Connexin37 1019 gene polymorphism in myocardial infarction patients and centenarians

Keywords: Connexin37; Atherosclerosis; Myocardial infarction (MI); Longevity

To the Editor,

In their recent paper on atherosclerosis, Wong et al. have pointed out the question: “Do allelic variants of the connexin37 1019 gene polymorphism differentially predict for coronary artery disease and myocardial infarction?” In their report, the authors have shown that the Connexin37 (Cx37) 1019C allelic variant is associated with both coronary artery disease (CAD) and myocardial infarction (MI), but not with any of the established CAD risk factors examined in their study. Thus, their results strengthen the importance of screening for the Cx37-C1019T single nucleotide polymorphism (SNP) in CAD and MI risk assessments [1]. Their results are in contrast with other studies, including a large Japanese study and a study from our laboratory performed on a small but very homogeneous sample of young Sicilian patients. Actually, both the studies showed an increase of 1019T SNP in MI patients [2,3]. As discussed by the authors, these discrepant results might depend from a number of reasons, including the use of small sample sizes, sampling biases, mismatches between case and control groups, phenotypic heterogeneity, racial differences, and a failure to recognize gene–gene and gene–environment interactions [1].

To check the validity of our results, we have analysed the distribution of C1019T SNP in centenarian men (age >99) from our homogeneous Sicilian population, since our previous studies have demonstrated that alleles associated to MI susceptibility are not included in the genetic background favouring longevity. Individuals with exceptional longevity possess indeed genetic factors that modulate ageing processes and, in particular, are protective versus cardiovascular diseases. So, pro/anti-inflammatory alleles have a role in determining susceptibility or resistance to immune-inflammatory diseases, including atherosclerosis, and reciprocally in determining or not the possibility to reach the extreme limit of life [4,5]. It is intriguing that in a mouse model of atherosclerosis, the mouse Cx37 protein was shown to be atheroprotective by properly regulating leukocyte recruitment, namely one of the first inflammatory steps in atherosclerotic process [6]. Hence, Cx37 gene may be considered as an inflammatory one. Thus, we have hypothesized that in our longevous population the allele involved in MI susceptibility should be underrepresented. To verify our hypothesis, we typed Cx37-C1019T SNP 56 centenarian men. Centenarian age was verified by researching archival records in the City Hall and/or Church registries, paying attention to the concordance between reported age and personal chronologies (age of marriage and of military service for men, age of first and last pregnancy for women, age of children, among others). They did not have any cardiac risk factors or major age-related diseases (e.g. CAD, severe cognitive impairment, severe physical impairment, clinically evident cancer, or renal insufficiency), although some had decreased auditory and visual acuity.

Genotyping was performed as previously described and obtained results were compared with those of our previous study on the role of Cx37-C1019T SNP on MI [3]. According to our hypothesis, Table 1 shows that the TT genotype 1019 and the T allele were underrepresented in centenarian men, over-represented in male patients whereas age-related controls displayed intermediate values (p = 0.0035 and 0.0007, respectively).

In conclusion, these results support our previous data showing that T allele is a risk factor for MI in the Sicilian population. Besides, centenarian genetic background studies may contribute to clarify the role of key genetic components influencing age associated diseases which are characterized by a multifactorial aetiology, as CAD and MI.
Table 1
Frequency of genotypes and alleles for 1019 C/T Cx37 SNP in 97 young male patients and in 196 healthy age-related male controls and 56 centenarian men from Sicily

<table>
<thead>
<tr>
<th></th>
<th>CC (34%)</th>
<th>CT (44.3%)</th>
<th>TT (21.6%)</th>
<th>+1019C (56.2%)</th>
<th>+1019T (43.8%)</th>
</tr>
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<tbody>
<tr>
<td>AMI patients</td>
<td></td>
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<tr>
<td>Young controls</td>
<td>86 (43.9%)</td>
<td>85 (43.4%)</td>
<td>25 (12.7%)</td>
<td>257 (65.6%)</td>
<td>135 (34.4%)</td>
</tr>
<tr>
<td>Centenarians</td>
<td>36 (64.3%)</td>
<td>15 (26.7%)</td>
<td>5 (9.0%)</td>
<td>87 (77.6%)</td>
<td>25 (22.3%)</td>
</tr>
</tbody>
</table>

Data on MI patients and young controls are from [3]. Significance was obtained by \(\chi^2\) (3 × 3 and 3 × 2 table, respectively): genotypes \(p = 0.0035\) and alleles \(p = 0.0007\). The genotype distribution was in Hardy–Weinberg Equilibrium.

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References


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