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Utilisation of a Whole-Genome Approach to Characterize a Novel Immunodeficiency Disorder and Implicate IL25

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Primary immunodeficiency disorders (PIDs) affect ~2 people in 100,000 and predispose affected individuals to recurrent infections and the development of other disorders such as lymphoma. Diagnosis of PIDs uses case history information, immunological interrogation of cellular repertoires and immunoglobulin isotypes, as well as genetic tests to detect mutations. However, when an individual does not fit the immunological characteristics of defined disorders, and genetic tests for common immunodeficiency syndromes yield no diagnosis, there is no protocol for characterization of the disorder. In this study, we have used genome-wide SNP and gene expression microarrays to provide insight into the etiology of one such disorder. DNA copy number analysis using Affymetrix 250K Sty SNP arrays revealed quadraploidy of chromosome 14q11.2 mapping over an area of approximately 280Kbp. This amplification was confirmed by MassArray-based DNA copy number analysis of SNPs within the candidate region. The genetic locus harbouring the copy number alteration is rich in coding sequences but only two of these genes had a role in lymphocyte signalling - T-cell Receptor Delta-Alpa (TRD\(\alpha\)) and Interleukin-25 (IL25). From microarray data, TRD\(\alpha\) showed down-regulation, however IL25 showed increased expression. Using qPCR analysis, IL25 exhibited a 2.49 fold increased expression compared to control lymphocytes following anti-CD3 T-cell activation. Microarray data supported the hypothesis of an aberrant Th2 switch resulting from the IL25 over-expression, with down regulation of expression of TBX21 (0.24 fold) and IRF2 (0.28 fold) which induce the expression of Th1-associated genes. There was also significant up-regulation of genes associated with a Th2 phenotype, as well as down-regulation of genes associated with a Th1 phenotype. Overall our results thus identified hyperploidy of a genetic region centromeric to 14q11.2, which causes over-production of IL25 in response to T-cell stimulation, and is associated with a gene expression pattern indicative of a Th2 switch. Recurrent infections associated with this disorder may therefore be associated with the inadequate clearance of pathogens that are normally addressed with Th1 responses. This disorder may provide further insight into the function of IL25 and the regulation of Th1 and Th2 responses. In conclusion, we have used a whole-genome approach to characterize the molecular etiology of a novel immunodeficiency disorder.