Finding genetic factors in the Sardinian population for both levels of immune cells and molecules, and correlated autoimmune disease pathogenesis

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Genome-Wide Association Scans (GWAS) have greatly expanded our understanding of the genes involved in autoimmunity. Major challenges now are to increase the spectrum of disease loci, to reduce the associated variants at each locus to the causal change—the "fine mapping" stage -- and to link genes and variants with function to explain pathogenesis. To meet these challenges, we have started 3 integrated initiatives in the founder, autoimmunity-prone Sardinian population. In one initiative, whole genome sequencing of >2,000 Sardinians yielded over 17,600,000 variants for marker imputation in association testing. In a second initiative, we assembled cohorts of ~3,000 Sardinian multiple sclerosis cases, ~2,000 diabetes Type 1 cases, and ~4,000 controls, and performed a sequencing based genome-wide association study (GWAS), finding some new disease loci and refining known ones to likely candidate causal variants. The third initiative was designed to profile comprehensively the inherited phenotypic structure of the human immune system in ~3,500 of the ~7,000 volunteers of the SardiNIA cohort longitudinal study (see Abstract of David Schlessinger) to identify variants by sequencing- based GWAS that regulate the levels of different immune cell types and soluble molecules, and relate them to autoimmune disease risk alleles. Several variants associated at $p < 10^{-8}$ were found, with some of them overlapping known autoimmune disease risk variants. Taken together, the 3 approaches can thus relate specific immune phenotypes to disease risk, providing an entrée to functional studies of steps in pathogenesis.