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BRIEF COMMUNICATION

Ataxia-telangiectasia mutated (ATM) genetic variant in Italian centenarians

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Abstract Lifespan is attributable to genetic factors and some studies have attempted to identify putative genes implicated in human longevity. Several genetic loci have been associated with longevity, but some of these are not replicable, probably due to the vast differences among ethnicities. We analyzed in 128 Italian long-lived individuals and 150 unrelated healthy subjects, the recently reported association between rs189037 in the ataxia-telangiectasia mutated gene promoter and longevity in Chinese nonagenarians/centenarians. Our study confirms the association between the rs189037 C/T genotype and longevity in Italian centenarians, with an odds ratio of 1.85 (95 % CI 0.99–3.45). To understand the genetic basis for longevity is an extraordinarily difficult task, and therefore it is important to replicate any positive findings, especially if detected in other ethnic groups, in order to reach reliable conclusions on the real effect that candidate genes have on longevity.

Keywords Longevity · ATM · Single nucleotide Polymorphism · Genes · Healthy aging · Genetic heterogeneity

Introduction

The average human lifespan in developed countries ranges from about 80 to 85 years [1], and the frequency of centenarians is 1 in 10,000. However, this number is increasing rapidly due to changes in diet, other environmental factors and, last but not least, the possibility to recover from diseases [2]. Furthermore, studies have been performed to evaluate the role genetic factors play in exceptional longevity [1–3], but only the apolipoprotein E (ApoE) gene has been replicated and confirmed in several populations [4, 5]. This could be due to the great differences in allele and genotype frequencies in the studied polymorphisms among ethnicities [2, 6].

Following the ApoE association with longevity, the most studied pathway has been the lipid metabolism, but there is some evidence that extreme longevity could be associated with increased resistance to oxidative stress [6, 7].

Chen and colleagues [8] reported an association between a genetic variant (rs189037) in the ataxia-telangiectasia mutated (ATM) gene promoter and longevity in Chinese nonagenarians/centenarians. The encoded protein is important in the resistance to oxidative stress through its role in the detection of reactive oxygen species lesions and DNA repair defects [9, 10]. Chen's study [8] demonstrated that the rs189037C/T genotype is significantly associated with longevity and has an effect on ATM transcription, as well. Indeed, the study showed that the C/T genotype is associated with moderate levels of ATM gene expression, suggesting that the best way to prolong lifespan is via a moderate level of ATM.

In light of these findings, we analyzed ATM polymorphism distribution in Italian long-lived individuals (LLIs) to confirm the role the ATM gene plays in our population.

Materials and methods

Our study group consisted of 278 Italian subjects: 128 LLIs (78.1 % females, mean age at examination 98.7 ± 5.1 years;

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52.3 % aged 100 years) and 150 unrelated healthy subjects, as a control group, (56.7 % females, mean age at examination 67.2 ± 9.1 years) (Table 1).

All subjects were enrolled at the Neurology Unit of the Department of Neurological and Psychiatric Sciences of the University of Florence. The control group was carefully assessed using a rigorous clinical history evaluation and were interviewed to exclude the presence of relatives of past generations with exceptional longevity. The LLIs were recruited from the same geographical area and were in good health, relative to their very advanced age, and did not present the more common age-related pathologies (e.g., severe physical impairment, clinically evident cancer or renal insufficiency), although many had decreased auditory and visual acuity, as observed in other studies on healthy LLIs [3, 11]. Informed consent for genetic screening was obtained from the study participants and the study protocol was approved by the local ethics committee and conducted in accordance with the provisions of the Helsinki Declaration.

DNA was extracted from white blood cells using the phenol–chloroform procedure and all genotyping was performed by KBioscience, Ltd., which uses their own fluorescence-based competitive allele-specific PCR system (KASPar) assay. Accuracy >99 % was achieved and routine quality control measures were performed on all genotyping (http://www.kbioscience.co.uk/). Odds ratio (OR) and corresponding 95 % confidence intervals (CIs) were calculated using logistic regression models adjusted for gender and age. A power analysis was performed using COMPARE2 software (http://www.brixtonhealth.com/). Comparisons of genotype and allele frequencies were performed using the χ^2 test.

Results

We examined the distribution of the C/T genotype frequencies with respect to the other genotypes (C/C + T/T) in the LLI group compared to the controls, due to a dose-dependent effect of this genotype on ATM production [8]. We did not find any significant difference in the distribution of C/T genotypes in the LLI group compared to the controls ($p = 0.12$) (Table 2).

The LLI group was divided into two subgroups (<100 years and ≥100 years, the latter considered centenarians), and we did find a statistically significant difference in the C/T genotype in centenarians compared to the controls ($p = 0.037$) (Table 2).

The rs189037 genotype and allele distributions were in the Hardy–Weinberg (HW) equilibrium in the control group ($p = 0.59$), but not in the LLI group ($p = 0.03$). This could be attributed to the centenarians group ($p = 0.028$), providing further evidence of the association of the locus with longevity. Indeed, if genotype distribution does not follow the HW equilibrium in the control population, this indicates that the results should be treated with caution. However, if it is the studied population that does not follow the HW equilibrium, as in this case, this may confirm a correlation between the investigated genetic locus and longevity.

Table 1 Demographic characteristics of all studied subjects

	Controls, *N* (%)	Centenarians, *N* (%)
Total	150	128
Age at examination (mean ± SD)	67.2 ± 9.1	98.6 ± 5.1; 52.3 % aged 100 years
Gender		
Females	85 (56.6)	99 (77.3); 55.5 % aged 100 years
Males	65 (43.3)	29 (22.6); 41.4 % aged 100 years

Discussion

Lifespan is the result of multiple processes involving environmental factors and many plausible candidate genetic factors, thus some human genetic studies have investigated putative associations, but only a few replications have been observed across human populations. The main problems of "longevity" case/control association studies are the small sample size, the lack of precise phenotyping and variations in ethnic population stratification; thus it is important to replicate any positive findings, especially if detected in different ethnic groups, to reach reliable conclusions on the effect that putative candidate genes have on longevity.

To date, there is only one study on the role played by the ATM gene in longevity in the Chinese population and our data report, for the first time, the association of the ATM gene variation in Caucasian LLIs.

Our study, having a 78.9 % power to detect an OR of 2.0 at a 5 % significance rate, confirms in Italian centenarians the role of the rs189037C/T genotype in the ATM gene promoter previously described in Chinese nonagenarians/centenarians [8]. Despite the small number of enrolled subjects, our result is quite reliable. All participants are from the same restricted geographical area (a small region in Central Italy) and the confounding factors are not present, thus we can speculate that predominantly genes influence longevity.

The genetic basis of longevity could improve the understanding of the central mechanisms of ageing and

Table 2 Distribution of the ATM genetic variant in Italian long-lived individuals (LLIs) subdivided by age and control subjects

	N	CC + TT *N* (%)	CT *N* (%)	*p* value	OR (95 % CI)
Controls	150	90 (60 %)	60 (40 %)		
LLI total	128	65 (50.8 %)	63 (49.2 %)	0.12	1.45 (0.88–2.41)
LLI ≥100 years old (centenarians)	67	30 (44.7 %)	37 (55.3 %)	0.037*	1.85 (0.99–3.45)
LLI <100 years old	61	35 (57.3 %)	26 (42.7 %)	0.72	1.11 (0.58–2.13)

* Statistically significant

disease, thus providing a new insight for the study of prevention and treatment of late-life disabilities and diseases.

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Conflict of interest All authors declare the absence of any conflict of interest.

References

1. Sebastiani P, Solovieff N, Dewan AT, Walsh KM, Puca A, Hartley SW, Melista E, Andersen S, Dworkis DA, Wilk JB, Myers RH, Steinberg MH, Montano M, Baldwin CT, Hoh J, Perls TT (2012) Genetic signatures of exceptional longevity in humans. PLoS One 7(1):e29848
2. Novelli V, Viviani Anselmi C, Roncarati R, Guffanti G, Malovini A, Piluso G, Puca AA (2008) Lack of replication of genetic associations with human longevity. Biogerontology 9(2):85–92
3. Cellini E, Nacmias B, Olivieri F, Ortenzi L, Tedde A, Bagnoli S, Petruzzi C, Franceschi C, Sorbi S (2005) Cholesteryl ester transfer protein (CETP) I405 V polymorphism and longevity in Italian centenarians. Mech Ageing Dev 126(6–7):826–828
4. Christensen K, Johnson TE, Vaupel JW (2006) The quest for genetic determinants of human longevity: challenges and insights. Nat Rev Genet 7:436–448
5. Schächter F, Faure-Delanef L, Guénot F, Rouger H, Froguel P, Lesueur-Ginot L, Cohen D (1994) Genetic associations with human longevity at the APOE and ACE loci. Nat Genet 6(1): 29–32
6. Bostock CV, Soiza RL, Whalley LJ (2009) Genetic determinants of ageing processes and diseases in later life. Maturitas 62: 225–229
7. Lee HC, Wei YH (2012) Mitochondria and aging. Adv Exp Med Biol 942:311–327
8. Chen T, Dong B, Lu Z, Tian B, Zhang J, Zhou J, Wu H, Zhang Y, Wu J, Lin P, Zhang J, Xu H, Mo X (2010) A functional single nucleotide polymorphism in promoter of ATM is associated with longevity. Mech Ageing Dev 131:636–640
9. Lavin MF, Birrell G, Chen P, Kozlov S, Scott S, Gueven N (2005) ATM signaling and genomic stability in response to DNA damage. Mutat Res 569:123–132
10. Lombard DB, Chua KF, Mostoslavsky R, Franco S, Gostissa M, Alt FW (2005) DNA repair, genome stability, and aging. Cell 120:497–512
11. Piaceri I, Bagnoli S, Lucenteforte E, Mancuso M, Tedde A, Siciliano G, Piacentini S, Bracco L, Sorbi S, Nacmias B (2011) Implication of a genetic variant at PICALM in Alzheimer's disease patients and centenarians. J Alzheimers Dis 24:409–413