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1027T

Gene network analysis of candidate loci for human anorectal malformations. *M. Garcia-Barcelo[1,3,4], E.H.M. WONG[2], C.H. NG[1], V.CH. LUI[1,4], M.T. SO[1], S.S. CHERNY[2,3], P.C. SHAM[2,3,4], P.K. TAM[1,4].* 1) Dept Surgery, Univ Hong Kong, Hong Kong, NA, Hong Kong; 2) Dept Psychiatry, Univ Hong Kong, Hong Kong, NA, Hong Kong; 3) Center for Genomic Sciences, Univ Hong Kong, Hong Kong, NA, Hong Kong; 4) 4Centre for Reproduction, Development, and Growth Univ Hong Kong, Hong Kong, NA, Hong Kong.

Anorectal malformations (ARMs) are birth defects that require surgery and carry significant chronic morbidity. Our genome-wide copy number variation (CNV) study had provided a wealth of candidate loci. To find out whether these candidate loci are related to important developmental pathways, we have performed an extensive literature search coupled with currently available bioinformatics tools. This has allowed us to assign both genic and non-genic CNVs to interrelated pathways known to govern the development of the anorectal region. We have linked 11 candidate genes to the WNT signaling pathway and 17 genes to the cytoskeletal network. Interestingly, candidate genes with similar functions are disrupted by the same type of CNV. The gene network we discovered provides evidence that rare mutations in different interrelated genes may lead to similar phenotypes, accounting for genetic heterogeneity in ARMs. Classification of patients according to the affected pathway and lesion type should eventually improve the diagnosis and the identification of common genes/molecules as therapeutics targets.

1028F

Comparison of gene expression induced by HIV-1 GAG peptides specific to HLA-A*01:01 and B*07:02 in PBMCs by mRNA-seq analysis. *L.R. Liu[1,2], P. LaCap[1], R. Capina[1], B. Liang[1,2], B. Fristensky[1,3], B. Ball[1,2], F. Plummer[1,2], M. Luo[1,2].* 1) HIV and Human Genetics Division, National Microbiology Laboratory. 1015 Arlington Street. Winnipeg, Manitoba. Canada R3E 3R2; 2) Department of Medical Microbiology, University of Manitoba. 745 Bannatyne Avenue. Winnipeg, Manitoba. R3E 0J9; 3) Department of Plant Sciences, University of Manitoba. 222 Agriculture Building University of Manitoba. Winnipeg, Manitoba. R3T 2N2.

Introduction: A subset of sex workers (CSW) enrolled in the Pumwani cohort in Nairobi, Kenya remain HIV negative despite repeated exposure through high risk sex work. Studies on genetic factors enriched within these highly HIV-1 exposed seronegatives (HESN) suggest this natural resistance to HIV-1 is multi-factorial, and associated with specific alleles of Human Leukocyte Antigens (HLA). HLA-A*01:01 was associated with reduced risk of HIV-1 infection, whereas B*07:02 was associated with increased risk. HLAs initiate cell-mediated immunity (CMI) by presenting antigens to T-cells. Systematic comparison of A*01:01 and B*07:02 HIV-1 Gag epitopes showed that A*01:01 recognized fewer epitopes than B*07:02, and recognition of more Gag epitopes is associated with susceptibility to HIV-1 infection. However, It is unclear whether the A*01:01 or B*07:02 and GAG peptide complex could differently induce downstream gene expression, and lead to differential T cell function. We conducted mRNA-seq analysis and compared gene expression induced by A*01:01 and B*07:02 specific peptide using PBMCs of an individual express both A*01:01 and B*07:02. **Approach:** PBMCs from a single blood draw was split into equal proportions, and stimulated with peptide NSSKVSQNY (A*01:01 specific) or SPRTLNAWV (B*07:02 specific). 8-hours post-stimulation, the PBMCs were harvested for RNA-seq analysis. RSEM (RNAseq by Expectation Maximization) workflow was used for read alignment, and transcript quantification. DESeq was used for differential expression analysis. **Results:** After correction for false-discovery, one gene was significantly differentially expressed, DEQ571357 (FDR P-value = 3.8×10^{-12}), and 190 gene-isoforms (FDR P-value ≤ 0.05). **Implications:** This study aims to inform vaccine design by evaluating host gene expression induced by HLA-specific epitopes. Significant differences were identified however the results need to be validated by qRT-PCR and in other A*01:01 and B*07:02 co-expressed individuals.

1029W

Protein altering variants found in ciliary and polarity genes in biliary atresia patients. *E.A. Tsai[1], C.M. Grochowski[2], L.D. Leonard[2], R.P. Matthews[3,4], K.M. Loomes[3,4], B.A. Haber[5], N.B. Spinner[2,6], M. Devoto[3,7,8,9].* 1) Genomics and Computational Biology Graduate Group, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA; 2) Department of Pathology and Laboratory Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA; 3) Department of Pediatrics, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA; 4) Division of Gastroenterology, Hepatology and Nutrition, The Children's Hospital of Philadelphia, Philadelphia, PA; 5) Hepatology, Infectious Diseases Clinical Research Department, Merck Research Laboratories, North Wales, PA; 6) Department of Pathology and Laboratory Medicine, University of Pennsylvania, Perelman School of Medicine, Philadelphia PA; 7) Division of Human Genetics, The Children's Hospital of Philadelphia, Philadelphia, PA; 8) Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; 9) Department of Molecular Medicine, University La Sapienza, Rome, Italy.

Biliary atresia (BA) is a bile duct disorder that presents within the first few months of life and causes necroinflammatory obliteration of the extrahepatic biliary tree. Children with BA have severe liver disease, and BA is the most frequent indication for pediatric liver transplantation in the United States. BA is thought to result from a combination of genetic and environmental risk factors, but no specific gene responsible for BA has been identified yet. Absence of immotile cilia on the surface of endothelial cells is apparent upon inspection of intrahepatic as well as remnant extrahepatic bile ducts, suggesting a loss of cell polarity. Manipulation of polarity genes leads to biliary defects in model organisms, and some BA patients demonstrate other anomalies consistent with polarity defects. We compiled a list of genes that participate in the establishment or maintenance of cell polarity (n=280) as well as genes with a role in the composition or function of cilia (n=291). We hypothesize that rare or novel damaging mutations in these genes may contribute to the development of BA. We performed exome sequencing with the Agilent SureSelect All Exon V4+UTR capture kit on 30 Caucasian, isolated BA patients. Variant filtration was performed to analyze only variants with frequency ≤5% in the 1000 Genomes Project Phase I and the NHLBI Exome Sequencing Project (ESP). Notably, one male patient had a nonsense variant in the X-linked polarity gene, *ATP6AP1*. This variant, rs201620814, was not observed in 1000 Genomes, but heterozygous variants in 4/1949 females and a hemizygous variant in 1/1283 males in the ESP cohort (<0.1%) was observed. Additionally, mutations in vacuolar H^+-ATPase subunits have been shown to cause biliary defects in zebrafish. Another patient had two missense variants in trans in *DNAL1*, which encodes for part of the outer dynein arm of cilia. We have identified several other changes in polarity and cilia genes that we suspect are contributing to BA in these patients. Our results support the hypothesis that polarity and cilia genes may be important in BA etiology but also suggest a high level of genetic heterogeneity in this disorder.