561 Genetics of Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) Syndrome

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RATIONALE: Periodic Fever, Aphthous stomatitis, Pharyngitis and Adenitis (PFAPA) syndrome is an autoinflammatory disorder of childhood and little is known about the underlying etiology. While mutations involving the IL-1 pathway have been identified in other recurrent fever disorders, including TNF-receptor associated periodic syndrome (TRAPS) and cryopyrin-associated periodic syndrome (CAPS), there is no clear genetic basis for PFAPA.

METHODS: Patient data and detailed family histories were collected for over 170 children with recurrent fevers including 70 patients with PFAPA to create a prospective cohort over a 4-year period. DNA was isolated from blood or tonsillar tissue from recurrent fever patients, and *NLRP3* and *TNFRSF1A* were sequenced. Quantitative real time PCR was used to evaluate *IL-36* transcripts in tonsils.

RESULTS: Our cohort reflects the diversity of San Diego, without predilection for any specific ethnic background. Family histories revealed 21% of patients have a first degree relative with recurrent fevers and 12% with tonsillitis in childhood, with only 1.4% reporting a history of recurrent infections. We have identified over 30 families with 2-8 affected members. These patients do not possess mutations commonly seen in other autoinflammatory disorders such as CAPS or TRAPS, suggesting that a novel gene may be involved. Upregulation of IL-36 gene expression in tonsils identifies the IL-1 family member IL-36 as a candidate gene.

CONCLUSIONS: A substantial portion of our families with PFAPA report childhood histories of recurrent fevers that resolved either spontaneously or with tonsillectomy, indicating a possible dominantly inherited trait that impacts the developing immune system, including the tonsils.

562 Targeted Deep Resequencing of Thirteen Candidate Genes Reveals Novel Variants Determining Asthma Risk in Individuals of African Ancestry

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RATIONALE: Numerous genome-wide association studies (GWAS) have implicated common risk variants for asthma. These are tagging SNPs not causal variants and account for a small fraction of total risk. To elucidate the role of rare variants in previously implicated genes, and to elucidate causal variants implicated in the tagging GWAS approach, we performed targeted deep resequencing of 13 asthma genes in individuals of African ancestry.

METHODS: *ADRA1B, AOAH, CLDN1, DPP10, GLIS1, HMMR, IL13, KCNMA1, ORMDL3, PRNP, TAF1B, IL33* and its receptor *IL1RL1* were sequenced using Illumina's HiSeq2000 in 183 asthmatic cases and 192 controls from the Genomic Research Asthma in the African Diaspora study. Common variants (MAF≥5%) were analyzed using the Armitage trend test and additive model, and rare variants (MAF <5%) were tested using Fisher's exact test and dominant model.

RESULTS: We identified 6,266 variants, the majority of which were rare (N=4,841). While most common variants (99%) were previously reported in dbSNP, 74% of rare variants were novel and not previously catalogued in public databases. The four strongest associations (p<0.001) mapped to *IL33*, *AOAH*, and *PRNP*. The strongest association (OR=7.34) was an intronic variant in *IL33*(overall MAF=3%); this variant was not observed in public catalogs of subjects of European ancestry.

CONCLUSIONS: Sequencing 13 asthma genes revealed novel associations with rare variants not observed by GWAS. Given the absence of the *IL33* intronic variant showing significant association with risk to asthma in European ancestry populations, follow-up work is ongoing to fully explore this variant in an additional 3,000 subjects of African ancestry.

563 Novel Interleukin-7Rα (IL-7Rα) Mutations Causing Delayed Onset Isolated T Cell Immunodeficiency Disease

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RATIONALE: Mutations within the IL-7Rα complex are a rare cause of severe combined immunodeficiency disease. Generally infants with this disorder develop fatal opportunistic infection within the first year of diagnosis without hematopoietic cell transplantation (HCT).

METHODS: We identified a 10 yo female with history of recurrent sinusitis, bronchiectasis, chronic hypoxia, and failure to thrive who had profound T cell lymphopenia, T-B+NK+ phenotype. The patient has been treated for several bacterial and Aspergillus infections of her lungs, but has not been infected with *Pneumocystis jiroveci*or other opportunistic organisms. Parents are healthy.

RESULTS: Investigations revealed profound CD3 lymphopenia (37 cells/mm^3), and normal B and NK cell enumerations. Lymphocyte response to Candida, phytohemagglutinin, and concanavalin A stimulation was poor (response = 1.7 SI, 4,904 cpm, and 10,127 cpm, respectively), but normal to tetanus (response = 13.1 SI) and moderately low to pokeweed stimulation (response 31,207 cpm). Her IgG and IgM levels were normal while IgA was elevated. Vaccine responses showed protective tetanus and pneumococcal titers but low to diphtheria vaccine. Her NK function was normal. TREC counts were low. Short tandem repeat analysis showed no evidence of maternal T cell engraftment. Two novel frameshift mutations were identified in two alleles of IL-7Rα gene (c.589_598delCCGGCAGCAA and c.993delA).

CONCLUSIONS: Mutations in IL-7Rα gene can result in a late clinical presentation of recurrent infection with profound deficiency in T cell numbers and function and normal B cell function, suggesting this novel compound heterozygous mutation is associated with partial IL-7Rα function that preserves B cell development.

564 Genetic Variations On IL10 Gene and Helicobacter Pylori Infection

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RATIONALE: *Helicobacter pylori (H. pylori)* is a strong risk factor for gastric cancer, likely due to the extensive inflammation in the stomach mucosa caused by this bacterium. Many studies have reported the modulatory effect of *H. pylori* in human immune system. The aim of the study was to evaluate the association between *IL10* genetic variants, *H. pylori* infection and IL-10 production by peripheral blood leukocytes.

METHODS: We genotyped 12 *IL10* SNPs in 1,353 children aged 4-11 years living in a poor urban area in Salvador, Brazil, using TaqMan probe based, 5' nuclease assay minor groove binder chemistry. Association tests were performed by logistic regression for *H. pylori* infection and linear regression for IL-10 spontaneous production (whole blood cultures) including sex, age and principal components for informative ancestry markers as covariates, using PLINK.

RESULTS: Our results shown that SNPs rs1800896 (p=0.02), rs1878672 (p=0.05) and rs3024491 (p=0.04) on *IL10 gene* were associated with increased *H. pylori* infection. The same SNPs associated to *H. pylori* infection were also associated with increased production of spontaneous IL-10 (p=0.04 for rs1800896, p= 0.04 for rs1878672 and p= 0.01 for rs3024491).

CONCLUSIONS: *IL10* variants rs1800896, rs1878672 and rs3024491 increase the risk for *H. pylori* infection probably by its modulatory effect on IL-10 production.

MONDAY