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Genome-Wide Homozygosity Analysis of the Longevous Phenotype in the Amish Population

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Abstract : Introduction: Numerous research efforts have focused on searching for 'longevity genes'. However, attempting to decipher the genetic component of the longevous phenotype have resulted in limited success and the mechanisms governing longevity remain to be explained. We conducted a genome-wide homozygosity analysis (GWHA) of the founder population of the Amish community in central Ohio. While genome-wide association studies using unrelated individuals have revealed many interesting longevity associated variants, these variants are typically of small effect and cannot explain the observed patterns of heritability for this complex trait. The Amish provide a large cohort of extended kinships allowing for in depth analysis via family-based approach excellent population due to its. Heritability of longevity increases with age with significant genetic contribution being seen in individuals living beyond 60 years of age. In our present analysis we show that the heritability of longevity is estimated to be increasing with age particularly on the paternal side. Methods: The present analysis integrated both phenotypic and genotypic data and led to the discovery of a series of variants, distinct for stratified populations across ages and distinct for paternal and maternal cohorts. Specifically 5437 subjects were analyzed and a subset of 893 successfully genotyped individuals was used to assess CHIP heritability. We have conducted the homozygosity analysis to examine if homozygosity is associated with increased risk of living beyond 90. We analyzed AMISH cohort genotyped for 614,957 SNPs. Results: We delineated 10 significant regions of homozygosity (ROH) specific for the age group of interest (>90). Of particular interest was ROH on chromosome 13, $P < 0.0001$. The lead SNPs rs7318486 and rs9645914 point to COL4A2 and our lead SNP. COL25A1 encodes one of the six subunits of type IV collagen, the C-terminal portion of the protein, known as canstatin, is an inhibitor of angiogenesis and tumor growth. COL4A2 mutations have been reported with a broader spectrum of cerebrovascular, renal, ophthalmological, cardiac, and muscular abnormalities. The second region of interest points to IRS2. Furthermore we built a classifier using the obtained SNPs from the significant ROH region with 0.945 AUC giving ability to discriminate between those living beyond to 90 years of age and beyond. Conclusion: In conclusion our results suggest that a history of longevity does indeed contribute to increasing the odds of individual longevity. Preliminary results are consistent with conjecture that heritability of longevity is substantial when we start looking at oldest fifth and smaller percentiles of survival specifically in males. We will validate all the candidate variants in independent cohorts of centenarians, to test whether they are robustly associated with human longevity. The identified regions of interest via ROH analysis could be of profound importance for the understanding of genetic underpinnings of longevity.

Keywords : regions of homozygosity, longevity, SNP, Amish
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