

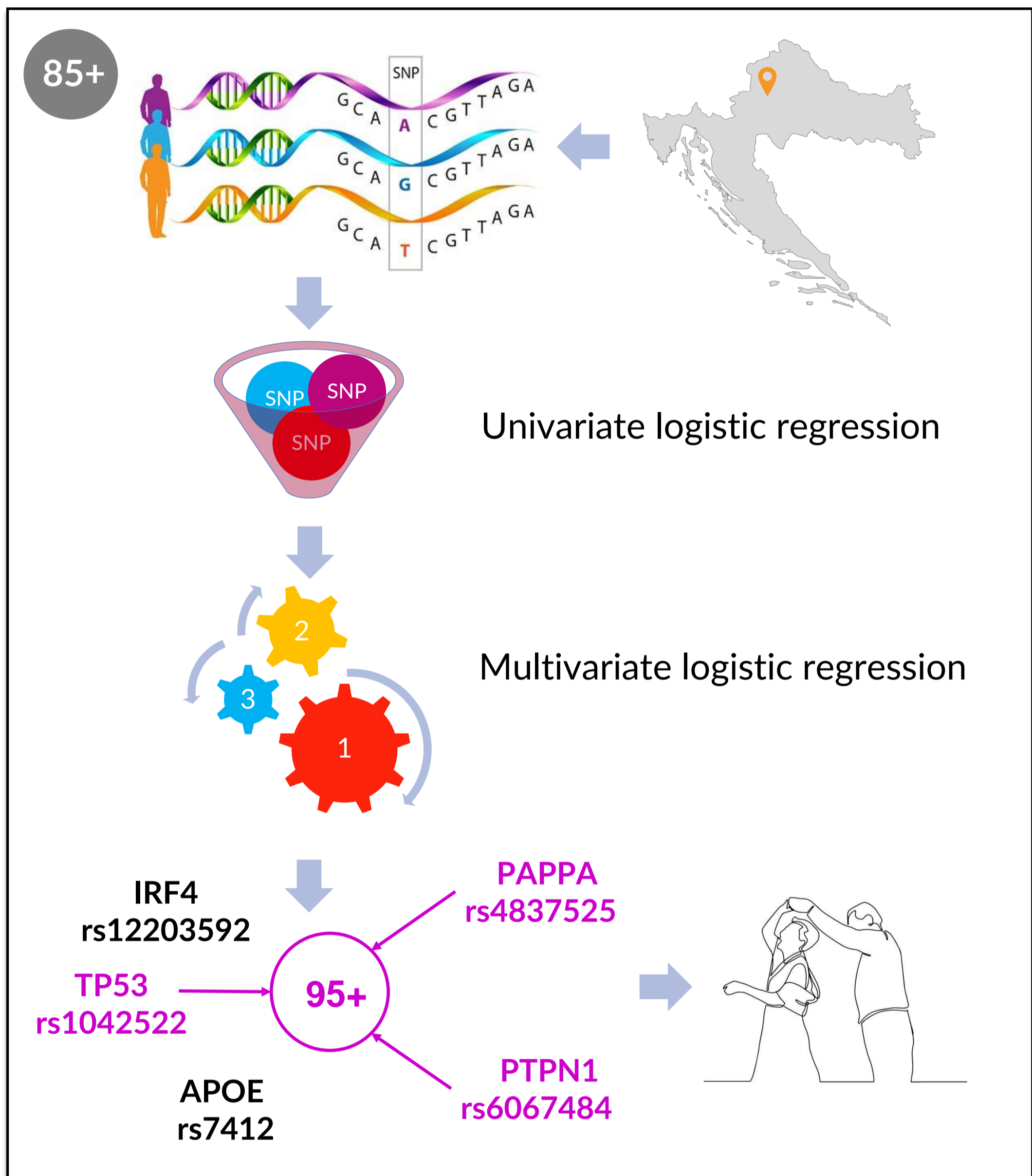
Reaching 95.0 years of age: The genetic association in the elderly Croatian population



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INTRODUCTION

- Human longevity is influenced both by genetic and non-genetic factors, and genetic variability accounts for approximately 25% of variation in life expectancy.
- Genes that can positively influence lifespan and the ageing process are known as longevity genes.
- We aimed to elucidate single nucleotide polymorphisms (SNPs) that are significantly related to longevity as defined by the cut-off age of 95.0 (the threshold age for extreme longevity) in a sample of elderly persons of European origin.



METHODS

- Genotype data were obtained for 42 SNPs from 28 putative longevity genes, which were selected due to strong and/or replicated association to human longevity and their role in different signalling pathways of cellular ageing and senescence.
- Univariate and multivariate logistic regression were performed with genotypic data coded as: 2 = longevity allele homozygotes; 1 = heterozygotes; 0 = non-longevity allele homozygotes.
- Out of the initial 42 SNPs, 10 SNPs that reached the inclusion criteria of having a p-value of $p < 0.2$ in univariate logistic regression entered the series of multivariate logistic regressions.

PARTICIPANTS

- The study sample comprised of 314 unrelated individuals from Croatia who were above 85.0 years of age when the data were collected.
- As the sample was gathered in the period between 2007 and 2009, the age at death for each individual has been determined from the national mortality register 10 years after the initial sampling.
- This enabled us to differentiate between truly long-lived individuals that had survived beyond 95 years of age and those that died before reaching 95 years, thus elucidating which SNPs are a key component for extreme longevity in the Croatian population.

RESULTS

- The best model, explaining 9.3% of the variance for survival to the age of 95.0, consisted of five SNPs.
- Three SNPs that were significantly (at $p < 0.05$ level) associated with reaching 95.0 years of age are *PTPN1* rs6067484, *PAPPA* rs4837525, and *TP53* rs1042522.
- Two remaining SNPs were marginally significant (*APOE* rs429358; $p = 0.053$) or not significant (*IRF4* rs12203592) but they both contribute to the strength of the model.
- Although the best model explains a considerable proportion of variance for surviving up to the 95-years-of-age phenotype, the modest associations of particular SNPs warrant replication in more powered studies.

Table 1. Best multivariate logistic regression model for survival up to the age of 95.0 years in the Croatian oldest-old sample (N=314).

Closest gene	SNP	Contrasting genotypes	B	Sig.	Exp(B)	95% C.I. for exp(B)	
						Lower	Upper
APOE	rs429358	CC, CT vs TT	0.852	0.053	2.345	0.988	5.563
IRF4	rs12203592	CC vs CT, TT	0.569	0.110	1.766	0.880	3.546
PAPPA	rs4837525	AA vs AG vs GG		0.119			
		AA, AG vs GG	0.766	0.127	2.151	0.804	5.757
		AA, GG vs AG	0.994	0.042	2.703	1.039	7.033
PTPN1	rs6067484	AA vs GA vs GG		0.116			
		AA, GG vs GA	0.116	0.685	1.123	0.640	1.970
		AA, GA vs GG	0.918	0.039	2.505	1.049	5.981
TP53	rs1042522	CC vs CG vs GG		0.123			
		CC, CG vs GG	1.174	0.048	3.233	1.013	10.322
		CC, GG vs CG	0.245	0.375	1.278	0.744	2.197
Nagelkerke R-squared		0.093					
Hosmer - Lemeshow Test		0.763					
% Correct		74.2					

