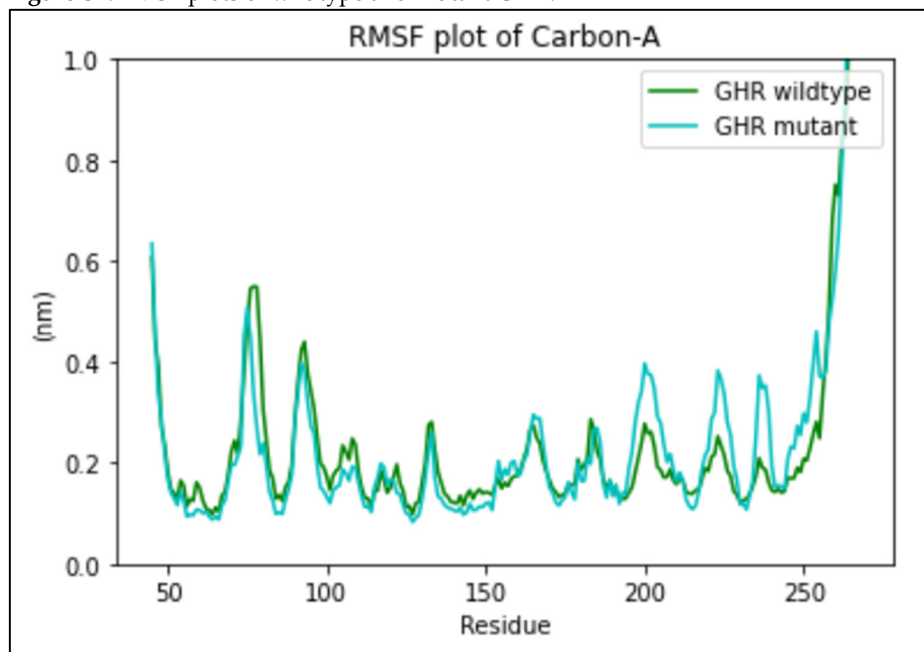


Figure S8. Wildtype structure of BBS9, serine 88 and glutamine 166 are highlighted in yellow.

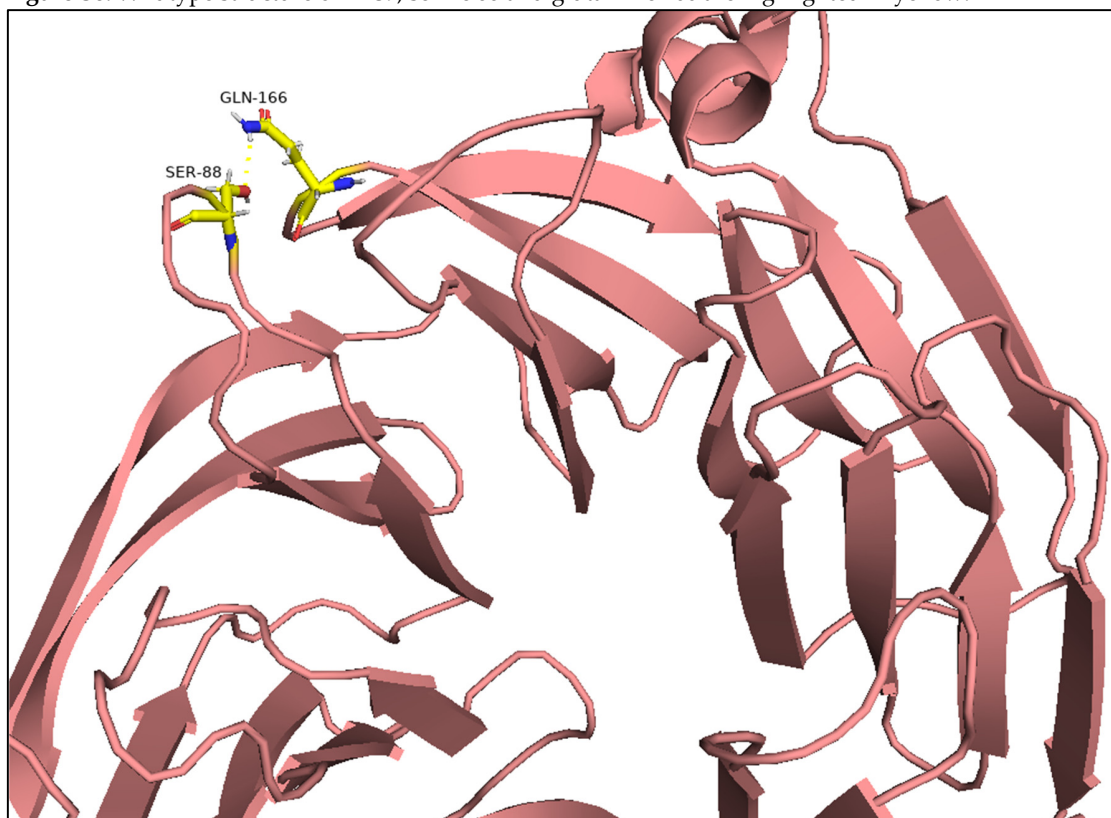


Figure S9. Mutant structure of BBS9, serine at position 88 is replaced by leucine, which is hydrophobic and is excluded from the hydrogen bond network formed by serine 88, glutamine 166, and arginine 149.

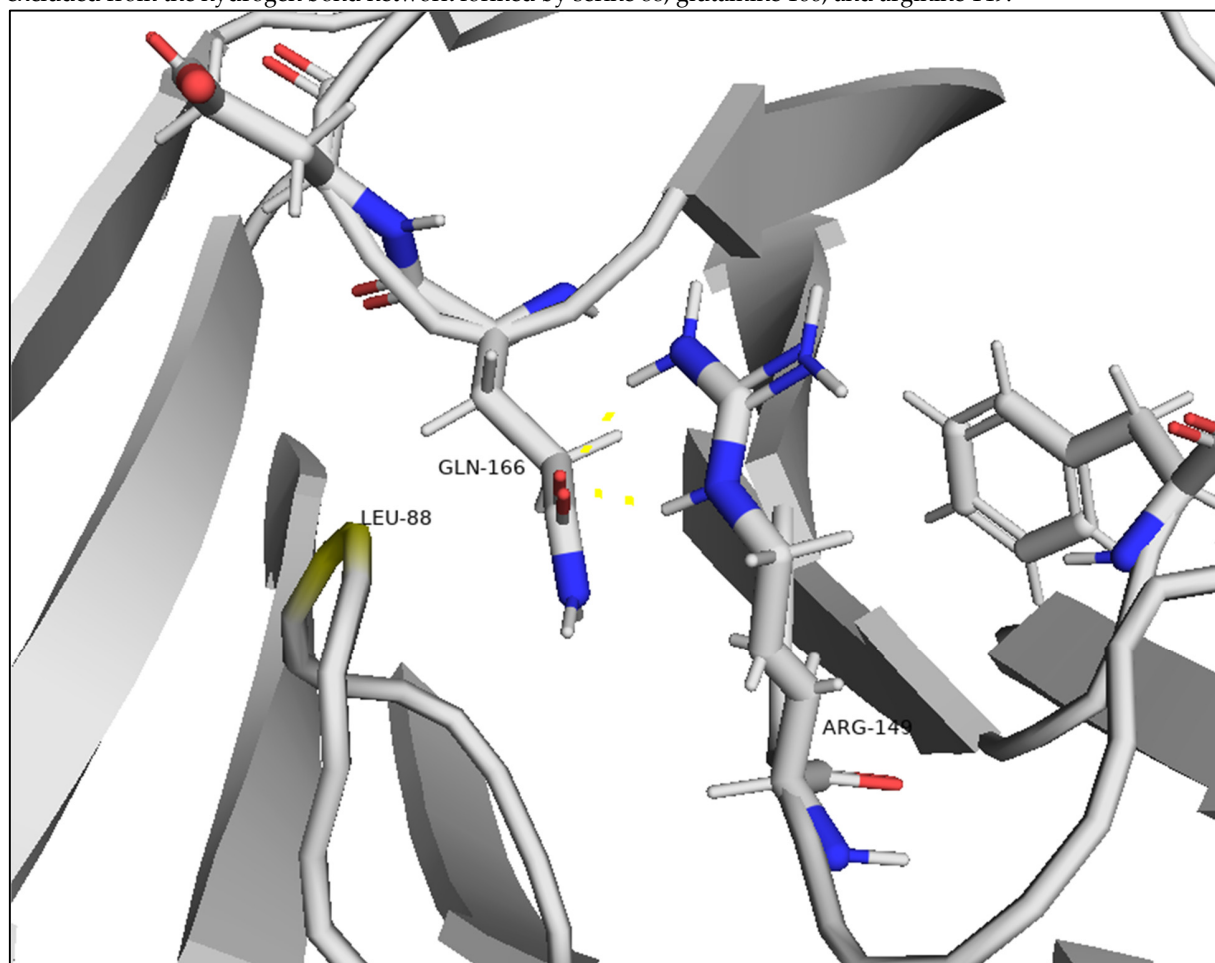


Figure S10. RMSD plots of wildtype and mutant BBS9.

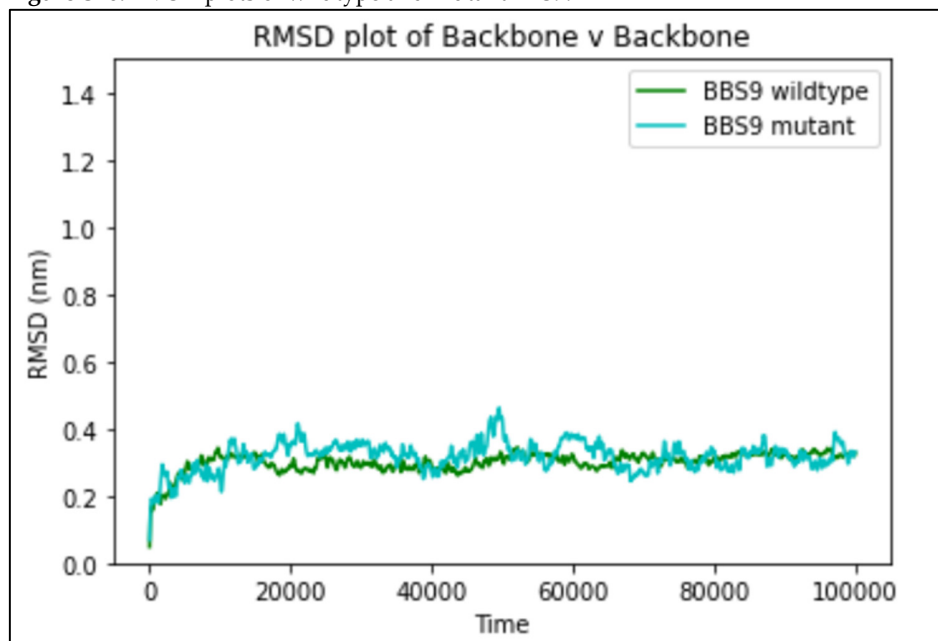


Figure S11. RMSF plots of wildtype and mutant BBS9.

