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ORIGINAL ARTICLE

Myocardial infarction before and after the age of 45: Possible role of platelet receptor polymorphisms

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KEYWORDS
Myocardial infarction and platelet polymorphisms;
GPIb-V-IX;
GPIa-IIa;
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Abstract
Introduction: We examined the potential role of polymorphisms of the platelet genes *GP1BA* (rs2243093, rs6065 and VNTR), *ITGB3* (rs5918), *ITGA2* (rs938043469) and *P2RY12* (rs2046934, rs6801273 and rs6798347) as risk factors for myocardial infarction (MI).
Methods: The study population was divided into three groups: controls (n=235), MI at age ≤45 years (MI ≤45, n=44), and MI at age >45 years (MI >45, n=78). The control group was further divided into two subgroups (control ≤45 and >45), and subgroups including only men were also considered for statistical analysis. Polymorphisms were detected by polymerase chain reaction and restriction fragment length polymorphism analysis.
Results: Regarding non-genetic risk factors, the control group differed statistically from the MI ≤45 group (p<00.5) in terms of smoking, hypertension, diabetes and obesity, and from the MI >45 group (p<0.05) in terms of hypertension, diabetes, obesity, family history of thrombosis and high cholesterol. For the studied *ITGA2* polymorphism, a statistical difference was found when MI >45 was compared with the control group, with a higher risk of MI in the TT genotype (OR 2.852; 95% CI: 1.092-7.451; p=0.032). In the *GP1BA* rs6065 polymorphism, a statistically significant difference was found between control ≤45 only men and MI ≤45 only men, with a higher risk in the CT genotype (OR 5.568; 95% CI: 1.421-21.822; p=0.016), despite the low numbers included. The other polymorphisms studied did not show any statistically significant correlations.

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Conclusion: There is a statistically significant association between the TT genotype of the *ITGA2* rs938043469 polymorphism and increased risk for MI >45.

PALAVRAS-CHAVE
Enfarte agudo do miocárdio e polimorfismos plaquetários;
GP Ib-V-IX;
GP Ia-IIa;
GP IIb-IIIa;
ADP P2Y12 receptor

Enfarte agudo do miocárdio antes e depois dos 45 anos: possível relação com polimorfismos dos recetores plaquetários

Resumo
Introdução: Determinou-se o papel de polimorfismos dos genes de expressão plaquetária GP1BA (rs2243093, rs6065 e o VNTR p.Ser415_Thr428(0_4)), ITGB3 (rs5918), ITGA2 (rs938043469) e P2RY12 (rs2046934, rs6801273 e rs6798347) como fatores de risco para o enfarte agudo do miocárdio (EAM).
Métodos: A amostra foi dividida em três grupos: Controlo (n=235), EAM ≤45 anos (n=44) e EAM >45 anos (n=78). O grupo Controlo foi ainda dividido em dois subgrupos (Controlo ≤45 e >45). Subgrupos incluindo somente homens também foram considerados para fins estatísticos. Os polimorfismos foram estudados através de PCR e RFLP.
Resultados: Em relação aos fatores de risco não genéticos, o grupo Controlo diferia estatisticamente do grupo EAM ≤ 45 anos (p<0,05) em termos de hábitos tabágicos, hipertensão, diabetes e obesidade e também diferia do grupo EAM >45 anos (p<0,05) nas variáveis hipertensão, diabetes, obesidade, antecedentes familiares de trombose e colesterol. Para o polimorfismo estudado do gene ITGA2, verificou-se uma diferença estatisticamente significativa quando se compararam os grupos EAM >45 anos e Controlo, associando-se o genótipo TT a aumento de risco de EAM (OR 2,852; IC 95% de 1,092 a 7,451; p=0,032). No polimorfismo rs6065 do gene GP1BA foi encontrada uma diferença estatística quando comparados os grupos Controlo ≤ 45 só homens e EAM ≤ 45 só homens, associando-se o genótipo C/T a um maior risco de EAM (OR 5,568; IC 95% de 1,421 a 21,822; p=0,016), apesar do baixo n. Os outros polimorfismos não apresentaram correlação significativa.
Conclusão: Existe uma associação estatística significativa entre o genótipo T/T do polimorfismo rs938043469 do gene ITGA2 e o risco de EAM >45.

Introduction

Platelet receptors are central to physiological platelet responses. They are involved in platelet thrombus formation after vascular injury, being responsible for platelet adhesion to damaged vessel walls and aggregation. Four platelet receptors – glycoprotein (GP) Ib-IX-V, integrin $\alpha2\beta1$ (GPIa-IIa), integrin $\alpha2b\beta3$ (GPIIb-IIIa), and the $P2Y_{12}$ ADP receptor – are crucial for normal hemostasis.[1–4]

GPIb-IX-V initiates platelet adhesion to subendothelial von Willebrand factor (vWF) under high shear stress conditions.[5] The GPIb subunit is composed of two disulfide-linked polypeptides, alpha and beta. The GPIb alpha subunit contains the binding sites for vWF and alpha-thrombin, both of which activate platelets,[6] and is encoded by the *GP1BA* gene.[1]

Integrin $\alpha2\beta1$ is a specific collagen receptor found in platelets and other cell types that mediates platelet adhesion to collagen following platelet activation.[7] It is composed of two subunits, alpha2 and beta1, that are encoded by the *ITGA2* and *ITGB1* genes, respectively.[2]

Integrin $\alpha2b\beta3$ plays a pivotal role in platelet aggregation. The major ligands for this glycoprotein are fibrinogen and vWF, and interaction between these ligands and integrin $\alpha2b\beta3$ begins platelet plug formation.[8] Integrin alpha2b and beta3 are encoded by the *ITGA2B* and *ITGB3* genes, respectively.[3]

The purinergic receptor $P2Y_{12}$ is a Gi-coupled seven-membrane-spanning protein encoded by the *P2RY12* gene[4] that interacts with ADP.[4] ADP stimulates $P2Y_{12}$-mediated inhibition of adenylyl cyclase and activates intracellular signal transduction pathways that stabilize platelet aggregation.[4,9] The fact that this receptor is the target for prasugrel and clopidogrel, both $P2Y_{12}$ inhibitors used as antiplatelet therapy for patients with acute coronary syndromes, is of clinical relevance.[10]

These four platelet membrane receptors present genetic polymorphisms that can affect platelet responsiveness.

Three polymorphisms that influence the function and expression of GPIb-IX-V have been described: a variable number of tandem repeats (VNTR) polymorphism; rs6065 (also known as HPA-2); and rs2243093 (Kozak). All of them