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. Erdoes¹, L. Qin², L.L. Bonnycastle¹, A.J. Swift¹, A.G. Sprau¹, A.U. Jackson², C.W. Willer³, C.L. Yang⁴, S. Humphreys⁴, D.H. Ellison⁴, J. Tuomilehto⁵, R.N. Bergman⁶, M. Boehnke³, K.L. Mohlke², F.S. Collins¹ 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= 5.3x10⁻⁵) 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 ⁶⁵Zn⁺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.