Genome-wide linkage analysis for longevity in European nonagenarian siblings: Genetics of Healthy Ageing Study (GEHA)

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Nonagenarians and their first degree family members have a life-long survival advantage that can be attributed to a lower risk of coronary artery disease and type-2 diabetes despite the fact that they carry as many GWAS-identified disease risk alleles as the general population. We hypothesized that long-lived families carry alleles that lower disease susceptibility. To identify such longevity alleles, we performed a genome-wide linkage scan among 2118 nonagenarian Caucasian sibling pairs that have been recruited in fifteen study centers of eleven European countries in the Genetics of Healthy Ageing (GEHA) Study. In the joint nonparametric linkage analysis we observed four regions that show linkage with longevity; chromosome 14p11.2 (LOD=3.47), chromosome 17q21.32 (LOD=2.95), chromosome 19p13.2 (LOD=3.76) and chromosome 19q13.32 (LOD=3.57). Since the 19q13.32 region spans the *APOE* gene, known to contribute to longevity and mortality, we analyzed whether the APOEε2ε3ε4 alleles contributed to the linkage. An analysis in which association and linkage were additively modeled, using LAMP, showed that together the APOEε2 (P≤0.0001) and the APOEε4 (P=0.020) alleles explain the linkage at 19q13.32. To fine map these linkage results at the 14p11.2, 17q21.32 and 19p13.2 loci we used GWAS data in the nonagenarian siblings that contributed to the linkage results to test for associations explaining the linkage. For the association analyses 1058 unrelated nonagenarian cases were compared with 8776 younger controls of similar geographical origin as the cases. At 14p11.2 we tested 1023 SNPs for association, at 17q21.32 2969 SNPs, at 19p13.2 1850 SNPs and at 19q13.32 3805 SNPs. Using a fixed effect meta analysis approach, rs2075650 at 19q13.32 appeared the only SNP within these four linkage regions significantly associated with longevity. This SNP is in linkage disequilibrium with the APOEε2ε3ε4 polymorphisms and is known to reflect the effect of the *APOE* gene on longevity. We conclude that besides the effect of the *APOE* gene on longevity, at least three other loci play a role located at 14p11.2, 17q21.32 and 19p13.2. Since the linkage results are not explained by common variants, we suggest that rare variants at these regions contribute to human familial longevity.