Genetic Risk Factors for Complications due to Arrhythmia

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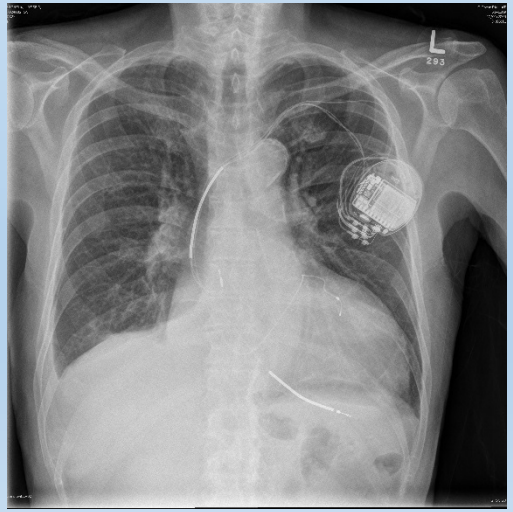
Background: Arrhythmia

- An arrhythmia is an irregular heartbeat, a condition which causes 250,000 deaths annually in the U.S.

- Internal cardioverter-defibrillator (ICD) is placed in the heart to prevent cardiac arrest by delivering a shock
  - Expensive ($30,000-$50,000)
  - Invasive open-heart surgery



Background: Genetics

- Single nucleotide polymorphisms (SNPs) are one letter variations in the DNA sequence
- Many SNPs do not have a noticeable effect, but some can lead to major health complications
- An individual's DNA can be examined using a chip called a gene microarray

A C G T C A A G
A C G T C T A G

GRADE Study

National Heart, Lung, and Blood Institute

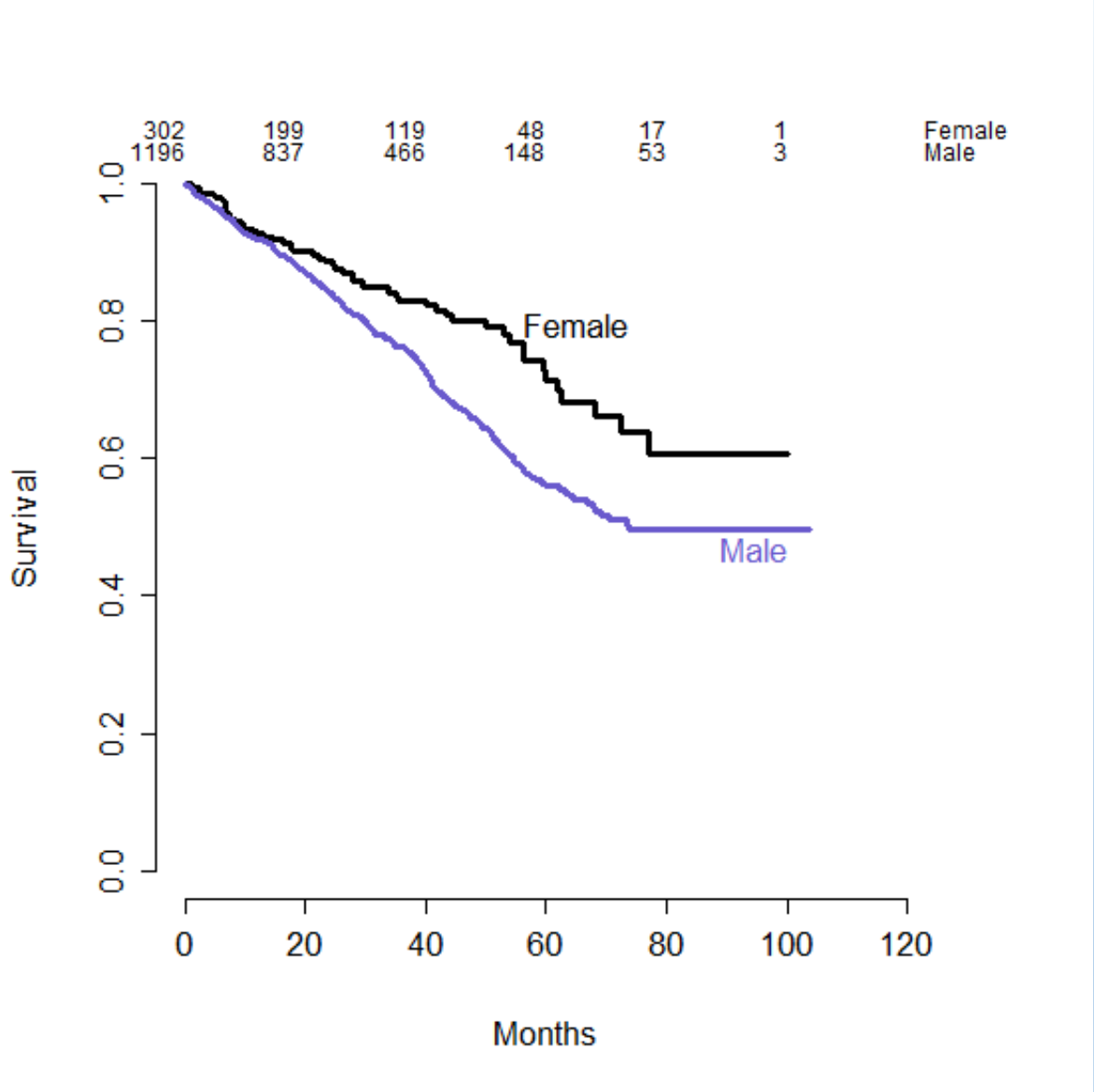
- Purpose: predict which arrhythmia patients would benefit most from ICD placement
- Data:
  - Clinical variables on 1654 arrhythmia patients from 6 different sites, including age, sex, BMI, past medical history, blood pressure, etc.
  - Records of patient outcomes – time until first shock or time until death, if those events occurred
  - Genetic data on 1195 of those patients for 600,000 SNPs

Analysis Methods

1) Determine effect of various clinical factors using Kaplan-Meier curves
2) Perform Cox regression to identify most important clinical factors to account for in the genetic analysis
3) Calculate significance of each SNP in predicting survival or time until shock, while accounting for important clinical factors
4) Find the most significant SNPs in a genome-wide analysis and a targeted analysis

Kaplan-Meier Curve

- Time-to-event: time from beginning of observation period to withdrawal from study
- Censored data: information about survival time is incomplete
- Shows survival probability at a given time



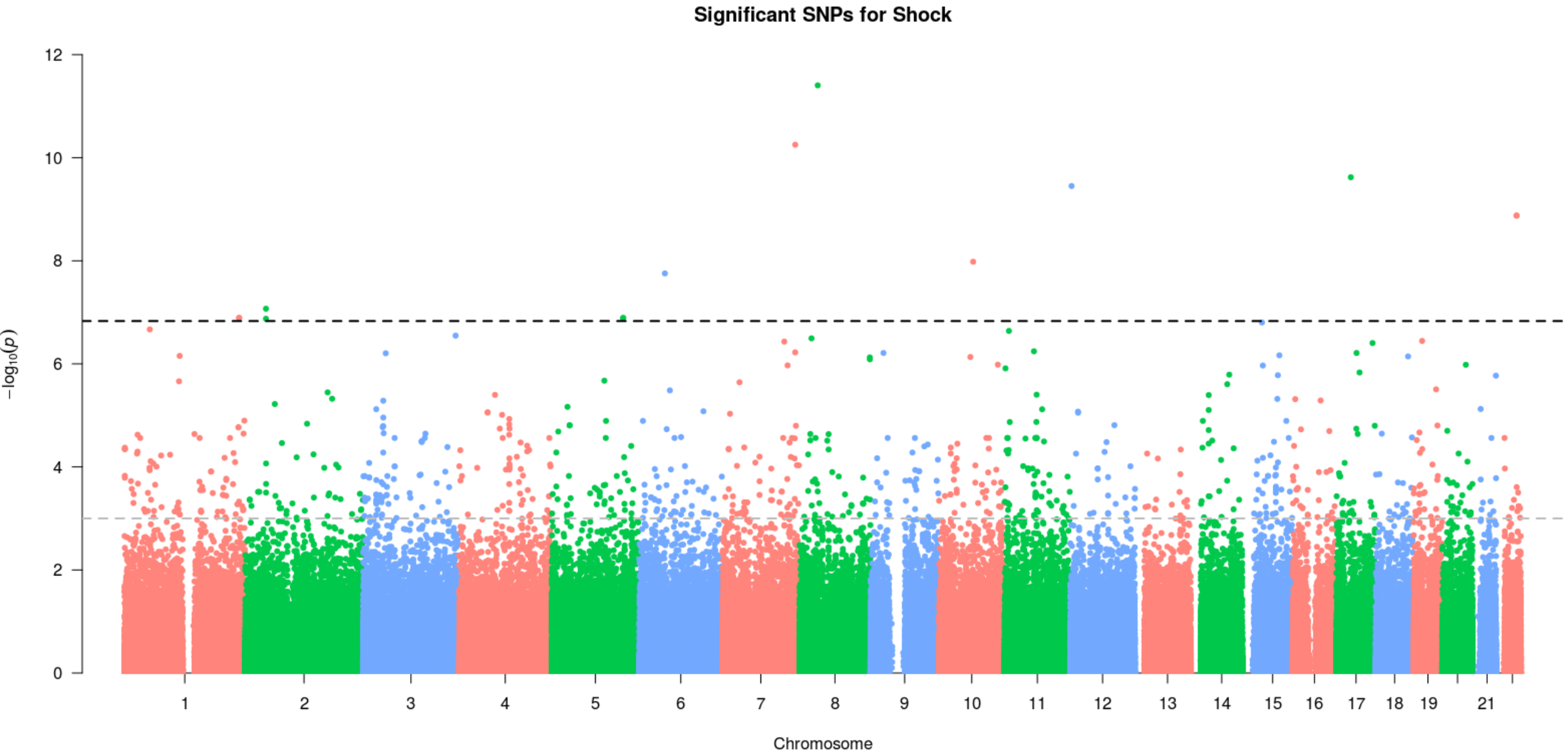
Cox regression

Shock model accounts for:

- Age
- Ejection fraction
- Whether patient uses antiarrhythmic medication
- Whether patient uses diuretics
- Gender

Death model accounts for:

- NYHA
- Age
- Gender
- Whether patient uses diuretics
- Whether the patient uses Digoxin
- Whether patient underwent ACE/ARB therapy


Significant SNPs for Shock
12
10
8
6
4
2
0
$-\log_{10}(p)$
1
2
3
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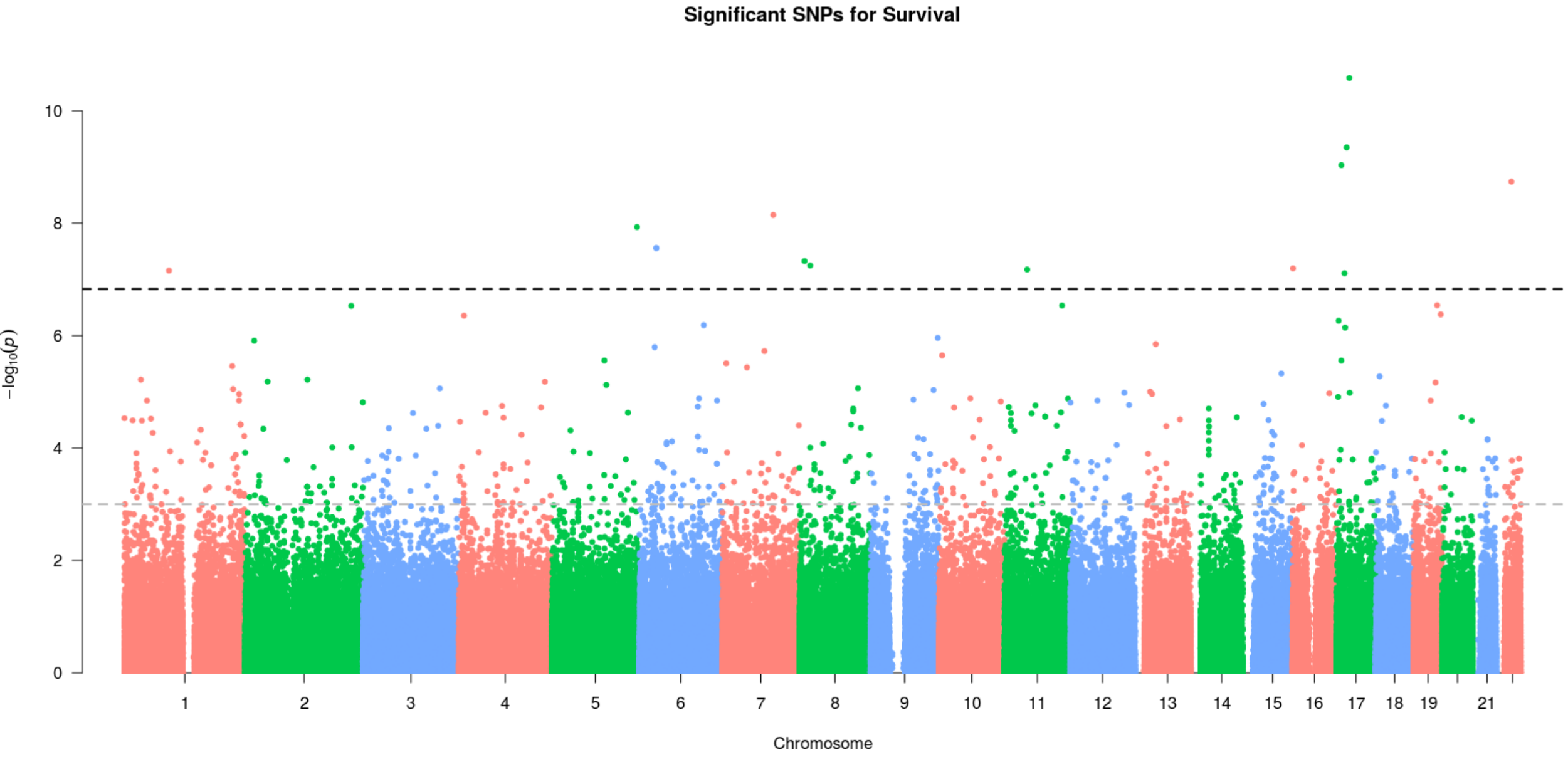
19
21
Chromosome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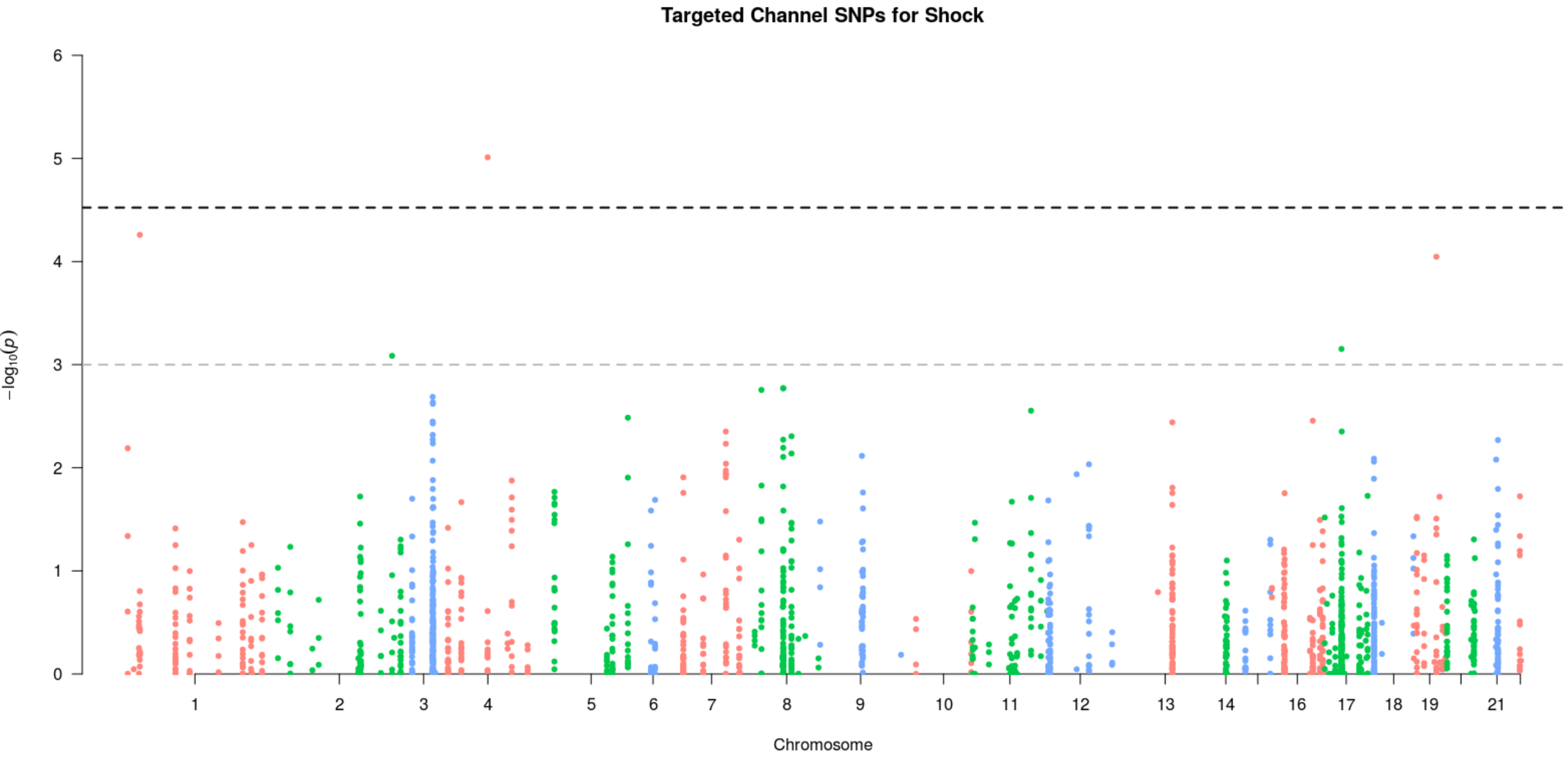
Targeted Channel SNPs for Shock
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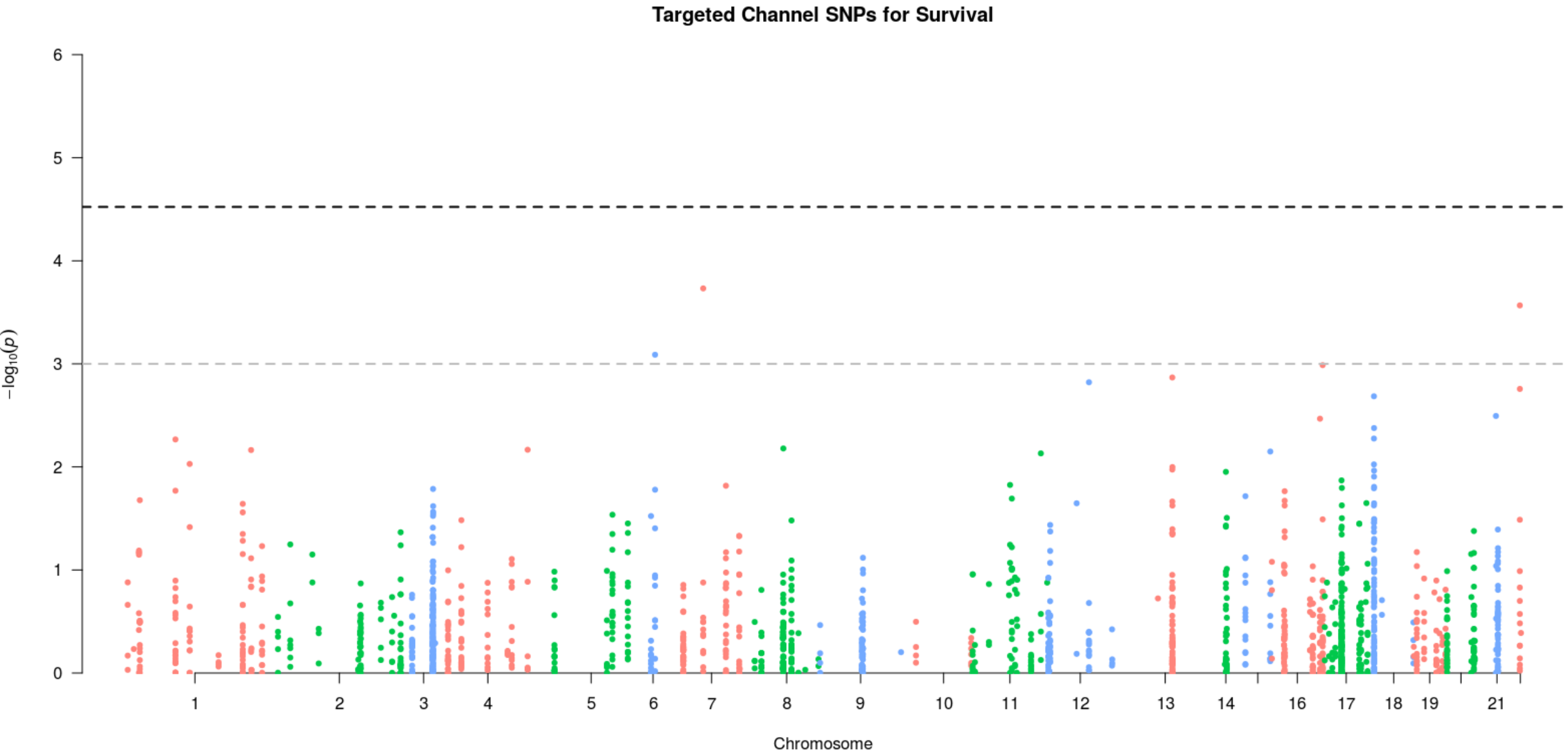
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Potentially important SNPs

Shock

Genome-Wide

exm162244
exm189283
exm189321
exm492794
exm555796
rs10062167
exm671119
exm695560
exm829568
exm975133
rs17246266
exm1612339
rs12168259

Targeted

rs12168259

Death

Genome-Wide

exm74690
exm505376
exm540297
kgp4285103
exm648371
exm681674
exm688044
exm903362
exm1198284
exm1294515
exm1298405
exm1304402
exm1305790
exm1600583

Corresponding important genes

ACTN2
OXER1
SPINK5
GSTA3
ADGRA2
DDX50
TEAD4
RAB11FIP4
ZC3H7B
NAGA
PKD2
TGFBR3
CDHR2
UHRF1BP1
PPARD
RINT1
RP1L1
PIWIL2
AMBRA1
WDR24
MYHAS,MYH1
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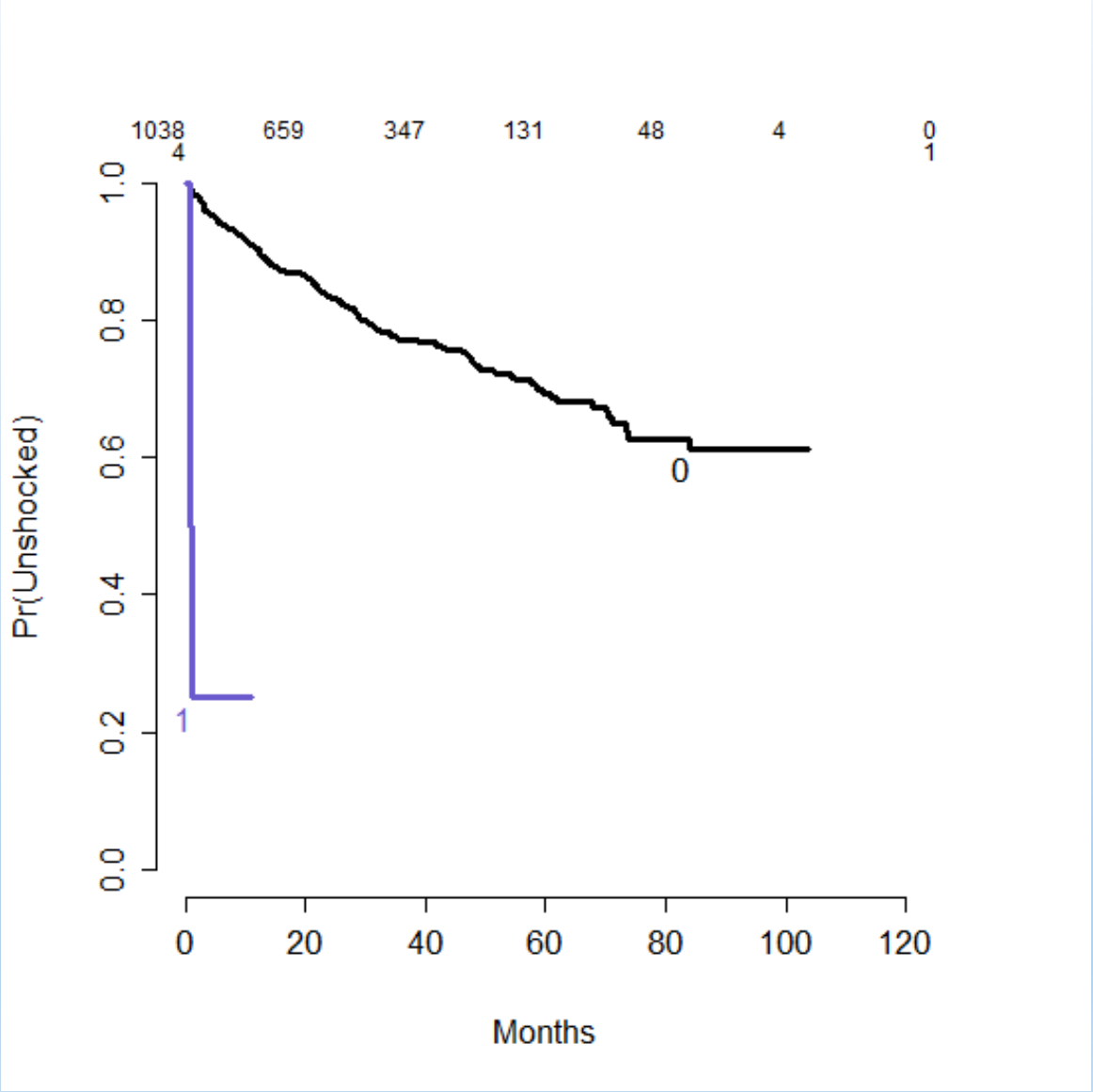
Discussion: ACTN2

- Chromosome 1
- Mutations in this gene are known to be associated with heart conditions
- High gene expression in the heart



Discussion

- Future rat studies to further analyze significant SNPs
- Adding to the general knowledge about genes
- Limitations:
  - Start time difference
- More things we could have done:
  - Take full advantage of the data by adjusting for fewer clinical variables
  - Use more accurate tests for rare SNPs

Acknowledgements

- ISIB program sponsored by the National Heart, Lung, and Blood Institute (NHBLI) HL131467
- Patrick Breheny
- Gideon Zamba
- Lauren Sager
- All our ISIB friends

Hazard ratios of having SNPs

SNP	Hazard Ratio	# of patients with SNP
exm505376	27.944	7
exm540297	3.915	4
kgp4285103	31.522	3
exm74690	0.840	5
exm648731	5.373	5
exm681674	4.601	5
exm688044	2.460	4
exm903362	4.356	6
exm1198284	3.360	4
exm1294515	6.560	7
exm1298405	2.486	3
exm1304402	3.550	6
exm1305790	8.455	10
exm1600583	3.525	5

SNP	Hazard Ratio	# of patients with SNP
exm162244	2.086	4
exm189283	1.976	8
exm189321	1.447 e-06	3
exm412686	10.004	6
exm492794	8.546	4
rs10062167	8.546	4
exm555796	3.439	6
exm671119	70.933	3
exm695560	2.716	4
exm829568	28.464	3
exm975133	7.5446	3
rs17246266	4.249	21
exm1612339	465.552	3
rs12168259	10.424	4