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Single nucleotide polymorphism in coronary artery disease as in-stent restenosis risk factor

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ABSTRACT

In-stent restenosis (ISR) is a challenging complication of coronary stent implantation in both stable coronary artery disease (CAD) and acute coronary syndrome (ACS). Recent scientific approach enables looking closely into its genetic background. This article briefly highlights the already known to increase susceptibility of ISR genetic polymorphisms and summarizes which were not proven to increase the risk of ISR and which may seem protective among CAD patients.

Keywords: polymorphism, genes, in-stent restenosis, coronary artery disease.

Introduction

In-stent restenosis (ISR) is recently challenging complication of coronary stent implantation in both stable coronary artery disease (CAD) and acute coronary syndrome (ACS). Since coronaroplasty is not only done using balloons, the stent era has pushed invasive cardiology further also to the new era of procedures' complications, including drawback due to ISR [1]. Single nucleotide polymorphism (SNP) is a genetic variation leading to change in one specific location causing significant change in coded protein. It leads to over 90% of genetic variation in human species and may vary among different population groups [2]. Linkage between ISR and SNPs may answer the question why in the era of modern cardiology we still need to struggle with repeating invasive procedures. The next question is whether we could isolate these patients and support them with genetic screening and increased number of control visits.

Many factors contribute to CAD, but only some have impact on ISR. SNPs would be a nice marker to examine before we implant stents in stable CAD subject. SNPs of genes coding angiotensin converting

enzyme (ACE – rs1799752), angiotensinogen (rs699), basic fibroblast growth factor (bFGF – rs308395) and renin (rs5705) lead to CAD, but not to ISR [3–5].

In CAD and ISR SNPs proven correlations exist for genes coding transforming growth factor beta 1 (TGF-β1 – rs1800470), platelet-derived growth factor beta (PDGFB – rs2285094), vascular endothelial growth factor A (VEGF-A – rs699947) and connexin 37 (CX-37 – rs1764391) [3, 6, 7]. ISR was found also among patients with CAD and genetic variant of interleukin 18 (IL-18 – rs187238) -137G/G which has not been proven for -137G/C and -137C/C variants obtained from non-CAD controls [8]. Also endothelial nitric oxide synthase (eNOS – rs1799983) was suspected to contribute to susceptibility of ISR in CAD patients its 298G/T variant was investigated together with glutathione peroxidase (GPx-1 rs1050450) 599C/T SNP and both of them were found to play role in ISR significantly [9]. eNOS CAD patients studied in other project were proven that carriers of the 298Asp allele of the eNOS (rs1799983) polymorphism showed a higher frequency of restenosis compared to 298Glu homozygotes [10]. Also cyclin-dependent kinase inhibitor p27

Table 1. Correlation between SNP and increased ISR prevalence

Gene	Polymorphism rs number	In-stent restenosis	Reference number
Angiotensin converting enzyme	Rs1799752	no	4
Angiotensinogen	Rs699	no	4
Renin	Rs5705	No	5
Basic fibroblast growth factor	Rs308395	No	3
Transforming growth factor beta 1	Rs1800470	yes	3
Platelet-derived growth factor beta	Rs2285094	yes	3
Vascular endothelial growth factor A	Rs699947	yes	3
Connexin-37	rs1764391	yes	7
Interleukin-10	Rs1800872	no	
Interleukin-18	Rs187238	yes	8
Glutation peroxidase	Rs1050450	yes	9
Endothelial nitric oxide synthase	Rs1799983	yes	9, 10
Cyclin-dependent kinase inhibitor p27	Rs36228499	yes	13
Cyclin-dependent kinase inhibitor p27	Rs2066827	no	13
Cyclin-dependent kinase inhibitor p27	Rs34330	no	13
Cyclin B1	Rs350099	Yes	11
Cyclin B1	Rs350104	yes	11
Cyclin B1	Rs164390	yes	11
Toll-like receptor 4	Rs4986790	no	15
Toll-like receptor 4	Rs4986791	no	15
Receptor for advanced glycation end products	Rs1800625	No, but roTECTIVE effect	12
CYP2C19*2	Rs4244285	no	14
Epidermal growth factor	rs4444903	no	3

SNP -838C/A (rs36228499) leads to ISR [11]. Cyclin B1 SNPs themselves demonstrate higher ISR risk (rs350099, rs350104, and rs164390) [11]. Interesting may seem protective SNP of receptor for advanced glycation end products (RAGE -374T/A – rs1800625) in -374AA lower susceptibility to ISR was found among 276 subjects [12]. All above data are listed in **Table 1** showing which genetic polymorphism is connected to CAD and ISR.

Although some findings may hopefully show that a kind of genetic marker perfect for screening for ISR would appear, other are unlikely to become one of them. Genes investigated for ISR and correlating neither with increased prevalence of CAD nor with ISR include: cyclin-dependent kinase inhibitor p27 (rs2066827 and rs34330), epidermal growth factor (EGF rs4444903) [3, 13]. Another case might be research done in the field of cytochrome P450 which is responsible for clopidogrel – leading antiplatelet drug – metabolism. 2015 findings indicated that CYP2C19*2 (rs4244285) allele in Arabic origin subjects with a functional CYP2C19*1 allele showed no linkage with ISR [14]. Involvement of immune system in case of Toll-like receptor 4 (TLR4 rs4986790 and rs4986791) [15], IL-10 in Chinese Han population (-592 C/A rs1800872) [16] was not supported.

Taking into consideration hormones, blood vessels controlling molecules, immune system particles and oxidative stress-related molecules that may influence process of ISR and require further investigation, also by means of genetic analysis from large cohorts of patients worldwide. Already provided data support the thesis of genetic background of higher susceptibility to CAD itself, some to atherosclerosis, also located in other than coronary vessels, but ISR is still in phase of analysis. According to the data yet obtained, genetics may play important role in development of ISR among CAD patients by means of either hormonal (ACE, angiotensinogen) or blood vessels controlling agents (eNOS, GPx-1, CX-37, cyclin, cellular growth factors). Thesis of contribution of immune system, supported by logical assumption about inflammatory background of atherosclerosis may not be totally correct since IL-18 genetic polymorphism was solely the only one supported by literature. Neither TLR4, nor IL-10 did not match this hypothesis in large investigated groups compared to patients without ISR. Some referential data exclude one another, but looking closely – investigator take into consideration genetically different populations, i.e. Caucasian and Asian groups should not be considered the same in the fields of genetic analysis. Different

populations although might be (and should be) investigated for finding the same SNPs increasing susceptibility to ISR, need to be also checked for their genetic potential to cause CAD first and, which seems crucial yet omitted in plenty of articles – compared to presence of the same SNP among non-CAD patients, not only investigating CAD subjects group. Another issue worth investigation might be differentiation between ISR, increased by genetic susceptibility and stent type. Important information include: do genes play role in ISR development in different types of stents, does the drug covering drug eluting stents matter among patients with higher presence of particular polymorphisms or does type of stent in comparison with higher susceptibility of ISR genetically proved leads to poorer prognosis. That kind of data would be useful as predictive value for ISR and prognosis among CAD patients, furthermore would lead to individualized therapy among patients subjected to coronaroplasty.

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Conflict of interest statement

The authors declare no conflict of interest.

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References

- Kim MS, Dean LS, In-stent restenosis. *Cardiovasc Ther*. 2011 June;29(3):190–198.
- McCarroll SA, Kuruville FG, Korn JM, et al., Integrated detection and population-genetic analysis of SNPs and copy number variation. *Nat Genet*. 2008 Oct;40(10):1166–74.
- Osadnik T, Strzelczyk JK, Reguła R, et al. The Relationships between Polymorphisms in Genes Encoding the Growth Factors TGF- β 1, PDGFB, EGF, bFGF and VEGF-A and the Restenosis Process in Patients with Stable Coronary Artery Disease Treated with Bare Metal Stent. Wallace GR, ed. *PLoS ONE*. 2016;11(3):e0150500. doi:10.1371/journal.pone.0150500.
- Osadnik T, Strzelczyk JK, et al. Relationship of the rs1799752 polymorphism of the angiotensin-converting enzyme gene and the rs699 polymorphism of the angiotensinogen gene to the process of in-stent restenosis in a population of Polish patients with stable coronary artery disease. *Adv Med Sci*. 2016 Mar 28;61(2):276–281. doi: 10.1016/j.advms.2016.03.006.
- Fragoso JM, Alvarez-León E, et al. The C4280A (rs5705) gene polymorphism of the renin (REN) gene is associated with risk of developing coronary artery disease, but not with restenosis after coronary stenting. *Exp Mol Pathol*. 2015 Aug;99(1):128–32. doi: 10.1016/j.yexmp.2015.06.012. Epub 2015 Jun 20.
- Fragoso JM, Zuñiga-Ramos J. The T29C (rs1800470) polymorphism of the transforming growth factor- β 1 (TGF- β 1) gene is associated with restenosis after coronary stenting in Mexican patients. *Exp Mol Pathol*. 2015 Feb;98(1):13–7. doi: 10.1016/j.yexmp.2014.11.007. Epub 2014 Nov 13.
- Yang Y, Guo SX, et al. [Association between 1019C/T polymorphism of Connexin 37 gene and restenosis after coronary stenting]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2013 Aug;30(4):456–60.
- Liu W, Liu Y, et al. Plasma levels of interleukin 18, interleukin 10, and matrix metalloproteinase-9 and -137G/C polymorphism of interleukin 18 are associated with incidence of in-stent restenosis after percutaneous coronary intervention. *Inflammation*. 2013 Oct;36(5):1129–35
- Shuvalova YA, Kaminniyi AI, et al. Association between polymorphisms of eNOS and GPx-1 genes, activity of free-radical processes and in-stent restenosis. *Mol Cell Biochem*. 2012 Nov;370(1–2):241–9.
- Gomma AH, Elrayess MA, et al. The endothelial nitric oxide synthase (Glu298Asp and -786T>C) gene polymorphisms are associated with coronary in-stent restenosis. *Eur Heart J*. 2002 Dec;23(24):1955–62.
- Silvestre-Roig C, Fernández P, et al. Genetic variants in CCNB1 associated with differential gene transcription and risk of coronary in-stent restenosis. *Circ Cardiovasc Genet*. 2014 Feb;7(1):59–70.
- Falcone C, Emanuele E, et al. The -374T/A variant of the rage gene promoter is associated with clinical restenosis after coronary stent placement. *Int J Immunopathol Pharmacol*. 2007 Oct-Dec;20(4):771–7.
- van Tiel CM1, Bonta PI, et al. p27kip1–838C>A single nucleotide polymorphism is associated with restenosis risk after coronary stenting and modulates p27kip1 promoter activity. *Circulation*. 2009 Aug 25;120(8):669–76.
- Nozari Y1, Vosooghi S, et al. The impact of cytochrome P450 2C19 polymorphism on the occurrence of one-year in-stent restenosis in patients who underwent percutaneous coronary intervention: A case-match study. *Anatol J Cardiol*. 2015 May;15(5):348–53. doi: 10.5152/akd.2014.5418.
- Beijk MA, Boekholdt SM, et al. Toll-like receptor 4 gene polymorphisms show no association with the risk of clinical or angiographic restenosis after percutaneous coronary intervention. *Pharmacogenet Genomics*. 2010 Sep;20(9):544–52
- Gao J, Cui RZ [Relationship of interleukin-10 gene polymorphism with restenosis after percutaneous coronary intervention in Chinese]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2011 Feb;28(1):42–6.

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