Supplement Materials

Supplement 1:

Whole-exome sequencing service provided by Macrogen Inc. (Seoul, South Korea), using the SureSelect V6-Post (Agilent Technologies, Santa Clara, CA). The paired-end of 150 bp sequencing was performed on the Illumina NovaSeq 6000 platform (Illumina, San Diego, CA). Each target base had at least 20X coverage, while the average exome had more than 100X coverage.

The sequence reads were mapped to the hg19/CRCh37 human reference genome by the Burrows-Wheeler Aligner tool (BMA.v0.07.12) and then marked the duplicates by Picard. Genome Analysis Tool Kit (GATK) and Samtools were employed to identify and detect single nucleotide variants (SNVs) and short insertions/deletions (Indels). All the false positive comprise variants that have depth read lower than 20× were screened and discarded for quality control. Short indels in the repeat areas and those within 10 bp of the beginning and end of the read were also removed. The residual variants were filtered from the public databases including 1,000 Genomes and Exome Aggregation Consortium (ExAC) and annotated using the ANNOVAR program. To identify the pathogenic variants that may cause metabolic abnormalities in the patient, the rare (minor allele frequency > 0.01) or novel variants in the Hyperammonemia and Urea Cycle Disorder panel: *ACADM, ACADS, ACADVL, ALDH18A1, ARG1, ASL, ASS1, ATP5F1E, ATPAF2, BCKDHA, BCKDHB, BCS1L, BTD, CA5A, CPS1, CPT1A, CPT2, DBT, DLD, ETFA, ETFB, ETFDH, GLUD1, GLUL, HADHA, HADHB, HCFC1, HLCS, HMGCL, HMGCS2, IVD, MCCC1, MCCC2, MMAA, MMAB, MMACHC, MUT, NAGS, OAT, OTC, PC, PCCA, PCCB, PYY, SLC22A5, SLC25A13, SLC25A15, SLC25A20, SLC7A7, SUCLA2, SUCLG1, TMEM70, TTC19, TUFM, UQCRB, UQCRQ*.

Sanger sequencing was used to validate the presence of variants in the patient and her family members. Polymerase chain reaction (PCR) was conducted with specific primers and synthesized by PHUSA Biochem Company (F: 5'-CCCTCTTCTGAGTGCATGG-3'; R: 5'-CGTGACCTTTGGGAGAATG-3').

The purified PCR product was sequenced in ABI 3500 Genetic Analyzer using BI Prism BigDye Terminator Cycle Sequencing Kit Version 3.1 in the forward and reverse direction (Applied Biosystems, Waltham, Massachusetts, USA).

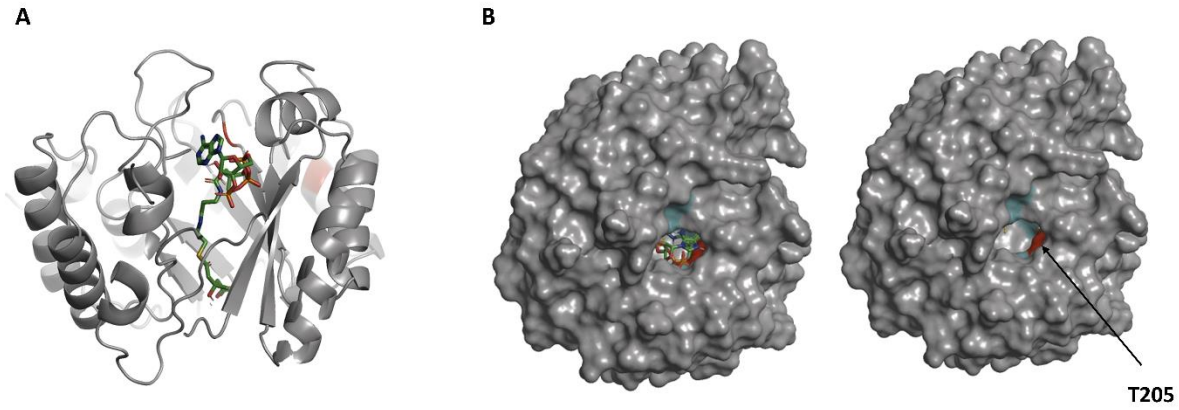

Figure S1. The model of the human HMGCL with its ligand. (**A**) Interaction of enzyme 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL) with ligand, HMGC, in vertical cut. (**B**) Human HMGCL surface representation with pocket cavity shown with and without ligand. T205 residue is indicated in red and neighbor residues in blue (PDB id: 2CW6)

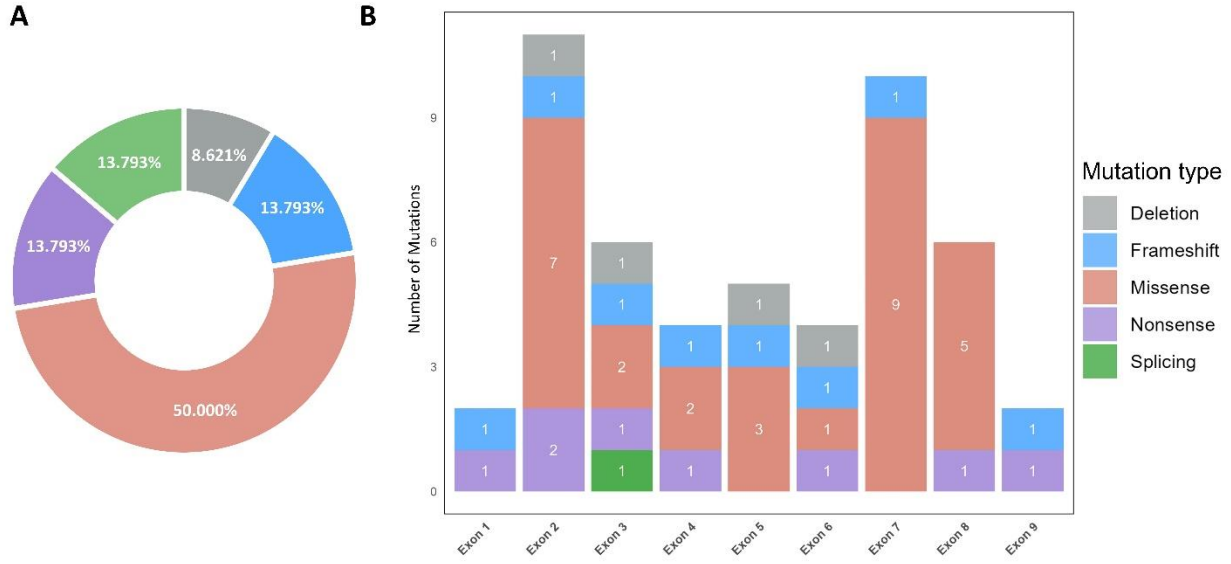

Figure S2. The graphic of reported *HMHCL* mutations. (**A**) The proportion of mutations is according to the type. (**B**) The number of mutations found in exons of the *HMGCL* gene