Genetic variants associated with age-related traits and diseases in the Sardinian population.

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Age-related diseases are "complex traits", influenced by many genes and environmental factors. Simplifying genetic studies, Sardinia provides a population that grew from an original cohort 10,000 years ago to a modern population of 1,500,000, and is relatively homogeneous but with excellent coverage of European genetic variation. Over 12 years the SardiNIA project has reported analyses in a group of 7,000 participants in a cluster of 4 towns, with comparable numbers of males and females aged 14 to 102, to find genetic factors affecting >300 quantitative traits. Participants repeat visits every 3 years to provide longitudinal information about diagnostic/prognostic value of findings. In >90 publications, genome-wide association studies have reported on anthropometric, blood chemistry, personality, pro-inflammatory molecules and cytokines, and recently, immune system cell traits (see Abstract of Francesco Cucca). Many of the genetic variants associated with traits are also risk factors for disease – for example, variants affecting both cholesterol and coronary artery disease. Based on sequencing of DNA and RNA of participants' lymphocytes, an enriched catalogue of non-coding RNA and coding gene variants provides further power to discriminate "causal" variants and mechanisms at loci identified by GWAS; analyses often reveal more than one associated variant in the same gene and thus account for an increasing fraction of heritability. In a direct assessment for a disease phenotype closely related to possible clinical intervention, variants in the transcription factor BCL11A were shown to prolong the formation of fetal hemoglobin – and thus alleviate thalassemia and sickle cell disease.