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Associations between STR autosomal markers and longevity

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Abstract Life span is a complex and multifactorial trait, which is shaped by genetic, epigenetic, environmental, and stochastic factors. The possibility that highly hypervariable short tandem repeats (STRs) associated with longevity has been largely explored by comparing the genotypic pools of long lived and younger individuals, but results so far have been contradictory. In view of these contradictory findings, the present study aims to investigate whether HUMTHO1 and HUMCSF1PO STRs, previously associated with longevity, exert a role as a modulator of life expectancy, as well as to assess the extent to which other autosomal STR markers are associated with human longevity in population from northern Spain. To that end, 21 autosomal microsatellite markers have been studied in 304 nonagenarian individuals (more than 90 years old) and 516 younger controls of European descent. Our results do not confirm the association found in previous studies between longevity and THO1 and CSF1PO loci. However, significant association between longevity and autosomal STR markers D12S391, D22S1045, and DS441 was observed. Even more, when we compared allelic frequency distribution of the 21 STR markers between cases and controls, we found that 6 out of the 21 STRs studied showed different allelic frequencies, thus suggesting that the genomic portrait of the human longevity is far complex and probably shaped by a high number of genomic loci.

Keywords Longevity · Autosomal STRs · THO1 · CSF1PO · D22S1045

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Introduction

Life span is a complex and multifactorial trait, which is shaped by genetic, epigenetic, environmental, and stochastic factors. The genetic component of the longevity has long been investigated by association studies in unrelated centenarians and younger people from the same population (Bathum et al. 1998; Bladbjerg et al. 1999; Broer et al. 2015; De Benedictis et al. 1997; Deelen et al. 2014; He et al. 2014; Minster et al. 2015; Schachter et al. 1994; Slagboom et al. 2011; Tan et al. 2001a; Tan et al. 2001b) and correlation studies in twins and families (Herskind et al. 1996; Kim et al. 2015; McGue et al. 1993; Yashin et al. 1999). Although the

number of genes that could affect the interindividual life span variability was expected to be high, there is only one genetic association, apolipoprotein E (*APOE*), which has been consistently replicated (Brooks-Wilson 2013). This may be because (a) genetic factors only account for about a quarter of the variance in adult human (Herskind et al. 1996; vB Hjelmborg et al. 2006), (b) genetic architecture of the human life span is expected to be determined by many, still uncharacterized, genes, or (c) genomic portrait of the human longevity may be affected by extraordinarily complex gene-gene and gene-environment interactions.

Microsatellites, or short tandem repeats (STR), consist of tandemly repeated units ranging from one to six nucleotides. While many repeats are located within coding or regulatory regions, most of these STRs are within gene deserts. However, an increasing body of evidence shows that the STR sequences involved in the regulation of gene expression and function need not be limited to promoter or coding sequences (Gemayel et al. 2010). In fact, STRs in 5′ and 3′ UTRs of transcripts as well as in intronic sequences, emerge now as potentially important non-coding sequence elements (Riley and Krieger 2005), not only because of their specific biological functions, but also because they might confer faster rates of evolution of genes due to their intrinsic instability (Riley and Krieger 2005). Even more, STRs in non-coding intergenic regions could also have a regulatory function by altering the structure of the chromatin (Gemayel et al. 2010). In addition, it has also been established that non-coding polymorphic regions, such as STRs, may provide information about nearby coding regions, among which some might be disease-causing coding variants. Therefore, studying both the genomic context and the distribution of the microsatellites throughout the human genome could have the potential to explain various biological phenomena that have defied complete explication as it happens with human longevity and multifactorial diseases of the elderly (Toth et al. 2000).

Some of the STRs are widely used in routine forensic DNA profiling, since being the number of tandem repeats in STR markers highly variable among individuals, they can be employed for human identification purposes. Given that some of these STR loci correlate with physical traits, it has been speculated that they could confer additional information that could reveal genetic traits or predispositions for inherited diseases of a given individual. Specifically regarding human life span, the forensic STRs *HUMTHO1 (THO1)* and *HUMCSF1PO (CSF1PO)* have been previously linked to human longevity (De Benedictis et al. 1998; Tan et al. 2002; von Wurmb-Schwark et al. 2011, Hui et al. 2011). The *THO1* STR (11p15.5) is located within the first intron of the tyrosine hydroxylase 1 gene (*THO1*), the rate-limiting enzyme for synthesis of catecholamines, amino acid-derived molecules produced by the sympathetic nervous system in response to stress. Given *THO1*'s role in stress response, it has been suggested that variability of *HUMTHO1* may affect life span and healthy aging. De Benedictis et al. (De Benedictis et al. 1998), who were the first to report a significant association of *THO1* with longevity, found that the frequency of homozygotes of long *THO1* tetranucleotide repeats (>9) was lower in male centenarians after comparing 196 centenarians and 358 controls (p value=0.004). However, subsequent *HUMTHO1*-longevity studies yielded contradictory results. For instance, Tan et al. (Tan et al. 2002) reported that allele 9.3, especially in the homozygous genotype, conferred a beneficial influence that reduce the carriers' hazards of death (965 Italian subjects aged from 13 to 109 years old, adjusted p value=0.03), but these results could not be replicated by von Wurmb-Schwark et al. (von Wurmb-Schwark et al. 2011), who after investigating 471 long-lived individuals and 462 younger controls from Germany, suggested that the *THO1* STR locus exhibited no significant influence on the ability of attaining exceptional old age in Germans. With regard to the *HUMCSF1PO*-STR (5q33.3-34), it is a functional microsatellite polymorphism (AGAT)n located in intron 6 of the gene encoding the receptor for colony stimulating factor 1 (*CSF-1R*), which plays a central role in macrophage differentiation and hematopoiesis. Deficiencies in *CSF-1R* gene have been related to multiple developmental defects, and thus it is conceivable that genetic variations in *CSF-1R* might influence survival into old age (Bonifer and Hume 2008). In this respect, Hui et al. (Hui et al. 2011) observed that mean M values (a quantitative marker of variation for that particular STR allele) of *HUMCSF1PO*-STR in the longevity group (60 nonagenarians from Dalian, China) were significantly higher than those in the control (250 reference adults from the same region, p value=0.003); however, further studies would be needed to assess these associations in other populations.

In view of the inconclusive results concerning the involvement of *HUMTHO1* and *HUMCSF1PO* STR loci in attaining exceptional old age, and given the potential role of STR loci in gene regulation, the aims of the present study are (i) to investigate whether *HUMTHO1* and *HUMCSF1PO* STRs exert a role as a modulator of longevity as suggested by previous studies and (ii) to assess the extent to which other forensic STR markers are associated with human longevity in European population. To that end, 21 unlinked autosomal microsatellite markers have been studied in 304 nonagenarian individuals (more than 90 years old) and 516 younger controls of European descent.

Materials and methods

Study population

A total sample of 304 unrelated nonagenarians (over 90 years of age) from the north of Spain was selected for the current study. Nonagenarians were between 90 and 105 years of age at recruitment (243 women, 61 men). The sample of younger controls comprised 516 healthy and unrelated individuals aged less than 60 years (age range 18–60 years; 293 women, 223 men) from the same region in the north of Spain. All participants were clinically healthy. The study was conducted in accordance with the Declaration of Helsinki.

Sample preparation and genotyping

DNA was extracted from peripheral blood samples using Puregene DNA extraction kits (Puregene, Gentra Systems, MN, USA). DNA concentration and purity were measured spectrophotometrically using the NanoDrop ™ 1000 spectrophotometer (Thermo Scientific, NH, USA). Amplification of the 21 autosomal STR markers (*THO1*, *CSF1PO*, *D5S818*, *D7S820*, *D21S11*, *D2S441*, *D1S1656*, *D16S539*, *D3S1358*, *D18S51*, *D2S1338*, *TPOX*, *VWA*, *D8S1179*, *D19S433*, *D12S391*, *SE33*, *D13S317*, *FGA*, *D22S1045*, and *D10S1248*) was performed using the multiplex PCR I-DNASE21 system (Aznar et al. 2014). The PCR mixture consisted of 6 μl of Plus Qiagen Multiplex PCR Kit (Qiagen, Valencia, CA, USA), 5 μl of primer mix I-DNASE21, and 1 μl of template DNA at a concentration of 10 ng/μl. Amplification was performed in a thermal cycler GeneAmp PCR System 9700 (Applied Biosystems, Foster City, CA) following the manufacturer's amplification protocol.

Amplified DNA fragments were denatured using 9 μl of Hi-Di ™ Formamide (Applied Biosystems, Foster City, CA), 0.5 μl of GeneScan ™ 500 LIZ® Size Standard (Applied Biosystems, Foster City, CA), and 1 μl of the amplified DNA. The samples were heat-denatured at 96 °C for 6 min and chilled for 4 min in ice before performing capillary electrophoresis using an ABI PRISM® 3130 DNA Genetic Analyzer (Biosystems, Foster City, CA). We used the GeneMapper v4.0 software (Applied Biosystems, Foster City, CA) for the fragment length determination and allelic assignment.

Statistical analysis

For each of the 21 microsatellite markers, allelic frequencies were calculated using the Excel Microsatellite Toolkit v3.1.1 (Park 2001). Observed heterozygosity (Ho), expected heterozygosity (He), Hardy-Weinberg equilibrium (HWE), and polymorphic information content (PIC) were calculated using CERVUS v3.0.3 (Kalinowski et al. 2007), whereas pairwise linkage disequilibrium (LD) was estimated with Arlequin software v3.5.1.2 (Excoffier and Lischer 2010).

Genetic differences between nonagenarians and younger controls were tested using two different approaches. We first compared the allele distribution of nonagenarian cases and younger controls using the χ^2 test. Subsequently, odd ratios (ORs) were calculated using binary logistic regression as an estimate of the relative risk to evaluate the association between STRs and longevity. ORs were adjusted for sex, and for each STR, a reference allele was defined as that with the highest frequency in controls. It is of note that only the second approach (i.e., the binary logistic regression) was able to reveal allele-specific associations with longevity. The p values reported are two sided and nominal (not adjusted for multiple comparisons), while FDR-adjusted p values (also referred as q values) were adjusted for multiple comparisons within each STR using the p.adjust() function in R ("BH" method). For the adjustment, n was considered the number of tests made for each STR (i.e., number of alleles −1). Statistical analyses were conducted using SPSS v17.0 (SPSS Inc. Chicago, IL, USA) and R (R version 3.1.3). Statistical power

calculation of the sample sizes used in this study was calculated using the software "Power for Genetic Association Version 2.3" (Menashe et al. 2008). The statistical power was calculated specifying the values for a number of parameters such as "disease" allele frequencies (from 0.05 to 0.75), prevalence of longevity 0.10, expected risk estimates (from 1.05 to 1.45), r^2=1.0, case-control ratio=1.7, and α=0.05 (Supplementary Table S1).

Results

Allele frequency distribution for the 21 autosomal STRs in nonagenarians and younger control is shown in Supplementary Tables S2 and S3, respectively. In addition, observed and expected heterozygosities (Ho and He, respectively), polymorphic information content (PIC), as well as results of Hardy-Weinberg equilibrium (HWE) test are also displayed in Supplementary Tables S2 and S3. The observed allelic frequencies did not differ from Hardy-Weinberg equilibrium after Bonferroni correction, and no significant linkage disequilibrium (LD) between loci pairs was detected (data not shown). The most polymorphic microsatellites were *SE33* and *D2S391*, both showing a PIC value higher than 0.88, while the least polymorphic was *TPOX* with a PIC value lower than 0.58.

We next examined the association between the forensic STRs tested herein and longevity. Results of the allele frequency distribution and χ^2 test, as well as of binary logistic regression, are shown in Table 1 and summarized below (alleles with no significant association with longevity not even at *p* nominal levels were omitted for the sake of clarity). Based on the χ^2 analysis, we could not find a statistically significant difference in the allele frequency distribution of the *HUMTHO1* STR between the long-lived individuals and the younger controls, while other STR markers such as *CSF1PO*, *D12S391*, *D19S433*, *D22S1045*, *DS441*, and *SE33*, did show statistically significant differences (*p* value<0.05) (Supplementary Table S4). Further analysis of these significant STRs loci using binary logistic regression analysis revealed that only *D12S391*, *D22S1045*, and *D2S441* displayed significant associations with longevity after correction for multiple comparisons (*q* value<0.05). Specifically, alleles 16 and 17 in *D12S391* were negatively associated with longevity [OR adjusted by sex for allele 16=0.41 (95 % CI 0.23–0.71), *q* value=0.03; OR adjusted by sex for allele 17=0.5 (95 % CI 0.31–0.79), *q* value=0.045] when compared to the most frequent allele in the group control (allele 18). On the other hand, allele 11 in *D22S1045* as well as allele 15 in *D2S441* were positively associated with longevity [OR adjusted by sex for allele 11 in *D22S1045*=1.67 (95 % CI 1.17–2.39), *q* value=0.04; OR adjusted by sex for allele 15 in *D2S441*=2.16 (95 % CI 1.36–3.44), *q* value=0.009] after comparing them to the reference alleles for each of the STRs. On the other hand, the statistical power analysis suggested that the study had enough power (>0.8) to detect an OR value of 1.5 or above, when risk alleles frequency was ≥0.1 (i.e., the frequency of allele 11 in *D22S1045*), or an OR value of 1.7, when risk allele frequency was ≥0.05 (i.e., the frequency of allele 17 in D12S391 or allele 15 in *D2S441*) (see Supplementary Table S1). Specifically for alleles 9.3+10 in *THO1* (previously associated with longevity by Tan et al. 2002 but without a significant association in our study) and allele 10 in *CSF1PO* (previously related to longevity by Hui et al. 2011 and with a borderline significant trend in our study), statistical power calculations indicated that given the frequency of these alleles in controls (0.312 and 0.315, respectively) (Supplementary Table S3), we would have a power of 87 % to detect an OR≥1.35.

Discussion

The aim of the present study was to test the extent to which a group of STR markers (21 STRs including the previously reported *THO1* and *CSF1PO)* spread throughout the genome are associated with human longevity. Data from our nonagenarians and younger controls revealed that specific alleles at *D12S391*, *D22S1045*, and *D2S441* STR markers are strongly associated with the ability of attaining exceptional old age. However, *THO1*, which has been reported to be associated with longevity in Italian men (De Benedictis et al. 1998; Tan et al. 2002), did not exhibit a significant impact on longevity in northern Spain population even after applying the same study design used by the authors (i.e., grouping the alleles as small (S) or large (L)) (data no shown). Our results are in line with those of von Wurmb-Schwark and colleagues (von Wurmb-Schwark et al. 2011), whose results did not support the involvement of the *THO1* locus in the modulation of human longevity in Germans. The distribution of *THO1*, specifically that of the allele 9.3, shows a geographic gradient

Table 1 Main effect of the STRs showing a significant association with longevity

		χ^2 test			Controls		Cases		OR		
STR	χ^2	df	*p* value	Allele	*n*	%	*n*	%	OR (95 % CI)	*p* value	*q* value
CSF1PO	15.83	8	0.045*	Ref: 11	341	33.0	219	36.0	1		
				10	325	31.5	153	25.2	0.75 (0.57–0.97)	0.029	0.232
D12S391	30.55	15	0.010*	Ref: 18	133	12.9	112	18.4	1	–	
				1516	44	4.3	15	2.5	0.41 (0.22–0.79)	0.008	0.12
				16	63	6.1	22	3.6	0.41 (0.23–0.71)	0.002	0.03*
				17	98	9.5	39	6.4	0.5 (0.31–0.79)	0.003	0.045*
				17.3	37	3.6	15	2.5	0.5 (0.25–0.96)	0.037	0.55
D19S433	24.05	13	0.031*	[a]	–	–	–	–	–	–	–
D22S1045	20.49	9	0.015*	Ref: 16	432	41.9	218	35.9	1	–	
				11	92	8.9	75	12.3	1.67 (1.17–2.39)	0.005	0.04*
				12	6	0.6	9	1.5	2.94 (0.99–8.65)	0.05	0.4
				15	376	36.4	235	38.7	1.29 (1.02–1.63)	0.036	0.288
D2S441	22.83	9	0.007*	Ref: 14	382	37.0	189	31.1	1		
				15	45	4.4	45	7.4	2.16 (1.36–3.44)	0.001	0.009*
SE33	64.04	44	0.026*	[a]	–		–		–	–	–

[a] None of the alleles tested is significantly different from the reference allele with respect to longevity (p value>0.05)

*q value<0.05 (statistically significant after FDR correction)

of decreasing frequency from west to east and north to south (Huckenbeck et al. 2004; von Wurmb-Schwark et al. 2011), and it has been suggested that discrepancies in *THO1*-longevity studies might be due to a population-specific effect (von Wurmb-Schwark et al. 2011). This population-specific effect can also be seen in Supplementary Table S5, where the comparison of the genotypic frequencies of *THO1* across three different populations of nonagenarians and younger controls from Europe (northern Spain, Germany, and northern and southern Italy) clearly shows that the homozygous LL genotype is much less common in northern Italian men (0.06) as well as in southern Italian women (0.11) than in Germans (0.25) or northern Spanish (0.27). Therefore, more population-based case-control association studies together with more detailed functional studies are needed to shed light on this question. On the other hand, *CSF1PO* locus, also related to human longevity in a Chinese population, did show a different allele distribution between our cases and controls (χ^2 test, p value< 0.05). Specifically, allele 10 showed a negative association with longevity (OR adjusted by sex=0.75 (95 % CI 0.57–0.97), p value=0.029, q value=0.609), although this association did not reach statistical significance after correction for false discovery using BH procedure (Table 1). We note that the statistical power of a given study is of paramount importance; this is especially true where a lack of association is reported. On the basis of the power calculations carried out (Supplementary table S1) and given the frequency of alleles 9.3+10 in *THO1* and allele 10 in *CSF1P01* in controls, the current sample size (304 cases and 516 controls) provides a power of 87 % to detect an OR≥1.35, which suggests that the lack of significant association may be evidence that these STRs do not influence longevity. However, there is still a non-trivial chance that the association could have been missed, either due to a smaller size effect (i.e., OR<1.35) or just by chance, as with 87 % power, there is a probability of 13 % of not detecting a true association by chance.

It is of note that besides the *CSF1PO* marker, five additional STRs representing the 28.4 % of the STRs studied herein showed a different allele distribution between the long-lived individuals and the younger controls (χ^2 test, p value<0.05). Given no true association, we would expect that 1 out of 21 of the tests to be significant at the p<0.05 level, just due to chance. Thus, 6 significant associations out of 21 comparisons are more than what expected just by chance, which suggests an extensive existence of longevity associated genes in the genome.

Our results indicate that allele 11 in *D22S1045* was positively associated with the likelihood of becoming a nonagenarian in our cohort [OR adjusted by sex=1.67 (95 % CI 1.17–2.39), *q* value=0.04]. *D22S1045* (22q12.3) is the only of the three significant STRs located within an intragenic region. Specifically, *D22S1045* is located within intron 4 of the gene encoding the β subunit of the receptor for interleukin 2 (IL-2Rβ) and is primarily expressed in the hematopoietic system, where it is involved in the activation of T and NK cell subsets (Malek and Castro 2010). In this regard, studies in mice showed that the absence of *IL-2*, with the consequent failure of transmission of biological signal, causes a decrease of the autoimmune response and lower autoinflammatory response (Zheng et al. 2007). Therefore, alterations in the interleukin 2 receptor and consequently in the autoinflammatory response could have a significant impact on life expectancy. However, further studies on the linkage disequilibrium analysis between the *D22S1045* marker and relevant genetic variants in *IL-2* together with new population-based *D22S1045*-longevity studies will be necessary to clarify the effect of this marker on longevity.

With respect to *D12S391* (12p13.2), it is located in an intergenic region upstream of the *MANSC1* (MANSC domain containing protein 1) gene locus at 28.836 Mb. *MANSC1* contains a MANSC (motif at N terminus with seven cysteines) domain. This domain is a well-conserved seven-cysteine-containing motif that is present at the N terminus of higher multicellular animal membrane and extracellular proteins, including low-density lipoprotein receptor-related protein 11 (LRP-11), hepatocyte growth factor activator inhibitor 1 (HAI-1), and some uncharacterized proteins (Guo et al. 2004). *MANSC1* has been found to be deregulated in both human prostate cancer (Wu et al. 2006) and prostate cancer cell lines (Dozmorov et al. 2009), as well as in myeloid malignancies (Haferlach et al. 2011). On the other hand, *D2S441* (2p14) is also positioned in an intergenic region upstream of the nuclear matrix protein *C1D* coding gene locus at 29.033 Mb. *C1D* is an activator of the DNA-dependent protein kinase, which plays an essential role in the DNA double-strand break repair (Erdemir et al. 2002). In the current work, we did not carry a genetic linkage study through which we could test linkage disequilibrium between these STR markers and polymorphisms in *MANSC1* and *C1D*, which would ultimately be associated with human longevity. However, the strong negative association that we observed between alleles 16 and 17 in *D12S391* and allele 15 in *D2S441* and longevity [OR adjusted by sex for allele 16=0.41 (95 % CI 0.23–0.71), *q* value=0.03; OR adjusted by sex for allele 17=0.5 (95 % CI 0.31–0.79), *q* value=0.045; OR adjusted by sex for allele 15=2.16 (95 % CI 1.36–3.44), *q* value=0.009, respectively], suggests that these STRs might be associated with gene variants that have a negative impact on the ability of attaining exceptional old age in humans. We note that for *D12S391*, association is not centered in a particular allele, but in a series of consecutive alleles. This may be results from the exceptionally high mutation rate (0.0031) (Hering and Muller 2001) of the *D12S391* STR marker following the stepwise mutation model, by which other allelic variants apart from that with the founder effect would be created.

In conclusion, the data here presented does not support the involvement of *THO1* and *CSF1PO* STRs in the modulation of life expectancy in humans, but does show a clear association among *D12S391*, *D22S1045*, and *DS441* STR markers and longevity. Of special interest are alleles 11 and 12 in *D22S1045*, within the IL-2Rβ-coding gene, which could be related to a lower autoinflammatory response and therefore an increased life expectancy. In addition, we note that 28.4 % of the studied STRs, which are all spread throughout the genome, displayed different allelic frequencies between nonagenarians and controls, thus suggesting that the genomic portrait of the human longevity is far complex, and probably shaped by a high number of genomic loci.

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Conflict of interest The authors declare that they have no conflict of interest.

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