P1011. Primary ciliary dyskinesia (PCD): Identification of a novel locus in the Arabic population with atypical central pair transposition defect

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PCD is a rare autosomal recessive disorder characterised by respiratory tract infections and subfertility. The clinical phenotype results from dysmotility of the cilia, which is associated with a variety of structural abnormalities. The core or axoneme of cilia comprises a bundle of microtubules and associated proteins including dyneins, nexin links and radial spokes. About 50% of patients exhibit laterality defects, commonly *situs inversus*, association known as Kartagener syndrome. We have studied large consanguineous family from UAE. Parents are first cousins with three affected children (None of whom have *situs inversus*) and eight unaffected individuals. They have circular ciliary beat pattern which is consistent with atypical ciliary transposition defect. A genomewide scan identified a region consistent with linkage on 6p21.2. Using GENEHUNTER, a maximum multipoint LOD score of 2.9 was obtained between novel microsatellite *C6orf197-CA* and *D6S282*. This critical region spans approximately 6 megabases of genomic DNA. Work is in progress to using comparative genomics approach to identify potential candidate genes. There are 40 known genes in this region of which two have been identified as potential candidates. *DNAH8*, axonemal heavy dynein8, is an integral component of cilium. *DNAH5* (protein from same gene family) knock out mice exhibit phenotype similar to that of human PCD. Another candidate *KNSL8,* kinesin light chain8, is essential for intraflegellar transport of ciliary components. Both genes are expressed in the lungs and testes. *DNAH8* and *KNSL8,* therefore represents an excellent candidate gene for PCD. There genomic characterisation will be undertaken before performing mutational analysis in patients.

P1012. Association of B lymphocyte stimulator (BLyS) polymorphisms with systemic lupus erythematosus (SLE)

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Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by dysregulation of T and B lymphocytes, leading to production of autoantibodies and immune complexes (ICs). Recently, a promoter polymorphism of B Lymphocyte stimulator (BLys, also known as BAFF, TALL-1, zTNF4, TNFSF13B) was found to be associated with higher anti-Sm antibody level in Japanese. BLys promotes B cell differentiation, proliferation and survival. It is located in chromosome region 13q32, which is a susceptibility locus of SLE. In BLys-/- mice, number of B cells, serum IgG and IgM levels were decreased and B cell development was blocked at transitional T1 stage. Higher BLys level was found in SLE patients. Therefore, we hypothesized polymorphisms of BLys may affect the susceptibility and development of clinical features of SLE in our population.

Association of 4 promoter single nucleotide polymorphisms (SNPs) (-1283G/A, -871C/T, -514T/C, -353G/C) and 1 intronic SNP (IVS1-45C/G) of BLys were analyzed in 456 SLE patients and 760 healthy controls, using high-throughput Sequenom Assay.

No significant association was found in the promoter SNPs with disease susceptibility. However, frequency of G-carrier of the intronic SNP IVS1-45C/G was found to be higher in the controls (P = 0.03). In addition, -871CC was over-represented in patients with Anti-nRNP (P = 0.0046; OR 2.38; 95% CI 1.33-4.23).

This suggests that the allele G of the intronic SNP IVS1-45C/G of BLys may increase the risk for developing SLE, while -871CC is associated with the development of Anti-nRNP in SLE patients.

P1013. SPG7 in 139 patients with Hereditary Spastic Paraparesis

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Mutations in the SPG7 gene, which encodes paraplegin, are responsible for an autosomal recessive form of pure or complicated hereditary spastic paraplegia (HSP). All 17 exons of SPG7 were analyzed using DHPLC and/or direct sequencing in 139 probands with pure or complicated HSP and autosomal recessive inheritance, 41 with consanguinity.

We found 50 different heterozygous sequence changes, 40 of which were not previously reported. Twenty-six of these variants were found in 22 families and were absent in controls, 18 of them in coding regions. No homozygous mutations were identified, even in the 7 consanguineous families, but 5 out of 22 families had 2 heterozygous changes.

Two families with complicated HSP with cerebellar signs and onset at age 27 and 28, had mutations affecting the protein sequence: 850-851 delTTinsC and V581del in a Moroccan family and R294H and N730D in a Mauritanian family.

Two other families had the same association of a missense mutation (A2T) and a synonymous mutation (L67L) located in cis. One family associated 2 intronic variations and one synonymous mutation of unknown effect. We also identified 17 families with only one heterozygous mutation, including 4 with highly probable pathogenic mutations (M1L, IVS11-1-1457 del9, Q507X, Q82del).

In conclusion, mutations in the paraplegin gene are rare and represent < 2% (2/139) of the families studied. The frequency of rare nucleotidic variants was high, however, complicating routine diagnosis.

P1014. Association of CTLA-4 Gene Polymorphisms with Coeliac Disease in the Maltese Population

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Coeliac disease (CD) has an autoimmune component in genetically predisposed individuals triggered by environmental factor (gluten). The disease manifests in partial or total villous destruction of the small intestine with malabsorption and malnutrition. The main environmental triggering factor is a transglutaminated peptide within the gliadin component of gluten, found in wheat. CD has an established HLA component responsible to 35% of the genetic predisposition, rest being in the non-HLA region.

100 coeliac patients were recruited, having predominance of females over male coeliac patients (3:1, $\chi^2 = 25$, $p < 0.001$). The mean age at diagnosis for the whole group was 34 years (males 32 years, females 34 years, $t = -0.65$, N.S.). The predominant presenting symptoms were gastrointestinal related. A higher proportion of males reported a positive family history as compared to females ($\chi^2 = 5.44$, $p = <0.02$).

Two polymorphisms found within the CTLA*4* gene were studied amongst a sample of coeliac patients and cord blood DNA samples (n = 187) that acted as the control group. Polymorphisms within the CTLA*4* gene have been associated with other autoimmune conditions and the gene plays a very important role in immunoregulatory function. The coeliac individuals and cord blood samples were genotyped for the -318 C/T and +49 A/G SNPs. No association of the single polymorphisms or the combined haplotypes with the coeliac condition was apparent amongst the coeliac patients under study. The -318 C allele and the +49 A allele were in linkage disequilibrium amongst the cord blood samples.