## Platform Presentations in Biochemical/Molecular Genetics

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The A986S polymorphism of the calcium-sensing receptor (CASR) gene is a significant contributor to inter-individual variability of serum calcium. <u>D.E.C. Cole<sup>1,3</sup>, R. Vieth<sup>1,4</sup>, H. Trang<sup>3</sup>, B.Y.-L. Wong<sup>3</sup>, G.N. Hendy<sup>5</sup>, and L.A. Rubin<sup>2</sup>. Depts. of <sup>1</sup>Laboratory Medicine & Pathobiology, and <sup>2</sup>Medicine, Univ. of Toronto, <sup>3</sup>The Toronto General Hospital Genetic Repository, University Health Network, and <sup>4</sup>Mount Sinai Hospital, Toronto ON, and <sup>5</sup>Depts. of Medicine, Physiology, and Human Genetics, McGill Univ., Montreal QC, Canada.</u>

Serum calcium is under tight physiological control, but it is also a quantitative trait with a substantial genetic component. Mutations of the CASR gene cause familial hypocalciuric hypercalcemia and autosomal dominant hypoparathyroidism, depending on whether they decrease or increase, respectively, the activity of the protein. We described an association between ionized calcium and a common polymorphism (A986S) found in the cytoplasmic tail of this G protein-coupled receptor (Lancet 1999; 353:112). We report here on an independent study of 387 healthy young women. Genotyping was performed by allele-specific amplification and serum chemistries were measured by automated clinical assay. Frequencies of SS, AS, and AA genotypes were 6, 107, and 274, respectively, yielding a 986S allele frequency of 15%. Mean total serum calcium (Ca<sub>T</sub>) was significantly higher in the SS (9.88  $\pm$  0.29 mg/dL, p=.015) and AS groups (9.45 ± 0.05 mg/dL, p=.002), than in the AA group  $(9.23 \pm 0.04 \text{ mg/dL})$ . In multiple regression modelling, the A986S genotype remained an independently significant predictor of Ca<sub>T</sub> (p<.0001) when serum total protein, albumin, phosphate, magnesium, and creatinine covariates were included. These data are among the first to show significant association between a common polymorphism and a serum electrolyte assay. The A986S polymorphism is also a potential predisposing factor in disorders of bone and mineral metabolism.

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Connexin-26 deafness in the United States: Are we ready for the next Millennium? <u>A.Pandya<sup>1</sup>, K.Oelrich<sup>2</sup>, R. Morrell<sup>3</sup>, K.S. Arnos<sup>2</sup>, X.J.Xia<sup>1</sup>, X.Liu<sup>1</sup>, J.R. Albertorio<sup>2</sup>, S.H.Blanton<sup>1</sup>, T.Friedman<sup>3</sup>, W.E. Nance<sup>1</sup>, Virginia Commonwealth University, Richmond, VA, Gallaudet University, Washington D.C., NIDCD, NIH, MD.</u>

Profound hearing loss has an incidence of 1:1000 children, and is genetically determined in at least half of the cases. The GJB2 gene encoding the gap junction protein 2, also called Connexin 26, is one of a growing number of genes found to have mutations which can result in hearing loss. One particular GJB2 mutation, 35delG accounts for 50-80% of recessive deafness in the Caucasian population of European descent. A second mutation, 167delT has a high prevalence in the Ashkenazi Jewish population with a carrier frequency of about 4%. At least 40 other GJB2 alleles associated with hearing loss have been reported. There is significant phenotypic variability both in the severity and progression of hearing impairment. This, coupled with the relative ease of testing for mutations at this locus, has raised important ethical and social issues when counseling deaf probands and their families. To address these issues and to obtain more accurate estimates of the frequency of different mutations at the GJB2 locus in the US population, we ascertained deaf probands from both multiplex and simplex families through a national survey conducted by the Research Institute at Gallaudet University, as well as from the student body at Gallaudet University. Molecular analysis was performed by direct fluorescent sequencing of the coding region of the GJB2 locus. So far, we have observed five previously described and two new mutations. An Arg32Cys substitution at a highly conserved residue in the first transmembrane domain was observed in a compound heterozygote with congenital deafness. We also found a novel nonsense mutation at codon 136 in a compound heterozygote. Connexin deafness accounted for 24% of the 92 US probands, and 79% of the mutant alleles were 35delG. Analysis of audiometric data on more than half of these probands is presented with comparison to previous studies. Identification of the mutational spectrum at this locus will allow a careful genotype-phenotype correlation and provide more accurate estimates of the frequencies of various GJB2 alleles. This will enable provision of accurate diagnosis, prognosis and counseling for appropriate language and speech development as well as for future recurrence risk.