Association of \textit{CDKN2A/B}, \textit{ADTRP} and \textit{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, \textit{CDKN2A/B} (rs1333049), \textit{ADTRP} (rs6903956), \textit{PDGFD} (rs974819), \textit{TCF21} (rs12190287), \textit{COL4A1-A2} (rs4773144), \textit{HHIPL1} (rs2895811), \textit{ADAMTS7} (rs4380028), and \textit{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. \textit{CDKN2A/B} showed the most robust association with CSI and MI (\textit{p}=0.007 and OR=1.843, 95\% CI 1.293-2.629, \textit{p}=0.001, for CC+CG vs. GG). \textit{ADTRP} showed association with CSI and MI, but the risk allele was opposite from the original report (\textit{p}=0.008 and OR=1.652, 95\% CI 1.027-2.656, \textit{p}=0.038 for GG vs. AA+AG). \textit{PDGFD} showed a suggestive association with CSI in females, but not in males (\textit{p}=0.023). \textit{CDKN2A/B}, and \textit{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, \textit{p}=0.002 for CC+CG vs. GG; OR=1.839, 95\% CI 1.172-2.886, \textit{p}=0.008 for GG vs. AA+AG, respectively). The cumulative risk allele counting of \textit{CDKN2A/B}, \textit{ADTRP}, and \textit{PDGFD} indicated that increasing number of risk alleles associated with higher CSI (\textit{p}<0.001). Conclusions: Our data confirms the association of \textit{CDKN2A/B} with CAD, and suggests a different associated risk allele of \textit{ADTRP}. \textit{PDGFD} shows a gender specific association to CAD. The combination of multiple risk alleles may associate with higher risk of CAD.