Abstract/Session Information for Program Number 2456

Session Information

Session Title: Molecular Basis of Disorders With Complex Inheritance **Session Type:** Poster

Session Location: Exhibit Hall E **Session Time:** Wed 4:30PM-6:30PM, Thu 4:30PM-6:30PM, Fri 10:30AM-12:30PM

Abstract Information

Poster Board Number: 2456/F **Presentation Time:** Fri, Oct 26, 2007, 10:30AM-12:30PM

Keywords: Molecular Basis of Disorders With Complex Inheritance, KW033 - DIABETES, KW133 - SUSCEPTIBILITY LOCUS, KW113 - POLYMORPHISM, KW110 - PHENOTYPE, KW012 - CANDIDATE GENE

Abstract Content

Functional analysis of a nonsynonymous coding variant (R325W) in the pancreatic β-cell specific zinc transporter, *SLC30A8*, associated with type 2 diabetes. *M.R. Erdos[1], L. Qin[2], L.L. Bonnycastle[1], A.J. Swift[1], A.G. Sprau[1], A.U. Jackson[3], C.W. Willer[3], C.L. Yang[4], S. Humphreys[4], D.H. Ellison[4], J. Tuomilehto[5], R.N. Bergman[6], M. Boehnke[3], K.L. Mohlke[2], F.S. Collins[1]* 1) GTB, NHGRI, NIH, Bethesda, MD; 2) UNC, Chapel Hill, NC; 3) U Mich, Ann Arbor, MI; 4) OHSU, Portland, OR; 5) National Public Health institute, Helsinki, Finland; 6) USC, Los Angeles, CA.

Genome wide association studies have identified several novel susceptibility genes for type 2 diabetes (T2D) including *SLC30A8*, a pancreatic β-cell specific zinc transporter. Type 2 diabetes association with the SNP (rs13266634) that marks a non-synonymous coding substitution (R325W) in *SLC30A8* achieves genome wide significance (OR= 1.12, p= $5.3x10^{-8}$) in the combined analysis of three major studies (DGI, UKT2D, and FUSION). We now report that quantitative trait analyses in ~2380 FUSION individuals also suggest association with systolic blood pressure (p= .028), pulse pressure (p= .004), triglycerides (p= .036, p=.009 in controls), fasting free fatty acids (p= .024) and BMI-related traits (BMI, waist, whr; p= .033-.05). In db/db diabetic mice, dietary zinc supplementation has been shown to attenuate hyperglycemia and hyperinsulinemia. In a pilot study, normal glucose tolerant Finns homozygous for the risk allele (C, n=16) had modestly lower, but not statistically different, plasma zinc levels (72.6 ug/dl, SD= 15.0) than those homozygous for the non-risk allele (T, n=19; 75.9 ug/dl, SD= 11.5). We have synthesized both alleles of the full length SLC30A8 cDNA and transfected these into HeLa cells. We observed similar expression levels and cellular localization for each allele, and we are now examining zinc uptake with each allele using the cell permeable zinc fluorophore, Fluozin-3. In a second model system, we are injecting *Xenopus laevis* oocytes with *in vitro* transcribed cRNA for each allele of *SLC30A8* in the presence of $^{65}Zn^{+2}$ supplemented media, and monitoring the zinc transporter activity by radioactivity uptake. These studies may define the mechanism for this newly discovered risk factor for type 2 diabetes, with the potential for future therapeutic insights.