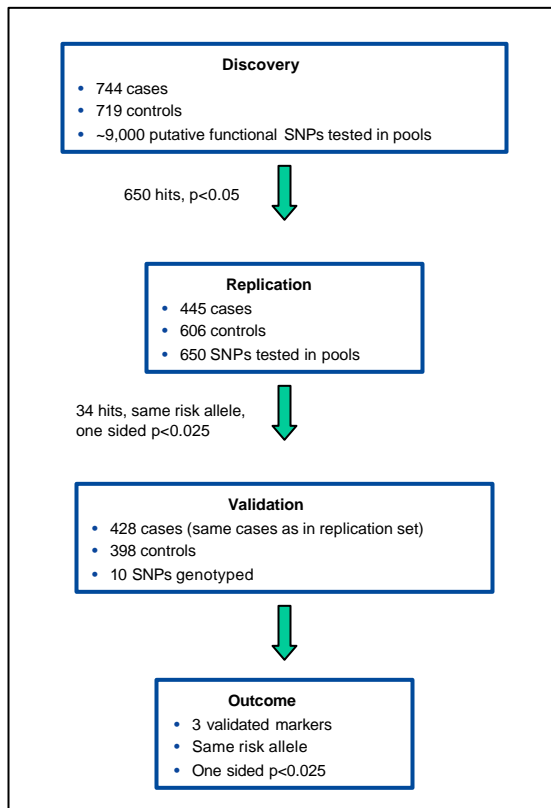


NOVEL GENETIC MARKERS ASSOCIATED WITH RISK OF MYOCARDIAL INFARCTION FROM A GENOMIC SCALE SCAN OF PUTATIVE FUNCTIONAL POLYMORPHISMS

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- Family history of coronary heart disease is an independent risk for myocardial infarction
- Few genetic risk markers have been identified so far
- We tested ~9,000 putative functional SNPs for association with MI
- We present associations that are replicated in two independent sets, and validated with a third set of independent controls



Discovery Set Characteristics
UCSF Genomic Resource Collection

	Cases ¹	Controls ²	p Value ³
Number	744	719	
Age ⁴	51 ±9	63 ±11	<0.001
Male gender	62%	53%	<0.001
Smoking ⁵	65%	45%	<0.001
Diabetes	20%	none ²	
Dyslipidemia ⁶	84%	56%	<0.001
Hypertension ⁶	60%	30%	<0.001

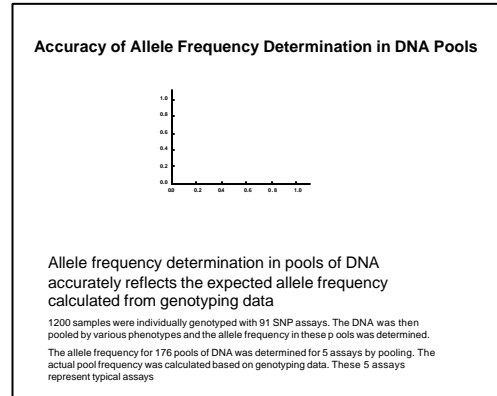
1. Cases: Caucasian, clinical MI
2. Controls: Caucasian, no MI diabetes or symptomatic vascular disease
3. Fisher exact and t-test
4. Age: age(±SD) of first MI for cases, age of collection for controls
5. Self reported and/or history of medication
6. Clinical history

Replication Set Characteristics
Cleveland Clinic Foundation Collection

	Cases ¹	Controls ²	p Value ³
Number	445	606	
Age ⁴	60 ±7	59 ±11	N.S.
Male gender	62%	62%	N.S.
Smoking ⁵	74%	54%	<0.001
Diabetes ⁶	39%	10%	<0.001
Dyslipidemia ⁶	94%	56%	<0.001
Hypertension ⁶	76%	50%	<0.001

1. Cases: Caucasian, clinical MI
2. Controls: Caucasian, no MI and minimal or undetectable stenosis
3. Fisher exact and t-test
4. Age (±SD) at recruitment
5. Self reported
6. Clinical history

- Validation Control Characteristics**
- Caucasian (398)
 - 36% males
 - No history of MI or symptomatic vascular disease
 - Smoking history (50%)
 - Hypertension treatment (28%)



KIAA1462

Discovery and Replication

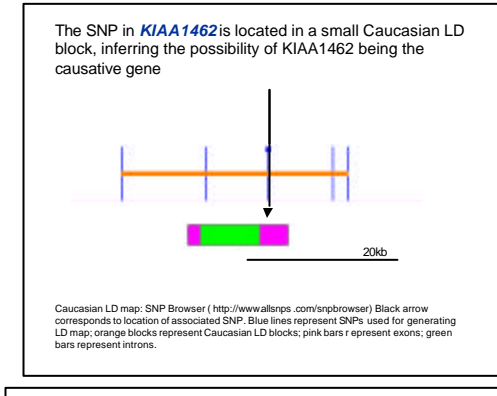
Study	Model	OR (95%CI) ¹	p-Value ²	Allele Frequencies	
				Case	Control
Discovery	Allelic	1.32 (1.14-1.52)	0.0002	0.44	0.39
Replication	Allelic	1.21 (1.02-1.44)	0.03	0.49	0.44

1. Allelic odds ratio
2. Fisher exact

Validation Study

Genotype	Case	Control	OR (95%CI)
CC	125	128	1
CG	199	204	1.0 (0.7-1.4)
GG	102	63	1.7 (1.1-2.5)

- KIAA1462 is a 1221 amino acid protein with unknown function
- Located on 10p12.1
- This SNP results in a Thr to Ser change in AA864; Ser is associated with risk
- KIAA1462 minor allele is associated with MI risk. The minor homozygotes had a ~1.7 fold higher odds of having an MI, compared to the major homozygotes in this population



Aquaporin 10

Discovery and Replication

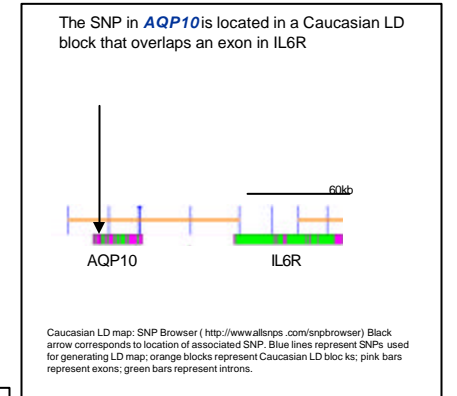
Study	Model	OR (95%CI) ¹	p-Value ²	Allele Frequencies	
				Case	Control
Discovery	Allelic	1.35 (1.14-1.59)	0.0006	0.24	0.22
Replication	Allelic	1.33 (1.18-2.00)	0.003	0.30	0.27

1. Allelic odds ratio
2. Fisher exact

Validation Study

Genotype	Case	Control	OR (95%CI)
CC	182	199	1
CT	186	162	1.2 (0.9-1.7)
TT	59	32	2.0 (1.2-3.2)

- AQP10 minor allele is associated with MI risk.
- The minor homozygotes had a two fold higher odds of having an MI, compared to the major homozygotes in this population
- Located on 1q22
- This SNP results in a Tyr to His change in AA123, the minor allele (His) is associated with risk
- This gene encodes a member of the aquaglyceroporin family of integral membrane proteins, which functions as a water-selective channel



- SUMMARY**
- ~9,000 putative functional SNPs were tested for association with MI
 - Replication and validation strategy was used to reduce the chance of spurious associations
 - Determination of allele frequency in pooled DNA samples can be used to identify novel SNPs associated with MI
 - We discovered association of SNPs in aquaporin 10 and a gene with unknown function that confer ~1.7-2 fold risk for MI in our study population
 - The allele frequency and odds-ratio for these SNPs are high enough to demonstrate allelic association in pooled studies, even though the effect seems to be recessive
 - The high frequency of these SNPs (30-50%) makes them common enough to evaluate risk in a large fraction of the general population