68th American Diabetes Association. scientificsessions
JUNE 6-10, 2008 • SAN FRANCISCO, CA

Control/Tracking Number: 2008-A-2211-Diabetes
Activity: Abstract
Current Date/Time: 1/4/2008 6:11:43 PM

Novel Genetic Loci for Fasting Glucose and Insulin Identified by Genome-wide Association in Caucasians

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Abstract:
Fasting glucose level (FG) reflects both glucose production and utilization and is diagnostic of diabetes. Fasting insulin level (FI) reflects both insulin resistance and insulin secretion. Identifying genes underlying these diabetes-related traits may lead to better understanding of diabetes pathophysiology. We carried out three independent genome-wide association studies (GWAS) for FG and FI: a scan of 4,305 Sardinians in large pedigrees from the SardiNIA study and a scan of 1,455 normal glucose tolerant Swedish and Finnish individuals from the Diabetes Genetics Initiative (DGI) both genotyped using the Affymetrix 500K chip set, and a scan of 1,256 mostly unrelated non-diabetic Finnish individuals from the FUSION study genotyped on the Illumina HumanHap300 chip. An imputation approach was used to impute genotypes for an additional 2.09 million SNPs. An additive genetic model was used to test for association between SNPs and FG or FI, adjusting for sex, age, and age^2. Quantile normalization was applied to each trait prior to association testing to minimize the impact of outliers and skewed distributions. GWAS results from the 3 studies were combined by meta-analysis. The strongest association that achieved genome-wide significance was with a cluster of SNPs (rs560887, rs853787, and rs853789), which we previously reported to be associated with FG (meta-analysis $p=1.3\times10^{-10}$, 4.0×10^{-10}, and 4.7×10^{-10}, respectively), and spans two genes: glucose-6-phosphatase catalytic unit 2 and ATP-binding cassette, sub-family B (MDR/TAP), member 11. The -30 glucokinase promoter variant also showed association with FG (FUSION $p=1.6\times10^{-2}$, SardiNIA $p=2.0\times10^{-3}$, DGI $p=3.0\times10^{-2}$) with a meta $p=9.1\times10^{-6}$. The strongest associations with FI were with a SNP that resides in an intron of a gene that encodes a neuronal cell surface protein, neuroligin 1 (*NLGN1*; FUSION $p=1.7\times10^{-3}$, SardiNIA $p=2.0\times10^{-5}$, DGI p=0.49; meta $p=5.9\times10^{-7}$) and with a SNP on chromosome 4 in a region with no known genes (FUSION $p=5.8\times10^{-5}$, SardiNIA $p=3.0\times10^{-4}$, DGI $p=4.6\times10^{-3}$; meta $p=8.7\times10^{-7}$). Evidence for possible association ($p<1.0\times10^{-5}$) with FG or FI was observed for 53 independent SNPs of which 21 fell within or nearby (~2 kb) known genes.
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Author Disclosure Information: **R.M. Watanabe**, None; **W. Chen**, None; **M.R. Erdos**, None; **R. Saxena**, None; **A.U. Jackson**, None; **V. Lyssenko**, None; **M. Uda**, None; **D. Schlessinger**, None; **L. Groop**, None; **F.S. Collins**, None; **D. Altshuler**, None; **G. Abecasis**, None; **M. Boehnke**, None; **A. Scuteri**, None.

Category (Complete): 13-B Genetics - Type 2 Diabetes
Keyword (Complete): genome-wide association ; glucose ; insulin
Presentation Preference (Complete): No Preference
Sponsor (Complete):
*** I am a member of the ADA's Professional Section and do not require a sponsor.**: Yes

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