FIRST PHARMACOGENOMIC ANALYSIS USING WHOLE EXOME SEQUENCING TO IDENTIFY NOVEL GENETIC DETERMINANTS OF CLOPIDOGREL RESPONSE VARIABILITY: RESULTS OF THE GENOTYPE INFORMATION AND FUNCTIONAL TESTING (GIFT) EXOME STUDY

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Background: Although on-treatment reactivity (OTR) while receiving clopidogrel is strongly associated with CYP2C19 genotype, the majority of the hereditability in clopidogrel response variability remains unexplained, supporting the contention that other important genetic determinants have yet to be identified. Whole exome sequencing - the sequencing of the entire protein-coding region of the genome - is a powerful, non-hypothesis driven approach that may identify novel loci associated with clinical traits.

Methods: Patients were enrolled in a genetic substudy of a large, randomized, multicenter trial (GRAVITAS). Whole exome capture was performed using Agilent SureSelect RNA hybridization probes, generating >50 megabase sequences per patient. This includes the protein-coding sequence of >21,000 genes, >700 microRNAs and >300 non-coding RNAs, comprising >1.5% of the human genome. The primary endpoint was OTR according to the VerifyNow P2Y12 test 12-24 hours and 30 days after PCI.

Results: The exomes of 392 subjects were sequenced for the discovery of single nucleotide and insertion/deletion polymorphisms. After adjustment for clinical characteristics and correction for multiple comparisons, 3 discrete genomic loci were significantly associated with OTR. These included the known CYP2C19 gene and its 5’-most neighbor, CYP2C18. Two additional, novel chromosomal loci were also detected including a member of the P-type primary ion transport ATPases that play a critical role in intracellular calcium homeostasis (p=2.0x10-5), and a guanine nucleotide exchange factor that activates RAC1 (p=3.1x10-5), which plays a central role in secretion-dependent platelet aggregation.

Conclusions: The GIFT-EXOME study represents the most powerful sequencing analysis ever applied to investigate the individual response to a therapeutic agent. Using this approach, we identified novel genetic determinants of platelet responsiveness while receiving clopidogrel. The influence of these additional non-CYP2C19 loci on clinical outcomes after PCI merits further investigation.