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Analysis of HLA-DRB1,DQA1,DQB1 haplotypes in Sardinian centenarians

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Abstract

Some genetic determinants of longevity might reside in those polymorphisms for the immune system genes that regulate immune responses. Many longevity association studies focused their attention on HLA (the human MHC) polymorphisms, but discordant results have been obtained. Sardinians are a relatively isolate population and represent a suitable population for association studies. Some HLA-DR and DQ alleles form very stable haplotypes with a strong linkage disequilibrium. In a previous study on Sardinian centenarians we have suggested that HLA-DRB1∗15 allele might be marginally associated to longevity. HLA-DR,DQ haplotypes are in strong linkage disequilibrium and well conserved playing a role in the association to diseases. Hence, we have evaluated, by amplification refractory mutation system/polymerase chain reaction (ARMS-PCR) the HLADQA1 and HLA-DQB1 allele frequencies in 123 centenarians and 92 controls from Sardinia to assess whether the association to HLA-DRB1∗15 allele may be due to the other genes involved in the HLA-DR,DQ haplotypes. The frequencies of HLA-DQA1,DQB1 haplotypes were not significantly modified in centenarians. Nevertheless by evaluating the frequency of DRB1∗15 linked haplotypes, we observed a not significant increase in centenarians of HLA-DQA1∗01,DQB1∗05 and HLA-DQA1∗01,DQB1∗06 haplotypes. These data suggest that these haplotypes might have a role in determining life span expectancy and longevity.

Keywords

Centenarians; HLA-DQA1; HLA-DQB1; Immune response; Longevity; Sardinia

1. Introduction

Longevity is the result of several interacting factors including genetic, environmental and behavioural components (Cournil and Kirkwood, 2001). However, several studies suggest that human longevity is inextricably linked to the optimal function of the immune system. Hence, genetic determinants of longevity might reside in the polymorphisms for genes that regulate

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immune responses as major histocompatibility complex (MHC) genes (Candore et al., 2003). The HLA (the human MHC) region encompasses over 4 Mb of DNA on the chromosome band 6p21.3 and its extensive characterisation has recently culminated in the determination of the nucleotide sequence of the entire region, confirming the presence of ~220 genes. The MHC is traditionally divided into the class I, class II and class III regions. Most HLA genes involved in the immune response fall into classes I and II, which encode highly polymorphic heterodimeric glycoproteins involved in graft rejection and antigen presentation to T cells. However, many genes of the class III region are also involved in the immune and inflammatory responses (Candore et al., 2004). Longevity has been shown to be associated with a positive selection of HLA alleles or haplotypes that confer resistance to infectious diseases, via peptide presentation or via antigen non-specific control of immune response, respectively. Some well planned and designed association studies performed in Caucasians suggest that longevity is associated with HLA-DR11 allele or HLA-B8,DR3 haplotype, whereas other studies do not confirm these observations. Association studies, indeed, are subjected to a number of possible confounding factors, among the others the homogeneity of the population in term of geographical origin (Caruso et al., 2000, 2001; Candore et al., 2004). Due to the lack of large-scale heterogeneity, the Sardinians represent a suitable population for association studies used to dissect the complex traits as longevity. The relatively homogeneous Sardinian population is indeed an ancient genetic isolate, which genetic pool is characterised by a relative little genetic flow from the different populations that have invaded the island during the last 3000 years (Carru et al., 2003; Lio et al., 2003). In a previous study, we have evaluated HLA-DRB1 frequencies in Sardinian centenarians and controls, showing that HLA-DRB1∗15 was increased in centenarians, although no more significant after Bonferroni's correction (Lio et al., 2003). On the other hand, HLA region contains a remarkable number of genes forming some very stable haplotypes, characterised by a strong linkage disequilibrium, probably conferring a selection advantage (Candore et al., 2004). Some of the highly conserved haplotypes are composed by the HLA-DR,DQ alleles and, in some instances, HLA-DQ alleles seem to play a central role in the association to diseases (Klein and Sato, 2000; Cataldo et al., 2003). So, in the present paper, we have evaluated whether the previously demonstrated association to longevity is due to HLA-DRB1∗15 per se or to other HLA-DQ alleles in linkage disequilibrium with this gene (Klein and Sato, 2000; Gaur et al., 1998).

2. Materials and methods

2.1. Subjects and study design

The AKEA study of Sardinian centenarians (the name “AKEA” is derived from Sardinian expression that means “health and life for 100 years!”) was carried out between January 1st and December 31st 1997 (Deiana et al., 1999). One hundred forty-one centenarians underwent a full interview and 129 donated a blood sample. The birth date of centenarians was checked by matching information from the census registry, the baptism registry of the local parish archive, the social security document, and the testimony of a first-degree relative. The Sardinian centenarians display a men/women ratio of 1:2 instead of the most common 1:4–1:10 ratio (Deiana et al., 1999; Franceschi et al., 2000). For each centenarian, a 60-year (±1 year) old control of the same gender was randomly selected from the inhabitants of the same province. This age was chosen based on the consideration that at this age both men and women have less than 1% probability of becoming centenarians (Vaupel, 1997). For all controls, those living in the same municipality were excluded to avoid excessive consanguinity. Overall 290 sexagenarians randomly selected within the four Sardinian provinces were invited to join the study as controls and 154 agreed to participate and to provide a blood sample. Written informed consent for enrolling in the study and for personal data management was obtained from all the subjects according to Italian laws. Blood specimens were collected in tripotassium EDTA

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sterile tubes and immediately stored at −70 °C. Genomic DNA was stored at −20 °C for the different genetic analyses.

2.2. HLA-DQ typing

DNA samples for HLA-DQ typing were available from 123 centenarians (83 women and 40 men) and from 92 controls (58 women and 34 men). One hundred twenty out of 123 centenarians and 86 out 92 subjects had been previously typed for HLA-DRB1 alleles (Lio et al., 2003). HLA-DQ alleles were genotyped by amplification refractory mutation system/ polymerase chain reaction using primer sets and PCR conditions described by Bunce et al. (1995) with mino modifications. Briefly, a low-intermediate resolution SSP (primer specific sequence) PCR typing were performed separately for HLA-DQA1∗ and DQB1∗ alleles using primer mix and annealing temperature reported in Table 1. Each PCR consisted of 10 ng of DNA mixed in a 13 μl total volume containing 200 μM dNTPs, 1.5 mM $MgCl_2$, 16.6 mM ammonium sulphate, 67 mM Tris, 1.0 μM of forward and revers primers. 0.2 U TAQ-polimerase were added to each PCR mixes. Cycling was performed at 96 °C for 5 min. and 30 cycle at 96 °C for 30″, DQA∗ or DQB∗ specific annealing temperature for 30″ (Table 2), and 72 °C for 45″ min, followed by a final extension of 2 min at 72 °C. Allele specific PCR products were detected by electrophoresis on 2% agarose.

2.3. Statistical analysis

HLADQA1 and DQB1 allele frequencies were evaluated by gene count and haplotype frequencies calculated by a maximum likelihood algorithm (Arlequin Software, University of Geneva). 2 × 2 tables were constructed to determine statistical significance (χ^2 test with Yate's correction) of differences in HLA haplotype frequencies between centenarians and controls. Obtained *P* values were multiplied for the number of alleles or haplotypes under study (Bonferroni's correction). The data were tested for the goodness of fit between the observed and expected genotype values and their fit to Hardy–Weinberg equilibrium.

3. Results

Table 2 shows the results of our study. Within each group of centenarians and controls, the haplotype distributions were consistent with those predicted by the Hardy–Weinberg equilibrium. Importantly, we need to point out that HLA frequencies obtained in our control population are not different from those obtained in other studies performed on Sardinians (Lampis et al., 2000). The frequencies of HLA-DQA1 and HLA-DQB1 alleles were not significantly different in centenarians (both in women and in men) with respect to controls. Apart from the association between HLA antigens and longevity, the association between heterozygosity at HLA loci and longevity has also been investigated, since heterozygote subjects are thought more fit for survival than homozygote ones (Caruso et al., 2000,2001). On the basis of haplotype distribution, we have been able to show an equal percentage of heterozygote subjects in centenarians and controls (11.4% vs. 15.2%). Moreover, by evaluating the frequency of the haplotypes linked to DRB1∗15 allele, previously found to be associated to longevity in Sardinians (Lio et al., 2003), we only observed a not significant increase in centenarians both of HLA-DQA1∗01,DQB1∗05 and HLA-DQA1∗01, DQB1∗06 haplotypes.

4. Discussion

MHC polymorphisms have been the focus of a vast number of ageing association studies. One of the limitations in the most reported studies is the number of aged individuals available of both genders, and the lack of complete background histories of health or ethnicity for study participants.

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Sardinians are characterised by a peculiar genetic background. In particular in their seminal paper Piazza et al. (1989) analysing the I and II class HLA allele and haplotype distribution in Italy showed an exclusive and peculiar HLA allele and haplotype distribution and frequency that was totally statistically different compared to the other Italian Regions. This prompt us to evaluate the role of HLA genes in favouring the relative higher frequency of centenarians, and in particular of male centenarians among Sardinians. Our attention was focused on DQ haplotypes associated to DRB1∗15 allele, marginally associated to longevity in Sardinian centenarians (Lio et al., 2003) follow or not the same trend.

Data herein reported suggest that different class II HLA genes have a different impacton life span expectation and longevity. Our results seem in good agreement with other reports on neutral effect of HLA-DQ genes on longevity (Caruso et al., 2000, 2001). Present data were recently confirmed by a family based study of Sardinian Centenarians from our group (Scola et al., 2006). Actually, typing the HLA-DQA1 and HLA-DQB1 alleles of 24 sib (age range 85–97) centenarian pairs we were unable to demonstrate a significant difference between the observed and expected percentage of DQA1∗ or DQB1∗ allele sharing.

On the other hand with the exception of Celiac Disease and some other diseases, most of the studies on association among HLA class II loci and disease have individuated the HLA-DR locus as the major susceptibility component (Caruso et al., 2001; Cataldo et al., 2003; Klein and Sato, 2000). Moreover, in the only study on association between centenarians and HLA-DQ alleles (Akisaka et al., 1997), results similar to our study were obtained. In fact in the Okinawan Japaneses, well known for their longevity, HLA-DRB1∗1401, HLA-DQB1∗0503, HLADQA1∗0101 = 0104 and HLA-DQA1∗05 were significantly increased in the centenarians. The significant increase of HLA-DQB1∗0503 and/or HLA-DQA1∗0101 = 0104 in the centenarians may be well explained by a linkage disequilibrium with HLA-DRB1∗1401 allele.

However, also taking into account well planned and designed studies, discordant results have been obtained. The discordant results obtained in MHC/ageing association studies, might be due to distinct linkage in different cohorts or to other interacting, genetic or environmental factors or to the heterogeneity of ageing. Nevertheless, bearing all the reported studies in mind, there is no convincing evidence of a strong, direct association between longevity and any MHC alleles (Caruso et al., 2000, 2001; Candore et al., 2004; Scola et al., 2006).

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Table 1

Primer sequences and annealing temperature used (T°) for low/intermediate resolution Typing of HLA-DQA1 and DQB1 alleles

Mix No.	5′ Primer	3′ Primer	*T*°	HLA-DQ specificities
1	CGGTCCCTCTGGCCAGTA	CCTCGCCCTGACCACCG	61 °C	DQA1∗0101-02 0104
2	CCATGAATTTGATGGAGATGAGC	CCTCGCCCTGACCACCG	61 °C	DQA1∗0102-03
3	ACGGTCCCTCTGGCCAGTT	CCTCGCCCTGACCACCG	61 °C	DQA1∗0103
4	GCCCTTGTGGAGGTGAAGA	AGTGGTTGGGGCTCTGGTTT	61 °C	DQA1∗01041
5	ACGGTCCCTCTGGCCAGTT	GCGGGTCAAATCTAAGTCTGT	61 °C	DQA1∗0201
6	CCCTCGCCCTGACCACCA	TG(T/C)GGAACAGAGGCAACT	61 °C	DQA1∗0201 0301-02
7	GTCCCTCTGGCCAGTA	CACATACCATTGGTAGCAGCA	61 °C	DQA1∗0401
8	CTCAGACAATTTAGATTTGACCC	GAGTTGGAGCGTTTAATCAGAC	61 °C	DQA1∗0501
9	CTCAGACAATTTAGATTTGACCG	GAGTTGGAGCGTTTAATCAGAC	61 °C	DQA1∗0502
10	ACGGTCCCTCTGGCCAGTT	GGTCAAATCTAAATTGTCTGAGA	61 °C	DQA1∗0601
11	TCAGACAATTTAGATTTGACCC	GAGTTGGAGCGTTTAATCAGGA	61 °C	DQA1∗0401 0601
12	TCATGCACTCACCCACAATGT	GAGTTGGAGCGTTTAATCAGAC	61 °C	DQA1∗0501 0502
13	GTCCGGTGGTTTCGGAATGA	TGCTCTGGGCAGATTCAGAT	58 °C	DQB1∗0201
14	TCCGGTGGTTTCGGAATGG	GTGCTCCACGTGGCAGGT	58 °C	DQB1∗0202-03
15	GACGGAGCGCGTGCGTTA	CTGTTCCAGTACTCGGCGT	58 °C	DQB1∗03 0601
16	GACGGAGCGCGTGCGTTA	CGTGCGGAGCTCCAACTG	58 °C	DQB1∗0301 0304
17	GTGCGTCTTGTGACCAGATA	TGGCTGTTCCAGTACTCGGCGG	58 °C	DQB1∗0302 0307
18	GACGGAGCGCGTGCGTCT	CTGTTCCAGTACTCGGCGT	58 °C	DQB1∗0203 03032 0306
19	GCTACTTCACCAACGGGACC	TGCACACCGTGTCCAACTC	58 °C	DQB1∗0305
20	CCCGCAGAGGATTTCGTGTA	CCCCAGCGGCGTCACCA	58 °C	DQB1∗0307
21	CACCAACGGGACOGAGCT	TGGTAGTTGTGTCTGCATACG	58 °C	DQB1∗0401
22	CACCAACGGGACCGAGCG	TGGTAGTTGTGTCTGCATACG	58 °C	DQB1∗0402
23	ACGGAGCGCGTGCGGGG	GCTGTTCCAGTACTCGGCAA	58 °C	DQB1∗0501
24	TGCGGGGTGTGACCAGAC	TGTTCCAGTAGTCGGCGCT	58 °C	DQB1∗0502
25	TGCGGGGTGTGACCAGAC	GCGGCGTCACCGCCCGA	58 °C	DQB1∗0503
26	GTGCGGGGTGTGACCAGAT	TGTTCCAGTAGTCGGCGCT	58 °C	DQB1∗0504
27	TTTCGTGCTCCAGTTTAAGGC	CCGCGGAACGCCAGCTC	58 °C	DQB1∗0601
28	GACGTGGGGGTGTACCGC	AACTCCGCCCGGGTCCC	58 °C	DQB1∗0602-03 0608 0610-11 0613
29	CGTGTACCAGTTTAAGGGCA	TGCACACCGTGTCCAACTC	58 °C	DQB1∗0602-04 0607-13 0302 0305 0307
30	GGAGCGCGTGCGTCTTGTA	TGCACACCGTGTCCAACTC	58 °C	DQB1∗0603-05 0607-09 0612

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Table 2

HLA-DQA1,DQB1 haplotype combination frequencies in 123 centenarians (246 aplotypes) and 92 gender and geographically matched controls (184 aplotypes)

	Centenarians						Controls					
	All (246 haplotypes)		Men (80 haplotypes)		Women (166 haplotypes)		All (184 haplotypes)		Men (68 haplotypes)		Women (116 aplotypes)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Blank	3	1.2	1	1.2	2	1.2	0	0	0	0	0	0
DQA1∗01	0	0	0	0	0	0	2	1.1	1	1.5	1	0.9
DQB1∗03												
DQA1∗01	82	33.3	23	28.8	59	35.5	51	27.7	18	26.5	33	28.4
DQB1∗05												
DQA1∗01	33	13.4	13	16.2	20	12.0	17	9.2	6	8.8	11	9.5
DQB1∗06												
DQA1∗02	7	2.8	2	2.6	5	3.0	7	3.8	4	5.9	3	2.6
DQB1∗02												
DQA1∗02	7	2.8	3	3.8	4	2.4	2	1.1	1	1.5	1	0.9
DQB1∗03												
DQA1∗03	8	3.3	3	3.8	5	3.0	2	1.1	2	2.9	0	0.9
DQB1∗02												
DQA1∗03	23	9.3	8	10.0	15	9.0	13	7.1	4	5.9	9	7.8
DQB1∗03												
DQA1∗03	1	0.4	1	1.3	0	0	2	1.1	0	0	2	1.7
DQB1∗04												
DQA1∗04	4	1.6	2	2.6	2	1.2	1	0.6	1	1.5	0	0
DQB1∗04												
DQA1∗05	50	20.3	16	20.0	34	20.5	50	27.2	15	22.1	35	30.2
DQB1∗02												
DQA1∗05	27	11.0	8	10.0	19	11.4	34	18.5	15	22.1	19	16.4
DQB1∗03												
DQA1∗06	1	0.4	0	0	1	0.6	2	1.1	1	1.5	1	0.9
DQB1∗03												

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	Centenarians						Controls					
	All (246 haplotypes)		Men (80 haplotypes)		Women (166 haplotypes)		All (184 haplotypes)		Men (68 haplotypes)		Women (116 aplotypes)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%

No statistical significant differences were observed comparing haplotype frequencies among centenarians and controls.