(p = 4.86E-08, OR=1.72 [95%CI=1.41-2.09], n = 314), but were not associated with Beijing lineage infected old age onset cases (p = 0.0870, OR=1.26 [95%CI=0.97-1.64], n = 155), when we compared them to the population matched 782 healthy controls. These SNPs were associated with both East-African Indian (EAI) and Euro-American lineages in the non-Beijing lineage group. These SNPs were located near *CD53*, which encodes a leukocyte surface glycoprotein and has not been reported to be associated with TB onset. However, interestingly, one of the significant SNPs was previously reported as a cis-expression quantitative trait locus (eQTL) of *CD53* expression level in dendritic cells infected by *M. tb*. This is the first report of TB pathogen lineage-based genome-wide association study and successfully identified a TB-associated locus at a genome-wide significance level. The present results indicated that host genetic risk in TB is affected by pathogen genetic background and demonstrate the importance of analyzing the interaction between host and pathogen genomic variations.

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Non-response to vaccines: still an enigma? B-cell transcription factor POU2F2/OCT2 is a potential candidate

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Unresponsiveness to vaccines affects 2-10% of individuals, representing an extraordinary limitation for infection prevention worldwide. Genetic determinants are still mainly unknown, although in recent years GWAS identified potential susceptibility loci (HLA-DQ, HLA-DR, CXCR5). We investigated a patient and her daughter with unresponsiveness to vaccines (tetanus, diphtheria, hepatitis B, poliovirus) and intermittent infectious episodes, but otherwise unremarkable clinical history. Lymphocyte proliferation assay to tetanus and diphtheria toxoids was highly impaired, with selective deficit of B-memory cells and IgM production. Whole-exome sequencing revealed a shared heterozygous frameshift variant (c.1285dupC;p.Leu429-ProfsTer73) affecting *POU2F2* (19q13.2), a non-OMIM gene with low tolerance to loss-of-function variations (pLI=0.97), encoding the transcription factor OCT2 (octamer-binding protein 2) that regulates immunoglobulin expression in germinal center B-cells. The variant was unreported in gnomAD and was shown to segregate in the family and to have occured *de novo* in the mother. Importantly, heterozygous knock-out mice show a pathological phenotype restricted to immune/hematopoietic system with reduction of B-cells and IgM, thus recapitulating our patients' phenotype. Analysis of mRNA from B-LCLs and fibroblasts of both carriers revealed a stable mutant trascript and excluded mRNA decay, suggesting a dominant-negative effect; in contrast, somatic *POU2F2* amplifications, leading to demonstrated overexpression, have been described in diffuse large B-cell lymphomas. Further functional assays showed severe deficiency of switched memory B-cells and reduced surface and intracellular immunoglobulin expression in both patients. In conclusion, our preliminary findings identified a novel gene likely involved in B-cell anergy and highlighted POU2F2 as an attractive target for enhancing humoral immune response to vaccination.

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P08 Intellectual Disability

P08.01A

Targeted NGS of the TSC1/TSC2 genes

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Tuberous sclerosis TSC (MIN:191100,613254) is an autosomal dominant disorder characterized by benign tumor growths in multiple organ systems. In 75-90% of cases TSC is due to mutations in the TSC1 (OMIM # 605284) or TSC2 (OMIM# 191092) genes. Somatic mosaicism potentially account for up to 26% of TSC cases. We report the results of NGS analysis in 3 familial and 8 sporadic unrelated cases referred with clinically diagnosed (9) or highly suspected TSC (2). DNA samples from peripheral blood leukocytes