CASE REPORT

Genetic Analysis of a Young Adult Presented with Acute Myocardial Infarction with No Traditional Risk Factors: A Novel Case Report

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ABSTRACT

Myocardial infarction (MI) in the young adults are more common among the Asians compared to the Caucasians. It is of great interest to investigate the genetic risks that increase the susceptibility of MI in young patients with no family history. We conducted a genetic analysis on a young adult diagnosed with acute MI. The coronary angiogram showed acute complete occlusion of the left anterior descending artery with 40% left ventricular ejection fraction (LVEF). Patient's DNA was subjected to genotyping using Infinium Asian Screening Array. The genotypes were annotated and associated with risks of cardiovascular diseases catalogued in GWAS database. Ninety-four genetic variants were detected. Patient has more than half of the genetic variants being homozygous risk genotypes for coronary artery and coronary heart diseases. Identifying the potential genetic modifiers associated with MI in young patients is of great interest to help the clinician make informed decisions to implement preventive and personalised medicine for this patient.

Keywords: Young onset myocardial infarction, ST-elevation, Infinium Asian Screening Array, Preventive and personalised medicine

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INTRODUCTION

Myocardial infarction (MI) is the death of myocytes due to prolonged ischemia, usually due to occlusion of coronary arteries. Men present with MI at an earlier age compared to women (64.9 vs 72.3 years) (1). Young MI, defined as an onset of MI < 40 years of age, is probably caused by pathogenic factors and pathways that are different from older patients. The prevalence of myocardial infarction (MI) in young individuals is less than 10%. In Malaysia, younger cohort of MI patients were more prevalent compared to the Caucasians (2).

Most of the cardiovascular risks in young MI patients have a predominant genetic component. The relationship between genetic predisposition to young MI has not been established but common genetic contributors for these diseases are well validated. We report here genetic analysis in a young patient with no risk factors who was admitted due to acute myocardial infarction. Recognizing genetic modifiers that affect disease phenotype may help identify young people at risk of MI before disease onset. This will help clinicians make informed decisions to implement preventive and personalised medicine.

CASE REPORT

A healthy 30-year-old gentleman presented to the emergency department at 2 a.m. due to sudden onset of angina. He was a non-smoker and has no traditional risk factors for coronary artery disease (CAD). He denied any use of recreational drugs or health supplements.

His ECG showed sinus rhythm with ST-elevation in the anterior leads. On physical examination, his body mass index (BMI) was 27.5 kg/m^2 from the height of 170 cm and weight of 79.6 kg. His blood pressure was 121/81 mmHg and heart rate of 64 beats per minute. Cardiac sounds were normal S1 and S2 with clear lung fields on auscultation. Bedside Transthoracic Echocardiogram

revealed akinetic areas over mid to apical anterior wall with left ventricular ejection fraction (LVEF) of 40%. Raised high sensitive Troponin-I of 16335 pg/mL (<14.5 pg/mL). No risk factors was identified on blood investigations: Total cholesterol 5.4 mmol/L, Triglyceride 1.19 mmol/L, LDL-cholesterol 3.53 mmol/L, HDL-cholesterol 1.32 mmol/L and fasting plasma glucose of 4.9 mmol/L. Coronary angiography showed acute total occlusion (ATO) of the mid left anterior descending (LAD) artery (Figure 1). He underwent Primary percutaneous intervention (PCI) which a 3.5 x 30 mm stent was deployed and post dilated with a 4.0 x 14 mm non-compliant balloon to the mid-LAD. Final results showed TIMI 3 flow down the LAD and diagonal branch. (Figure 2). We then sent his blood sample for genetic risk analysis to assess for any genetic predisposition for

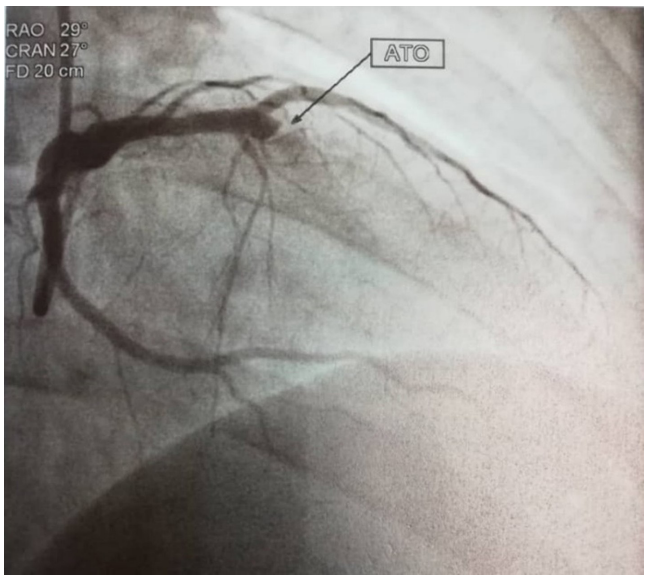

Figure 1: Illustration showing acute total occlusion (ATO) – absence of contrast flow beyond mid left anterior descending artery

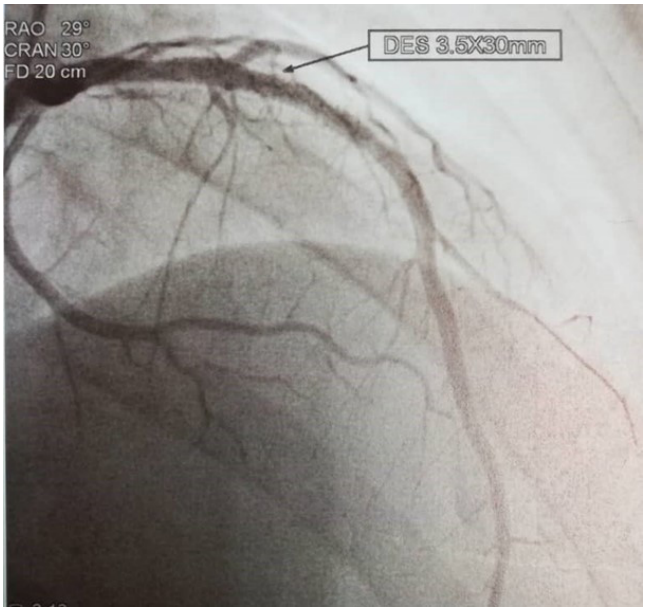

Figure 2: Post drug eluting stent (DES) deployment to the culprit lesion

coronary heart diseases and young onset myocardial infarction. Patient's DNA was extracted using QIAamp® DNA Blood Mini Kits following manufacturers' instructions (Qiagen Biotech Malaysia, Kuala Lumpur, Malaysia) and prepared according to the Infinium Asia Screening Array protocol (Illumina, San Diego, CA, USA). The genotyped SNPs or variants were called with GenomeStudio 2.0 software (Infinium Genotyping Data Analysis). The genotypes were then annotated against traits related to cardiovascular diseases in the GWAS database (3). Information retrieved from the GWAS database included the rsID, the traits, the risk alleles, odd ratio (or Beta value). The call rate of the Beadchip scanned was 97.48%. Ninety-four (94) Single Nucleotide Polymorphism (SNP)s were detected in this patient and annotated to the cardiovascular diseases risks in GWAS database (Table I). A total of 45 SNPs were associated with coronary artery disease (CAD) and coronary heart diseases (CHD); and 50% of the SNPs were homozygous. Six SNP (4 homozygous and 2 heterozygous) were annotated for risks of abdominal aortic aneurysm (odd ratio >1.0). Ten SNPs were associated with atrial fibrillation; only 2 are homozygous and the remaining are heterozygous. The patient has 2 heterozygous variants that are associated with Bechet's disease. Notably, the patient was identified to carry rs10428132 of SCN10A associated with BrS with an odd ratio of 2.55 which may be clinically important. Another variant, rs9388451 with an odd ratio of 1.58 was detected as heterozygous in patient. Two homozygous variants (rs11172113 and rs9349379) were associated with cervical artery dissection. Four out of 6 SNPs were associated with intracranial aneurysm; 4 heterozygous SNPs were associated with stroke. Interestingly 6 out of 7 SNPs detected in this patient were homozygous and associated with myocardial infarction. Only 1 of 6 SNPs were associated with venous thrombosis. Patient carries a homozygous SNP associated with Pulmonary arterial hypertension with an odd ratio of 1.97. At the same time, patient was homozygous for rs13333226(A) variant associated with risk of hypertension. The patient's calculated polygenetic risk score (PRS) is 100% for hypertension and pulmonary hypertension, while the calculated risk for myocardial infarction is 59.58% and early onset MI is 51.43% (Table S1). The risk score for Brugada syndrome is 60% and 65.17% for intracranial aneurysm. The PRS was calculated using the formula by Chen et al. (4).

DISCUSSION

As the medical history and the routine biochemistry evaluation were unremarkable, and the patient was not having any causal and treatable risk factors for MI such as hypertension, hypercholesterolemia or dyslipidemia, diabetes mellitus, and smoking; genetic variants that increase the risks for the clinical presentation of the patients was evaluated. In accordance with previous reports, MI in this young patient did not present diffuse

Table I: List of genetic variants annotated against cardiovascular traits in GWAS database

SNPS	TRAIT	GENE	OR	Risk allele	Genotype patient
rs6511720	Abdominal aortic aneurysm	LDLR	1.24	G	GG
rs2836411	Abdominal aortic aneurysm	ERG	1.11	T	TC
rs6511720	Abdominal aortic aneurysm	LDLR	1.32	G	GG
rs1466535	Abdominal aortic aneurysm	LRP1	1.15	C	CC
rs1795061	Abdominal aortic aneurysm	LINC02775 - SMYD2	1.13	T	TT
rs602633	Abdominal aortic aneurysm	CELSR2 - PSRC1	1.14	T	TG
rs10821415	Atrial fibrillation	AOPEP	1.11	A	AA
rs7193343	Atrial fibrillation	ZFHX3	1.21	T	TC
rs10824026	Atrial fibrillation	AC073389.2, SYNPO2L	1.15	A	AA
rs242557	Atrial fibrillation	MAPT, MAPT, MAPT	1.04	G	AG
rs1049334	Atrial fibrillation	CAV1	1.2	G	AG
rs1152591	Atrial fibrillation	ESR2, SYNE2	1.13	A	AG
rs639652	Atrial fibrillation	AL023495.1	1.14	G	AG
rs295114	Atrial fibrillation	SPATS2L	1.07	C	TC
rs3903239	Atrial fibrillation	AL023495.1	1.14	C	TC
rs883079	Atrial fibrillation	TBX5	1.1	T	TC
rs2617170	Behcet's disease	KLRC4-KLRK1, KLRC4	1.28	T	TC
rs7574070	Behcet's disease	STAT4	1.27	A	AC
rs9388451	Brugada syndrome	HEY2 - NCOA7	1.58	C	TC
rs10428132	Brugada syndrome	SCN10A	2.55	T	TT
rs11172113	Cervical artery dissection	LRP1	1.22	T	TT
rs9349379	Cervical artery dissection	PHACTR1	1.3	A	AA
rs1531070	Congenital heart malformation	MAML3	1.4	A	AG
rs2474937	Congenital heart malformation	RNA5SP56 - PSMC1P12	1.4	C	TC
rs1333049	Coronary artery disease	CDKN2B-AS1	1.24	C	GC
rs216172	Coronary artery disease	SMG6	1.05	C	CC
rs4977574	Coronary artery disease	CDKN2B-AS1	1.3	G	GG
rs4299376	Coronary artery disease	ABCG8	1.06	G	TG
rs7412	Coronary artery disease	APOE	1.15	C	CC
rs964184	Coronary artery disease	ZPR1	1.05	G	GC
rs17114036	Coronary artery disease	PLPP3, AC119674.2	1.15	A	AA
rs1746049	Coronary artery disease	AL137026.2 - AL137026.1	1.25	C	CC
rs1994016	Coronary artery disease	ADAMTS7	1.19	C	CC
rs646776	Coronary artery disease	CELSR2 - PSRC1	1.33	A	AG
rs11191416	Coronary artery disease	PFN1P11	1.08	T	TG
rs11556924	Coronary artery disease	AC073320.1, ZC3HC1	1.1	C	CC
rs12413409	Coronary artery disease	CNNM2	1.12	G	AG
rs4773144	Coronary artery disease	COL4A2	1.08	G	AG
rs602633	Coronary artery disease	CELSR2 - PSRC1	1.11	T	TG
rs11191416	Coronary artery disease	PFN1P11	1.08	T	TG
rs11556924	Coronary artery disease	AC073320.1, ZC3HC1	1.07	C	CC
rs9349379	Coronary artery disease	PHACTR1	1.11	A	AA
rs2107595	Coronary artery disease	HDAC9 - TWIST1	1.08	A	AG
rs2306556	Coronary artery disease	GUCY1A1	1.07	T	TT
rs1333049	Coronary heart disease	CDKN2B-AS1	1.47	C	GC
rs1746048	Coronary heart disease	AL137026.2 - AL137026.1	1.09	C	CC
rs216172	Coronary heart disease	SMG6	1.07	C	CC
rs4977574	Coronary heart disease	CDKN2B-AS1	1.2	G	GG
rs599839	Coronary heart disease	CELSR2 - PSRC1	1.11	A	AG
rs964184	Coronary heart disease	ZPR1	1.13	G	GC
rs12936587	Coronary heart disease	AC020558.5 - SMCR2	1.07	G	AG
rs1333049	Coronary heart disease	CDKN2B-AS1	1.36	C	GC
rs3869109	Coronary heart disease	HCG27 - AL662844.1	1.14	G	AG
rs4977574	Coronary heart disease	CDKN2B-AS1	1.29	G	GG
rs599839	Coronary heart disease	CELSR2 - PSRC1	1.29	A	AG
rs646776	Coronary heart disease	CELSR2 - PSRC1	1.14	T	TC
rs974819	Coronary heart disease	AP002989.1	1.07	T	TC
rs17465637	Coronary heart disease	MIA3	1.14	C	CC
rs2123536	Coronary heart disease	AC019055.1 - CISD1P1	1.12	A	AG
rs4773144	Coronary heart disease	COL4A2	1.07	G	AG
rs9268402	Coronary heart disease	TSBP1-AS1	1.16	G	GG
rs9349379	Coronary heart disease	PHACTR1	1.19	A	AA
rs944797	Coronary heart disease	CDKN2B-AS1	1.25	C	CC
rs11556924	Coronary heart disease	AC073320.1, ZC3HC1	1.09	C	CC
rs17114036	Coronary heart disease	PLPP3, AC119674.2	1.17	A	AA
rs3825807	Coronary heart disease	ADAMTS7	1.08	A	AA
rs7136259	Coronary heart disease	ATP2B1	1.11	T	TC
rs7865618	Coronary heart disease	CDKN2B-AS1	1.18	A	AA
rs9349379	Coronary heart disease	PHACTR1	1.34	A	AA
rs13333226	Hypertension	UMOD	5.42	A	AA
rs6842241	Intracranial aneurysm	PRMT5P1 - EDNRA	1.25	C	CC
rs11661542	Intracranial aneurysm	RPS4XP18 - RNU6-1032P	1.22	C	AC
rs12413409	Intracranial aneurysm	CNNM2	1.29	G	AG
rs1333040	Intracranial aneurysm	CDKN2B-AS1	1.32	T	TT
rs9298506	Intracranial aneurysm	RP1	1.28	A	AA
rs9298506	Intracranial aneurysm	RP1	1.35	A	AA
rs7193343	Ischemic stroke (cardioembolic)	ZFHX3	1.17	T	TC
rs2107595	Large artery stroke	HDAC9 - TWIST1	1.39	A	AG
rs3803915	Myocardial infarction	AP3D1	1.12	C	CC
rs4977574	Myocardial infarction	CDKN2B-AS1	1.22	G	GG
rs10757278	Myocardial infarction	CDKN2B-AS1	1.28	G	GG
rs1746048	Myocardial infarction (early onset)	AL137026.2 - AL137026.1	1.17	C	CC
rs4977574	Myocardial infarction (early onset)	CDKN2B-AS1	1.29	G	GG
rs17465637	Myocardial infarction (early onset)	MIA3	1.14	C	CC
rs646776	Myocardial infarction (early onset)	CELSR2 - PSRC1	1.19	A	AG
rs2217560	Pulmonary arterial hypertension (without BMPR2 mutations)	AC069114.1 - CBLN2	1.97	G	GG
rs12425791	Stroke	AC021054.1 - LINC02455	1.27	A	AG
rs2107595	Stroke (ischemic)	HDAC9 - TWIST1	1.39	A	AG
rs3756008	Venous thromboembolism	KLKB1 - F11	1.4	T	AT
rs687621	Venous thromboembolism	ABO, ABO	1.55	G	AG
rs2288904	Venous thromboembolism	SLC44A2	1.12	G	AG
rs3136516	Venous thromboembolism	F2	1.1	G	GG
rs6536024	Venous thromboembolism	FGG - LRAT	1.25	C	TC
rs7659024	Venous thromboembolism	FGA - FGG	1.53	A	AG

OR = odd ratio, the odd ratios were obtained from GWAS database *(Buniello et al., 2019)*

atherosclerotic coronary arteries but a single vessel disease. Troponin-I level was raised 16335 pg/mL (<14.5 pg/mL) and patient was diagnosed to have myocardial infarction. Coronary angiography showed acute total occlusion (ATO) of the mid left anterior descending (LAD) artery with a normal lipid profile suggested that there are genetic risks that confer such presentation. There are 45 genetic variants that increased the risks of patients for coronary artery and coronary heart diseases. Three homozygous variants (rs3803915, rs4977574, rs10757278) were associated with myocardial infarction; and 3 (rs1746048, rs4977574, rs17465637) of the 4 variants associated with early onset myocardial infarction were homozygous (Table I). The novelty of this case report is the description of genetic SNPs in a young Malay gentleman presented with a life-threatening ST-elevation myocardial infarction. To no surprise the presence of genetic predisposition in this gentleman may have led to the young onset of MI. It is of interest that 2 genetic variants that increase the risks for BrS were detected in this patient. These 2 variants were previously reported to increase the risks of BrS at a higher rate in Asian than the Caucasian (5). Our patient is probably at an increased risk for BrS and patient counselling and preventive measure was taken.

However, further analysis and clinical trials are required to ascertain specific SNP risk association with MI. This is because the genotype and phenotype annotated were based on information on the Caucasian and East Asians, the correlation might not be accurate for this patient. The limitation of using GWAS database would be resolved if an established database of the local population is available. A large genome wide study is therefore desirable before the implementation of precision medicine with specific targeted treatment and prevention which takes into account individual gene variability is possible. This is in contrast to a one-size-fits-all approach, in which management of patients are generalized for a particular cohort irrespective of background history. The use of genotypes to guide diagnosis in precision medicine is a form of evidence-based medicine which is always the key in clinical medicine and clinical guidelines should be updated to ensure the treatment given is optimum for each patient.

CONCLUSION

MI is a disease due to interactions between multiple genes and environmental factors. The genetic analysis suggested that patient is at increased risk for CHD, MI and BrS. The presence of genetic variants in this patient provides insightful explanation of the clinical presentation of the patient without clinical risk factors from medical history. He was discharged with double antiplatelets, statin, ACE inhibitor and Beta-blocker therapy. He is being followed up by cardiologists of our institution with no further complication. Identification of genetic risks allow personalized medicine or clinical intervention which helps to lower the occurrence of future events.

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