

Project 2

Driscoll Lab

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Background

- The etiology is unknown in the majority of cases of congenital heart disease (CHD)
- Presumably there are multiple genes involved
- Variability in expression may be explained by modifiers

Primary Aim

To investigate the genetic component of outflow tract malformations

Subjects

- 22q11 deletion, \approx 75% have CHD
- non-deleted patients and their parents, all with outflow tract anomalies

Genotyping

- Candidate genes
- Single nucleotide polymorphisms (SNPs)

Table 1. List of candidate genes involved in early heart development

GENE	# SNPs tested	# VCFS probands w/ data	# SCCOR trios w/ data
BMP4	1	150	355
CBS	2	160	315
dHAND	2	150	355
ECE1	3	150	355
EDN1	4	135	355
EDNRA	4	150	355
FOXC2	1	n/a	355
GATA4	3	150	n/a
JAG1	3	n/a	355
MS	1	145	315
MTHFR	2	150	315
MTRR	1	140	n/a
NKX2.5	4	150	355
NRP1	2	155	355
PAX3	3	150	n/a
PLXNA2	5	155	355
PLXND1	2	150	355
RARa	1	n/a	355
RARb	3	n/a	355
RARg	1	n/a	355
RXRA	3	n/a	355
SEMA3C	5	150	355
SHH	1	n/a	355
TBX1	2	70	355
TGFa	1	90	130
VEGF	3	150	n/a

Methods

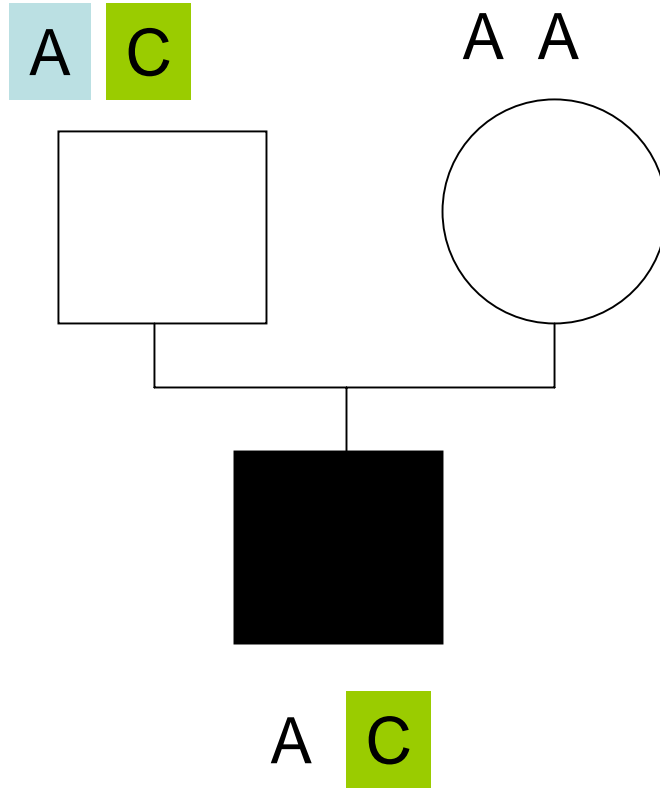
- DNA is obtained from Cell Culture, DNA and Microarray Core C
- High throughput single nucleotide polymorphism (SNP) genotyping at University of Pennsylvania Molecular Diagnosing & Genotyping Core
- Data management with Clintrials
- Statistical analysis
 - transmission disequilibrium test (TDT)

Statistical method

TDT =

compares the allele frequencies of non-transmitted and transmitted alleles

TDT



transmitted

non-transmitted

C

A

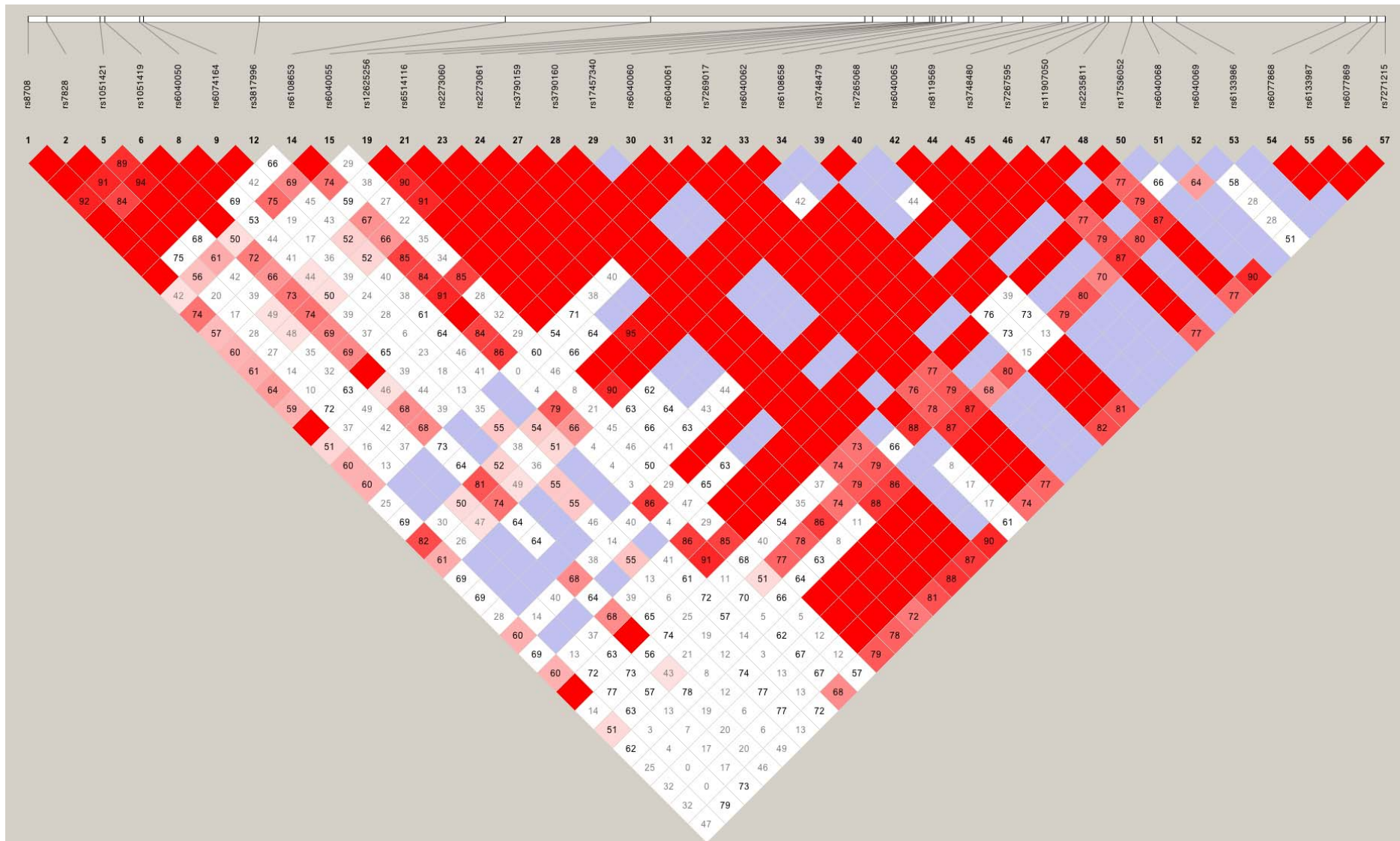
Jag1

- Involved in early cardiac development
- Notch signaling pathway
- JAG1 mutations have been associated with CHD

RARb

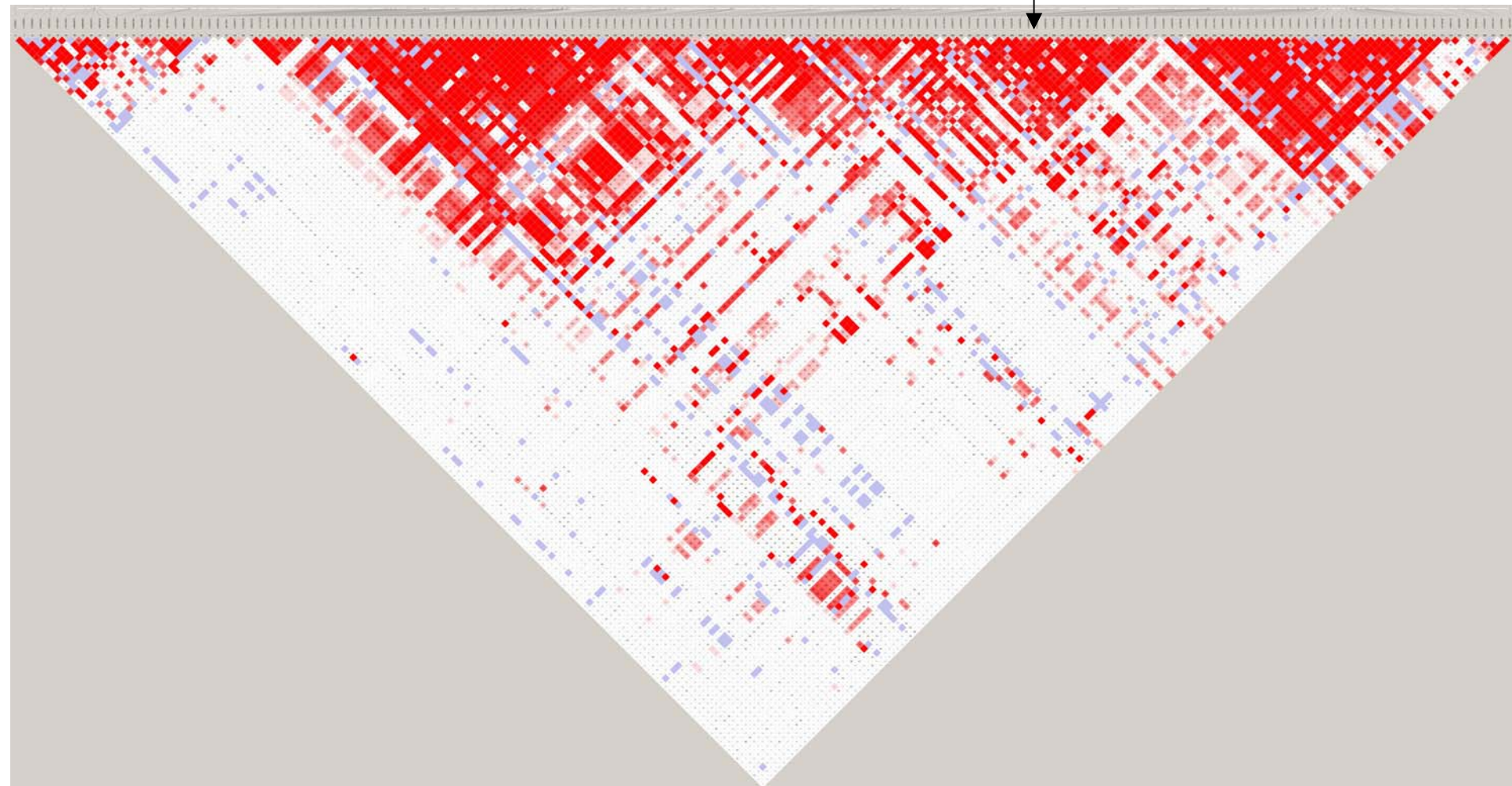
- Belongs to retinoic acid receptor (RAR) family
- Expressed during early heart development in mouse
- Imperative for vitamin A utilization
- Double mutant RAR mice exhibit cardiac defects including outflow tract abnormalities

JAG1 LD



RARb LD

RARb2



Limitations

- Proband sample size
 - do not have enough subsets for statistical sample
 - our population may be heterogeneous group
- SNP resolution
 - we will only cover common variants (>10%)
 - we will only cover functional variants in LD with our sampled SNPs

Next stage

- Genotype 2004/2005 trios with outflow tract malformations
- Better resolution SNP analysis using tag SNPs (choice based on Hapmap and ABI LD data)
- We will genotype 14 new SNPs
- Functional studies

Acknowledgements

- Charles Scott, Ph.D.
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