SUPPLEMENTARY MATERIALS

Clinical and biochemical features of the five FHBL kindreds - Clinical features of each proband/kindred are described herein. Proband FHBL-36 (subject II.2 in Fig. S1*A*) was admitted to hospital for the presence of chronic hepatitis type C and elevation of serum liver enzymes (Table 1) [aspartate aminotransferase (AST) 45 unit/liter, alanine aminotransferase (ALT) 89 unit/liter]. Mother of the proband (I.2) had lipid profile inconsistent with the diagnosis of FHBL (Table 1), probably because of the presence of other factors (*e.g.* the subject having sub-clinical thyroid dysfunction) that increase plasma LDL and apoB-100. Liver biopsy showed massive hepatic steatosis with mild signs of chronic inflammation. Proband FHBL-39 (subject III.2 in Fig. S1*B*) was diagnosed for the presence of FHBL at 18 years old with no elevation of serum liver enzyme (AST 11 unit/liter, ALT 19 unit/liter). Proband FHBL-44 (subject II.1 in Fig. S1*C*) was type 1 diabetic and anorexia nervosa (BMI =14.3 Kg/cm2) at age of nine, with mild elevation of liver enzymes (AST 47 unit/liter, ALT 37 unit/liter) and very low plasma levels of TC, LDL-C, and apoB. Father of proband FHBL-44 was diagnosed as heterozygous and had fatty liver and moderately elevated liver enzymes (see Table 1). Proband FHBL-45 (subject III.1 in Fig. S1*D*) had low plasma levels of TC, LDL-C and apoB at age 34, as well as mild elevation of liver enzymes (Table 1) (AST 31 unit/liter, ALT 68 unit/liter). FHBL-45 was also a carrier of H63D mutation in the *HFE* gene (hereditary hemochromatosis). Mother of proband FHBL-45 (subject II.2 in Fig. S1*D*) and another family member of the maternal line (subject II.3 in Fig. S1*D*) had low plasma LDL- C, and moderately elevated liver enzymes (Table 1). Proband FHBL-46 was diagnosed fatty liver disease and gallstones at age of 28 and showed FHBL (Table 1). He had a persistent mild elevation of serum liver enzymes (Table 1) and severe hepatic steatosis, and was negative for mutations in the *HFE* gene. Although varied considerably among these FHBL individuals, the plasma levels of LDL-C and apoB were invariably below 50 mg/dl and 40 mg/dl, respectively, which were similar to FHBL subjects carrying truncating mutations in *APOB* (TC = 94.0 ± 20.0 mg/dl; LDL-C = 32.9 ± 13.7 mg/dl; apoB = 22.9 ± 8.9 mg/dl). Analysis of apoB in probands' plasma lipoproteins separated by density gradient ultracentrifugation failed to detect truncated apoB proteins (data not shown).

Figure S1. **Five nonsynonymous nontruncating *APOB* gene mutations.** *Top*, pedigree of G945S (*A*), G912D (*B*), L324M (*C*), and A31P (*D*) kindreds. The *roman numerals* designate the generation numbers and the individual subjects in each generation are identified by *Arabic numerals*. The *arrows* indicate probands. *Middle*, nucleotide sequence encompassing mutations in genomic DNA of respective heterozygous FHBL subjects. Encoded amino acids are presented along with the nucleotide sequences. The positions of mutated nucleotides are underlined, and the resulting amino acid substitution is indicated below. *Bottom*, electropherogram tracings of the respective nucleotide sequences. Positions of mutated nucleotides are indicated by an *arrow*. Codon G912 lies at the junction between exon 18 and exon 19. Sequences of intron 18 are shown in lower case (panel *B*). Pedigree for FHBL proband carrying the G275S mutation is unavailable. Codon G275 lies at the junction between exon 8 and exon 9 (not shown).

Supplementary TABLE 1 Sequences of primers used for mutagenesis for generating FHBL apoB mutants

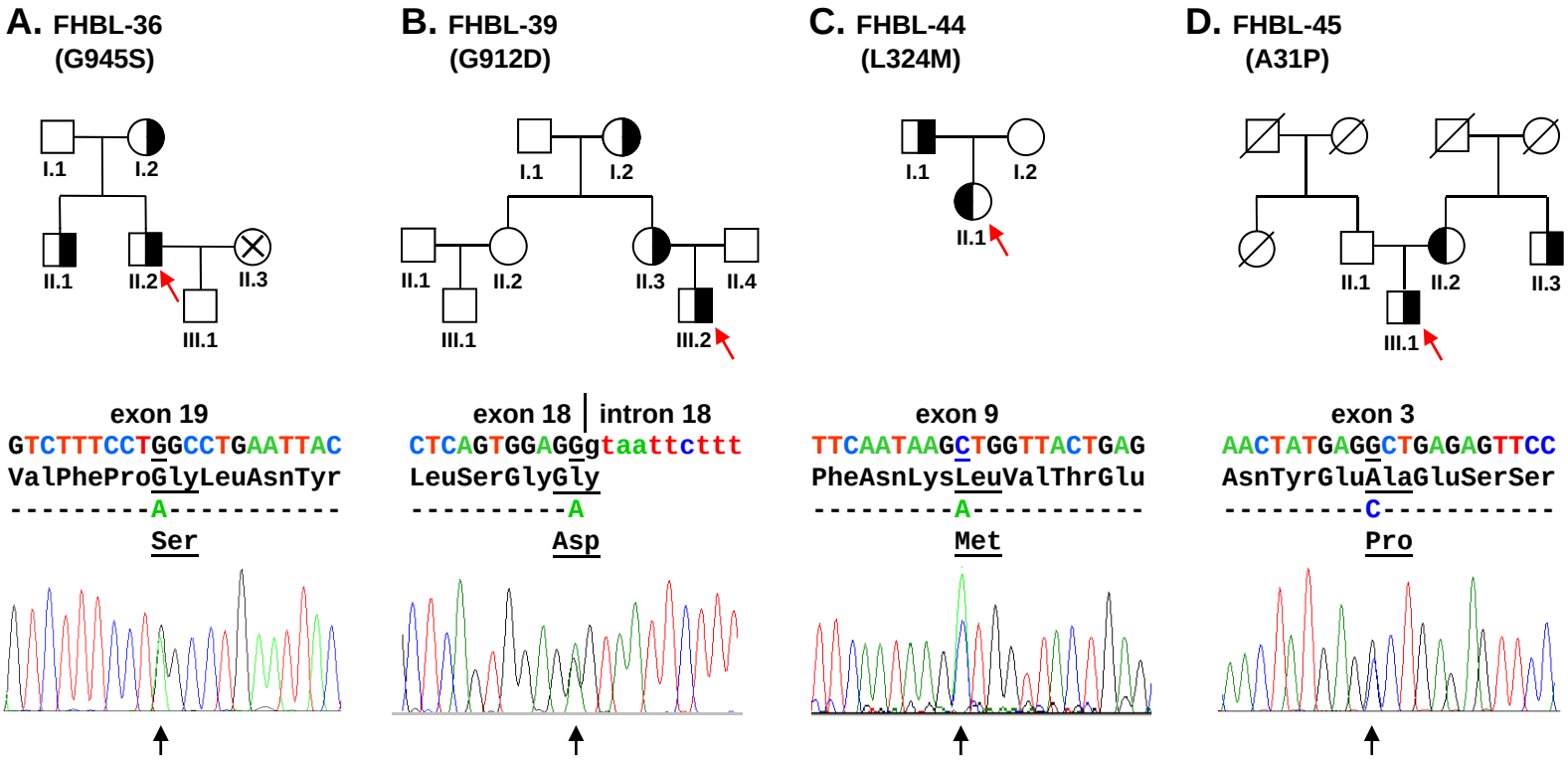
Primers	Sequence
pB48-A31P	5’ C ACA TAC AAC TAT GAG ***C****CT* GAG AGT TCC AGT GG 3’ (forward) 5’ CC ACT GGA ACT CTC *AG****G*** CTC ATA GTT GTA TGT G 3’ (reverse)
pB48-G275S	5’ C CGC TTC TTT GGT GAA ***A****GT* ACT AAG AAG ATG GGC C 3’(forward) 5’ G GCC CAT CTT CTT AGT *AC****T*** TTC ACC AAA GAA GCG G 3’(reverse)
pB48-L324M	5’ GCT AAT CTC TTC AAT AAG ***ATG*** GTT ACT GAG CTG AGA GG 3’(forward) 5’ CC TCT CAG CTC AGT AAC *CA****T*** CTT ATT GAA GAG ATT AGC 3’(reverse)
pB48-G912D	5’ AAG CTG CTC AGT GGA *GA****C*** AAC ACA TTA CAT TTG G 3’ (forward) 5’ C CAA ATG TAA TGT GTT *G****T****C* TCC ACT GAG CAG CTT 3’ (reverse)
pB48-G945S	5’ C AAG CAA GTC TTT CCT ***A****GC* CTG AAT TAC TGC ACC 3’ (forward) 5’ GGT GCA GTA ATT CAG *GC****T*** AGG AAA GAC TTG CTT G 3’ (reverse).

The mutated nucleotides are indicated in boldface. Codons specifying for amino acid changes are underlined.

Supplementary TABLE 2 Sequences of primers used for real-time RT-PCR (*Rattus norvegicus*)

Gene	Accession No.	Forward Primers (5' to 3')	Reverse Primers (5' to 3')
Acaca	NM_022193	TCCAGATGGCCGAGATGTCATTGT	TGACGGATTTCTTCTGCCAGTCCA
Cpt1a	NM_031559	AGACCGTGAGGAACTCAAACCCAT	CACAACAATGTGCCTGCTGTCCTT
Ppia	NM_017101	GTCCATGGCAAATGCTGGACCAAA	CAAAGACCACATGCTTGCCATCCA
Dgat1	NM_053437	GGCATTCACAGCAATGATGGCTCA	CCACACAGCTGCATTGCCATAGTT
Dgat2	NM_001012345	TGTCACCTGGCTCAACAGATCCAA	TATCAGCCAGCAGTCAGTGCAGAA
Fasn	NM_017332	TGGAGAAGCCCAGGAACAACTCAT	ACCGAGTAATGCCGTTCAGTTCCT
Lpin1	NM_001012111	GCAATTTGCCGACAACCCTGCTAT	AGGAGCTGCTGTTGTCCAGTTGTA
Lpin2	NM_001108236.1	ATGGCTTGTTGCAGTGTCACCTTG	ACTGATGCAACACTGATGGAGGGA
Lpin3	NM_001014184	TTTGACACCCTGGTTTGAGCTTGC	GTCAACTTGCAGCCCTTTGTTGGA
Nr1h3	NM_031627	AGAACTTCGTCCACAGAAGCGGAA	ATGTAGCGTGCTCCCTTGATGACA
Mttp	NM_001107727	AAGGCCAATATGGACATCCAGGGT	TGGTTATTACCACAGCCACCCGAT
Ppargc1a	NM_031347	GCACTCAGAACCATGCAAACCACA	TTGGTGTGAGGAGGGTCATCGTTT
Ppargc1b	NM_176075	AGCAAGCTCTGATGCTCTGAAGGA	ACCGAAGTGAGGTGCTTATGCAGT
Ppara	NM_013196	TTGTGACTGGTCAAGCTCAGGACA	TCCACCATGTTGAATGGTTGTGGC
Scd1	NM_139192	TTTCTTCTCTCACGTGGGTTGGCT	TCACCAGCTTCTCAGCTTTCAGGT
Srebf1	XM_213329	ATCTCCTGGAGCGAGCATTGAACT	AGCCATGCTGGAACTGACAGAGAA

Acaca, ACC1; *Ppia*, cyclophilin A; *Nr1h3*, LXRα; *Srebf1*, SREBP-1c.


A. FHBL-36
(G945S)
I.1
I.2
II.1
II.2
II.3
III.1
exon 19
GTCTTTCCTGGCCTGAATTAC
ValPheProGlyLeuAsnTyr
---------A----------
Ser
B. FHBL-39
(G912D)
I.1
I.2
II.1
II.2
II.3
II.4
III.1
III.2
exon 18 | intron 18
CTCAGTGGAGGgtaattcttt
LeuSerGlyGly
----------A
Asp
C. FHBL-44
(L324M)
I.1
I.2
II.1
exon 9
TTCAATAAGCTGGTTACTGAG
PheAsnLysLeuValThrGlu
---------A----------
Met
D. FHBL-45
(A31P)
II.1
II.2
II.3
III.1
exon 3
AACTATGAGGCTGAGAGTTCC
AsnTyrGluAlaGluSerSer
---------C----------
Pro