TMF: Systematic profiling and characterization of transcripts that are associated with quantitative blood disease traits through putative gain-of-function variants

Principal Investigator: Zeynep Coban Akdemir, PhD

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Abstract: One-third of transcripts associated with human genetic conditions and cancer are the result of protein truncating variants (PTVs) that lead to premature termination codons (PTCs). PTV-bearing mutant transcripts are actively degraded by nonsense-mediated decay (NMD), which is an evolutionarily conserved post-transcriptional mRNA surveillance mechanism – (NMD+, putative loss-of-function (LoF) allele). On the other hand, some transcripts with PTVs escape from NMD leading to production of truncated and/or altered proteins with a new function – (NMD-, putative gain-of-function (GoF) allele). Although much attention has been given to an improved understanding of potential LoF alleles' impact on human phenotypes and disease traits, the impact of GoF alleles on human phenotypes and disease traits, are generally overlooked in the field. Our previous studies of genetic variation in patients with rare Mendelian disease traits revealed that some genes will only display pathogenic phenotypes if their transcripts escape from NMD, resulting in truncated and/or altered protein products through a potential GoF mechanism. These observations lead to the central hypothesis that a systematic survey and characterization of transcripts present with putative GoF alleles will uncover novel genotype-phenotype correlations underlying a wide range of human phenotypes and disease traits. To test this central hypothesis, we propose the following three specific aims: 1) Establish enhanced predictive models and computational pipelines in a cloud-based computing environment for comprehensive annotation of NMD outcomes of PTVs (NMD+ vs. NMD-) using the whole genome sequencing (WGS) coupled with RNA-Sequencing (RNA-Seq) data available from the Genotype-Tissue Expression (GTEx) and TOPMed datasets; 2) Establish annotation of NMD outcomes of PTVs available from the TOPMed freeze 9 WGS dataset (Amish study, BioMe, CARDIA, CHS, COPDGene, FHS, GeneSTAR, HCHS/SOL, JHS, MESA and WHI) and 3) Assess the impact of NMD- PTVs (putative GoF alleles) on quantitative hematological and hemostatic traits in the setting of the TOPMed Hematology and Hemostasis (H&H) Working Group.

PI:	Zeynep Coban Akdemir
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