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Association of *CDKN2A/B*, *ADTRP* and *PDGFD* polymorphisms with coronary atherosclerosis in Japan

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Background: Genome-wide association studies have identified a series of susceptibility loci for coronary artery disease (CAD). Our study attempted to replicate the results for eight of these loci, *CDKN2A/B* (rs1333049), *ADTRP* (rs6903956), *PDGFD* (rs974819), *TCF21* (rs12190287), *COL4A1-A2* (rs4773144), *HHIPL1* (rs2895811), *ADAMTS7* (rs4380028), and *UBE2Z* (rs46522), in pathologically defined atherosclerosis of the coronary artery. Methods: Autopsy cases of elderly Japanese subjects were enrolled in the JG-SNP study (n=1536). Polymorphisms were genotyped, and their association with coronary stenosis index (CSI) and pathological myocardial infraction (MI) was investigated. Potential combinatorial effects of susceptibility loci were also investigated. Results: Among the eight loci tested, three gave a sign of positive association. *CDKN2A/B* showed the most robust association with CSI and MI (p=0.007 and OR=1.843, 95% CI 1.293-2.629, p=0.001, for CC+CG vs. GG). *ADTRP* showed association with CSI and MI, but the risk allele was opposite from the original report (p =0.008 and OR=1.652, 95% CI 1.027-2.656, p =0.038 for GG vs. AA+AG). *PDGFD* showed a suggestive association with CSI in females, but not in males (p =0.023). *CDKN2A/B*, and *ADTRP* were significantly associated with severity of CSI, in a case-control setting (top 75% vs. the rest: OR=1.683, 95% CI 1.219-2.323, p =0.002 for CC+CG vs. GG, OR=1.839, 95% CI 1.172-2.886, p =0.008 for GG vs. AA+AG, respectively). The cumulative risk allele counting of *CDKN2A/B*, *ADTRP*, and *PDGFD* indicated that increasing number of risk alleles associated with higher CSI (p <0.001). Conclusions: Our data confirms the association of *CDKN2A/B* with CAD, and suggests a different associated risk allele of *ADTRP*. *PDGFD* shows a gender specific association to CAD. The combination of multiple risk alleles may associate with higher risk of CAD.

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