

# Whole-Genome Sequencing to Identify Polygenic Contributions in Korean Patients with Early-Onset Acute Myocardial Infarction

2019.12.14 ver. For JCR

Youngjune Bhak

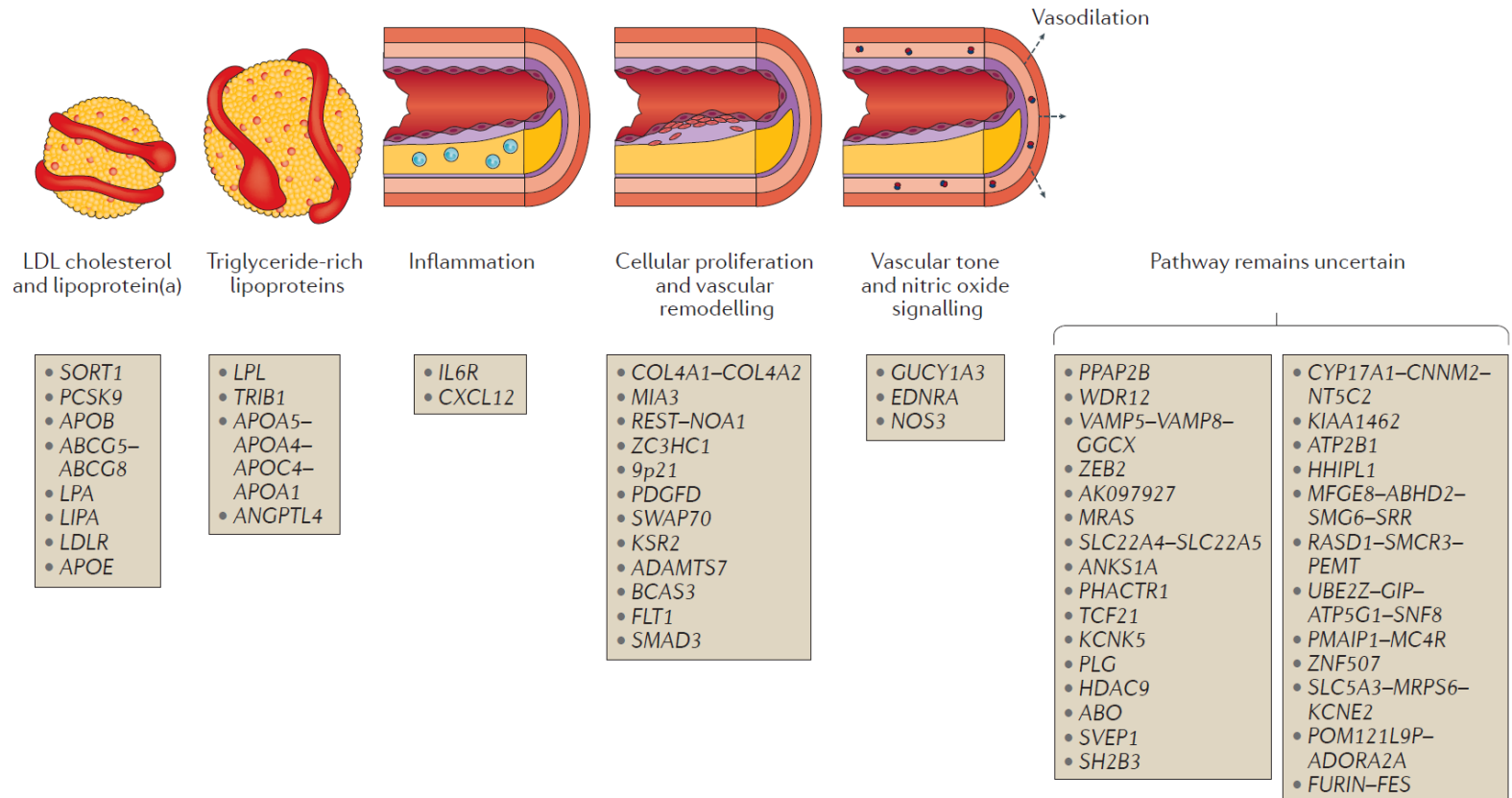
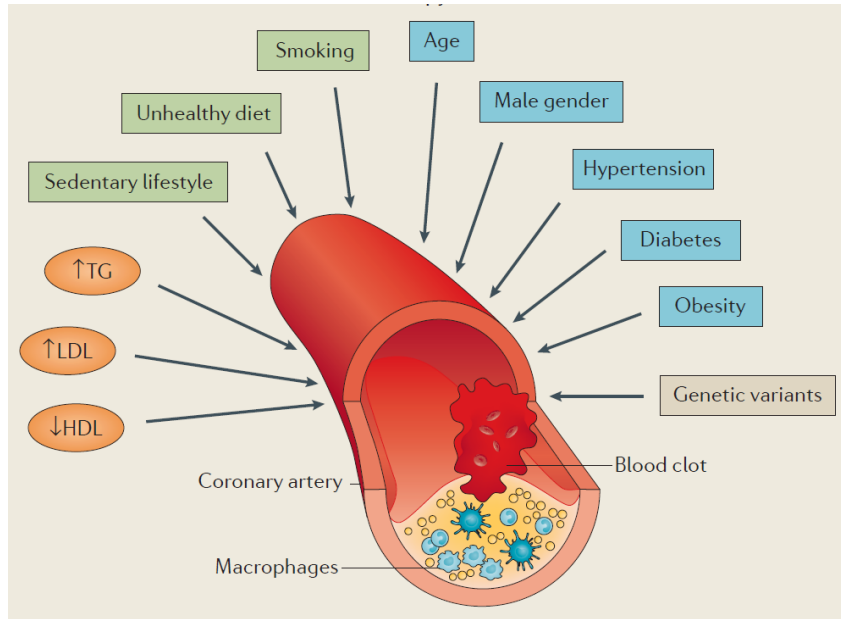
UNIST; KOGIC; Clinomics; Ulsan hospital



# Index

- 심혈관계 질환에 대한 유전적 영향
- Early-onset AMI에 대한 유전적 영향
- 한국인 대상 Early-onset AMI 연구 현황

# 심혈관계 질환에 대한 유전적 영향



Khera, Amit V., and Sekar Kathiresan. "Genetics of coronary artery disease: discovery, biology and clinical translation." *Nature Reviews Genetics* 18.6 (2017): 331.

# 심혈관계 질환에 대한 유전적 영향

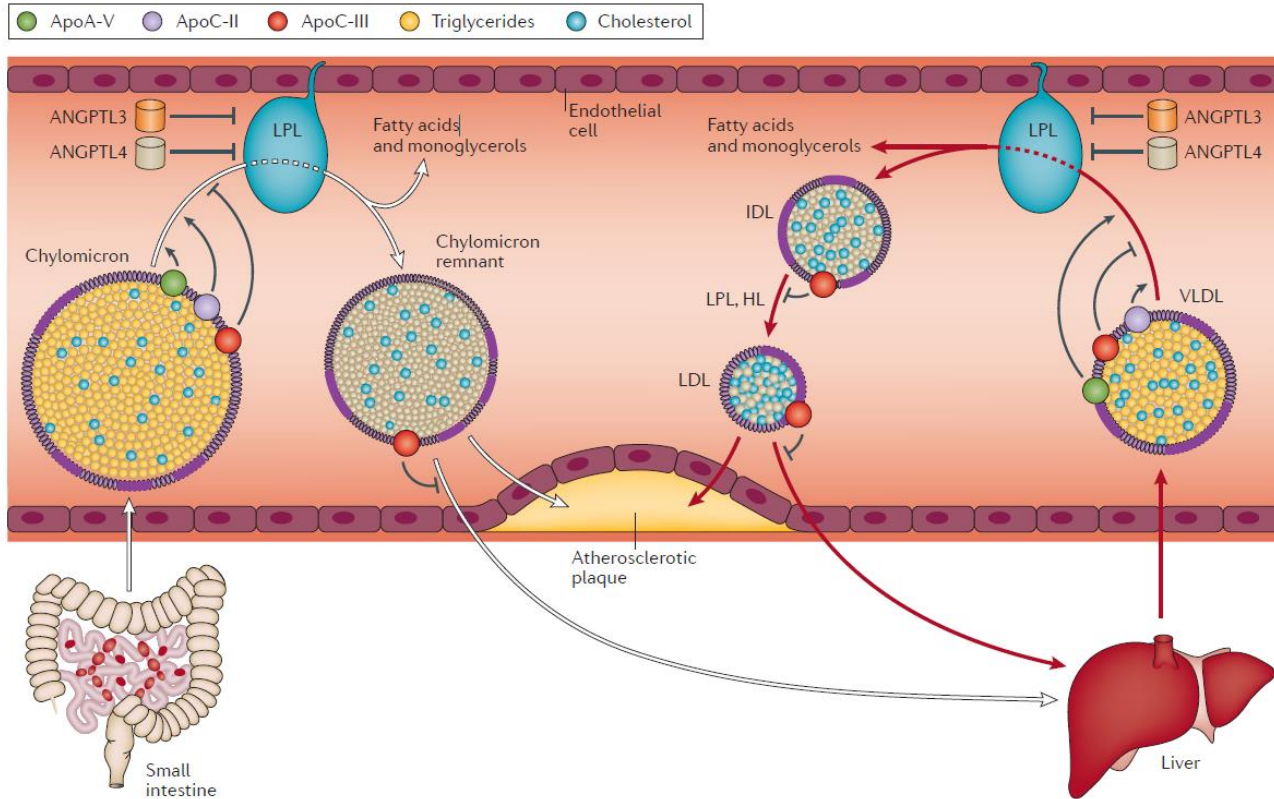


Table 1 | Summary of results from gene sequencing studies for CAD

Gene	Carrier frequency	Intermediate phenotype	CAD risk	Therapy to mimic protective variants	Refs
<i>Inactivating mutations confer increased risk</i>					
LDLR	1 in 221 (0.5%)	↑ LDL cholesterol	↑ 320%	Not applicable	48
LPL	1 in 249 (0.4%)	↑ Triglyceride-rich lipoproteins	↑ 84%	Not applicable	52
APOA5	1 in 216 (0.5%)	↑ Triglyceride-rich lipoproteins	↑ 120%	Not applicable	48
<i>Inactivating mutations confer decreased risk</i>					
PCSK9	1 in 50 (2%)*	↓ LDL cholesterol	↓ 88%	Alirocumab, evolucumab (approved by the FDA and EMA)	50
NPC1L1	1 in 650 (0.2%)	↓ LDL cholesterol	↓ 53%	Ezetimibe (approved by the FDA and EMA)	71
ASGR1	1 in 120 (0.8%)	↓ LDL cholesterol ↓ Triglyceride-rich lipoproteins	↓ 34%	None	51
APOC3	1 in 150 (0.7%)	↓ Triglyceride-rich lipoproteins	↓ 40%	Volanesorsen (formerly known as ISIS-APOCIII <sub>Rx</sub> ; phase III trials)	53,54
ANGPTL4	1 in 360 (0.3%)	↓ Triglyceride-rich lipoproteins	↓ 53%	REGN1001 (preclinical development)	43,55
LPA	1 in 285 (0.4%)	↓ Lipoprotein(a)	↓ 24%	AKCEA-APO(a)-L <sub>Rx</sub> (phase II trials)	90

Khera, Amit V., and Sekar Kathiresan. "Genetics of coronary artery disease: discovery, biology and clinical translation." *Nature Reviews Genetics* 18.6 (2017): 331.

# 심혈관계 질환에 대한 유전적 영향

**Table 1. Characteristics of the Participants at Baseline.\***

Characteristic	Atherosclerosis Risk in Communities (N=7814)	Women's Genome Health Study (N=21,222)	Malmö Diet and Cancer Study (N=22,389)	BioImage Study (N=4260)
Age — yr	54±5.7	54.2±7.1	58.0±7.7	69.1±6.0
Male sex — no. (%)	3555 (45)	0	8,515 (38)	1879 (44)
Clinical history — no./total no. (%)				
Hypertension	2020/7784 (26)	5164/21,217 (24)	13,553/22,389 (61)	2576/4258 (60)
Diabetes mellitus	632/7799 (8)	519/21,222 (2)	904/22,389 (4)	522/4257 (12)
Family history of premature coronary artery disease†	751/6812 (11)	2476/19,121 (13)	7,225/22,389 (32)	1717/4054 (42)
Body-mass index‡	26.9±4.8	25.9±4.9	25.7±3.9	28.8±5.5
Lipid levels — mg/dl§				
LDL cholesterol	136.7±38.7	124±34	161.2±38.6	113±33
HDL cholesterol	37.6±10.9	54±15	53.7±14.7	56±16
Median triglycerides (IQR)	110 (79–156)	119 (84–176)	102 (76–143)	148 (107–210)
Use of lipid-lowering medication — no. (%)	45 (1)	690 (3)	488 (2)	1467 (34)
Healthy lifestyle factors — no. (%)				
No current smoking	5873 (75)	18,784 (89)	16,162 (72)	3887 (91)
No obesity	6093 (78)	17,566 (83)	19,507 (87)	2729 (64)
Regular physical activity	2743 (35)	9,256 (44)	9,093 (41)	1967 (46)
Healthy diet	1515 (19)	7,251 (34)	2,795 (12)	610 (14)
Healthy lifestyle score — no. (%)				
3 or 4 healthy lifestyle factors	2459 (31)	10,516 (50)	7,210 (32)	1564 (37)
2 healthy lifestyle factors	3162 (40)	7,385 (35)	10,234 (46)	1598 (38)
0 or 1 healthy lifestyle factor	2193 (28)	3,321 (16)	4,945 (22)	1098 (26)
Genetic risk category — no. (%)				
Low	1563 (20)	4,280 (20)	4,478 (20)	846 (20)
Intermediate	4688 (60)	12,716 (60)	13,434 (60)	2557 (60)
High	1563 (20)	4,226 (20)	4,477 (20)	857 (20)

## Lifestyle factor

Healthy lifestyle factors	HR (CI)
No current smoking	0.56 (0.47 - 0.66)
No obesity	0.66 (0.58 - 0.76)
Regular physical activity	0.88 (0.80 - 0.97)
Healthy diet	0.91 (0.83 - 0.99)

Genetic risk,  
Low vs High HR: 1.96 (CI: 1.75 - 2.09)

Khera, Amit V., et al. "Genetic risk, adherence to a healthy lifestyle, and coronary disease." *New England Journal of Medicine* 375.24 (2016): 2349-2358.

# 조기심근경색에 대한 강한 유전적 영향

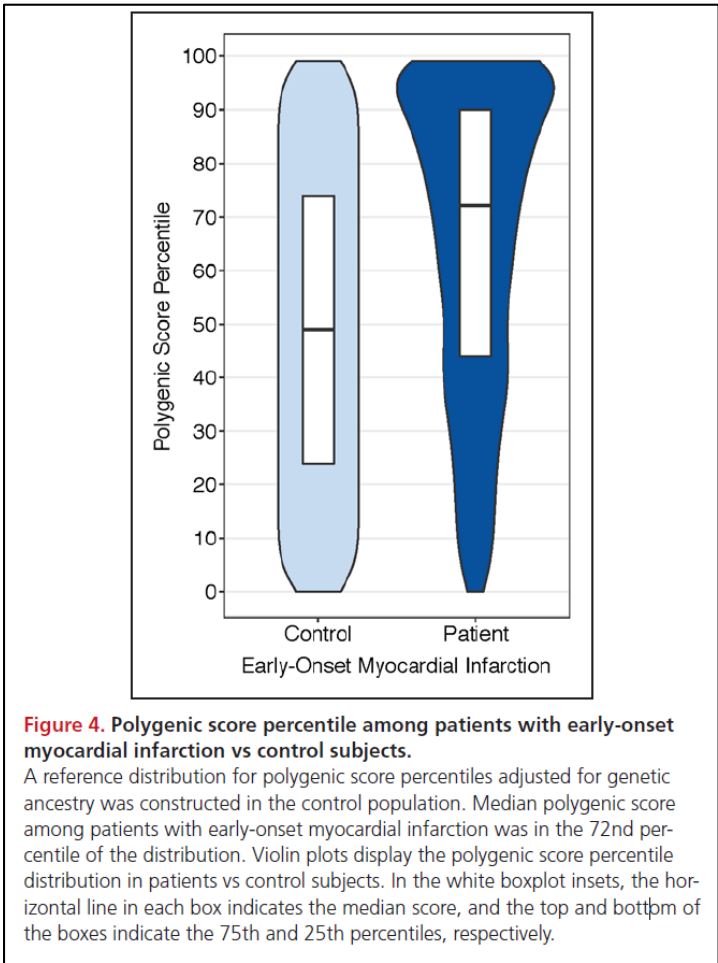
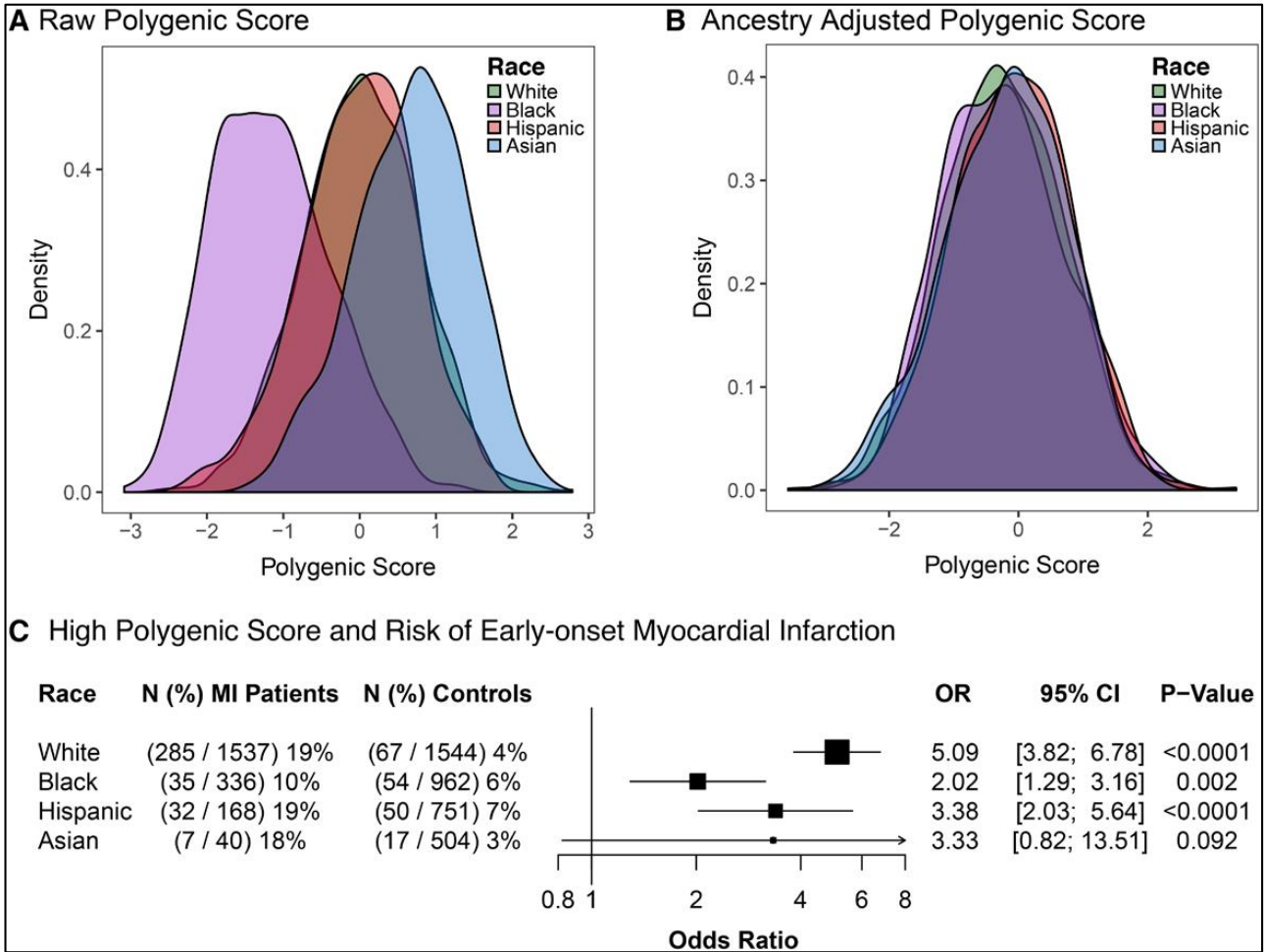
TABLE 1. Independent Variables in Patients with Early-onset Ischemic Heart Disease Compared with Matched Controls and Presented in the Descending Order of Risk Ratio

	Patients	%	Controls	%	Risk ratio	p <
IHD—1° relatives younger than 55 years	99/207	48	50/621	8	10.4	0.001
IHD—1° relatives younger than 65 years	126/207	61	112/621	18	7.1	0.001
J. diabetes-1° relative	9/140	6	2/140	1	4.7	0.05
Cholesterol > 270 mg/dl	50/207	24	43/621	7	4.3	0.001
Smoking > ½ pack/day	141/207	68	217/621	35	4.0	0.001
Stroke—1° relatives younger than 55 years	10/207	5	9/621	1	3.5	0.01
Exercise deficiency	199/207	96	546/621	88	3.4	0.001
Diabetes (in patient)	12/207	6	14/621	2	2.7	0.05
IHD-2° relatives younger than 65 years	59/140	42	32/140	23	2.4	0.001
Cholesterol > 240 mg/dl	77/207	96	130/621	21	2.2	0.001
BP ≥ 160/100 mm Hg	44/207	21	81/621	13	1.8	0.01
Hypertension—1° relative	41/140	29	26/140	19	1.8	0.05
Cholesterol > 220 mg/dl	120/207	58	304/621	49	1.8	0.05
Stroke—1° relatives younger than 65 years	25/207	12	43/621	7	1.8	0.05
Type A behavior	56/207	27	124/621	20	1.5	0.05
Triglycerides > 200 mg/dl	47/207	23	99/621	16	1.5	0.05
BP ≥ 140/90 mm Hg	60/207	27	138/621	22	1.4	0.05
Imprudent diet	155/207	75	422/621	68	1.4	NS
Relative weight > 1.20	83/207	40	211/621	34	1.3	NS
Relative weight > 1.20 excluding monogenic cases	80/176	45	174/528	33	1.7	0.01

Abbreviations: IHD = ischemic heart disease; 1° = first degree; 2° = second-degree; J. diabetes = juvenile-onset diabetes; BP = blood pressure.

Nora, J. J., et al. "Genetic--epidemiologic study of early-onset ischemic heart disease." *Circulation* 61.3 (1980): 503-508.

# 조기심근경색 환자의 유전적 위험도 점수 분포



Khera, Amit V., et al. "Whole-genome sequencing to characterize monogenic and polygenic contributions in patients hospitalized with early-onset myocardial infarction." *Circulation* 139.13 (2019): 1593-1602.

# Research in Korea. Ulsan 10K project



- Normal and patient individuals
  - Whole genome sequencing
  - Clinical characteristics and questionnaire
  - 10K individual
- 
- Discovery of association between genotype and phenotype
  - Identification of rare variants
  - Construction of AI supported genetic scoring system



# Take home message

- 심혈관계 질환에 대한 유전적 영향이 있음
- Early-onset AMI에 대한 유전적 영향이 있음
- 한국인 대상 Early-onset AMI 연구가 다양한 trait를 동반하여 진행되고 있음.

# Acknowledgment

