

**Genetics of Atrial Fibrillation (AF)
Progress Report to SAB: AFIC
Basic Science Studies**

Qing K. Wang, Ph.D., M.B.A.

Director
Center for Cardiovascular Genetics
Lerner Research Institute
Cleveland Clinic

Genetic Component of Common AF

- 1. Framingham Heart Study (2,234 offsprings):
 - Risk ratio (RR) = 1.85 for offsprings if at least one parent has AF
 - OR = 3.23 with study participants younger than 75 years or to 3.17 when offsprings with overt heart disease were excluded.
- 2. Icelandic Study (5,269 AF patients and 10,000 controls):
 - RR = 1.77 for the first-degree relatives
 - = 1.36 for the second-degree relative
 - = 4.67 for first-degree relatives under the age of 60 years
- 3. MGH Study (110 patients with lone AF)
 - RR = 8.1 for sons, 9.5 for daughters, 70 for brothers, 34 for sisters, 4 for mothers, and 2 for fathers¹⁷

Genetics of AF

- **Familial forms of AF are rare, but do exist**
- **Large AF families are instrumental in identifying AF genes**

Genetics of AF

AF Locus	Location	Gene
adAF1	10q	?
adAF2	6q	?
adAF3/LQTS adAF3/SQTS	11p15.1	KCNQ1
adAF4	21q22	KCNE2
adAF5	12p13	KCNA5
adAF6/SQTS	7q35	KCNH2
Somatic AF	1q21	CONNEXIN 40
arAF1	5p13	?

Mapping of the first autosomal recessive AF gene

Genome-Wide Linkage Scan Identifies a Novel Genetic Locus on Chromosome 5p13 for Neonatal Atrial Fibrillation Associated With Sudden Death and Variable Cardiomyopathy

Carlos Oberti, MD, MS^{*}; Lejin Wang, MD^{*}; Lin Li, PhD; Jiamei Dong, MD; Shaoqi Rao, PhD; Wei Du, BS; Qing Wang, PhD, MBA

Circulation. 2004;110:3753-3759

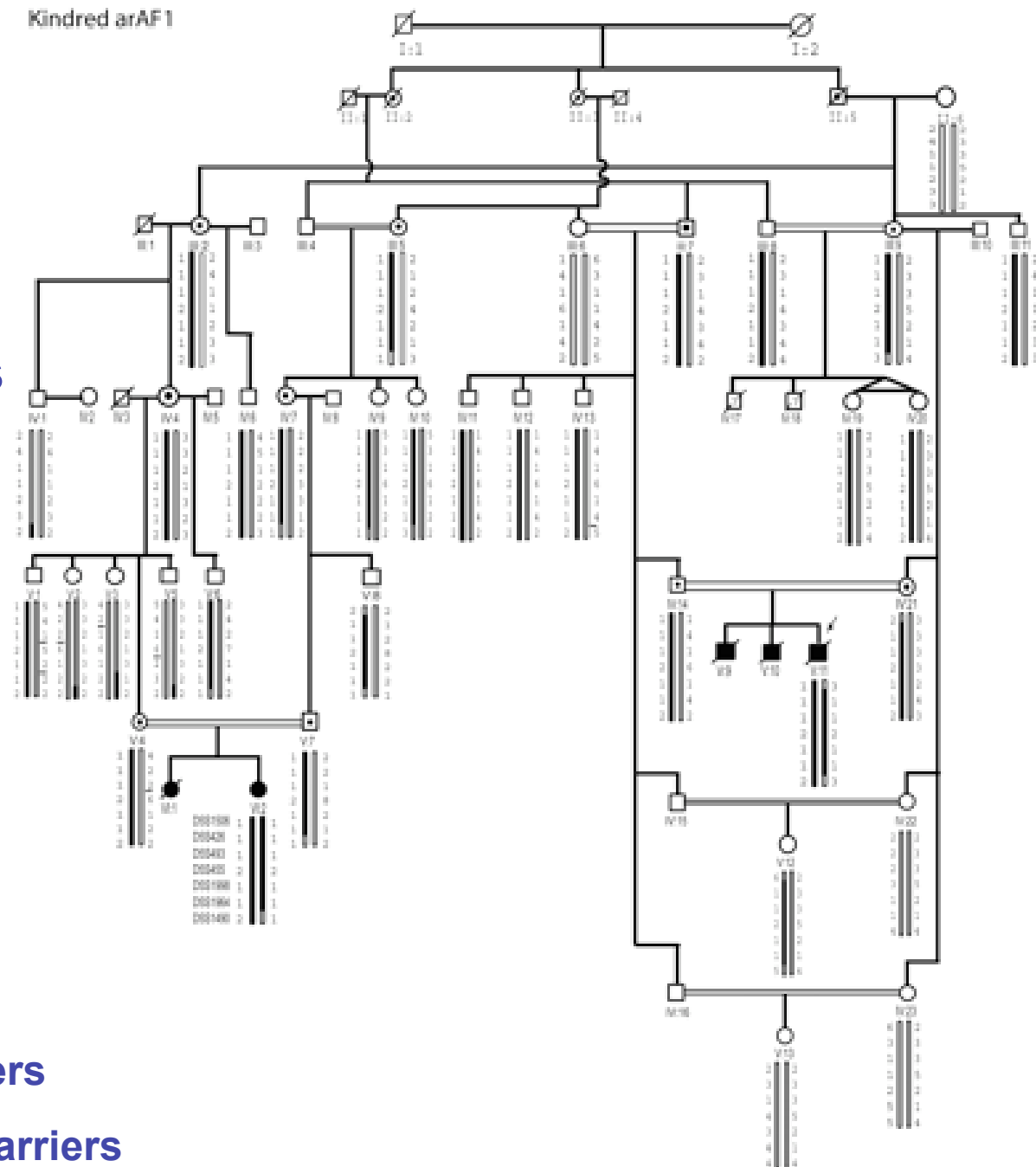
adAF family
 7
 consanguineous
 marriages
 57 family
 members
 32 males
 25 females

No LQTS

QTc:

412 ms for carriers

416 ms for noncarriers



Experimental Procedures

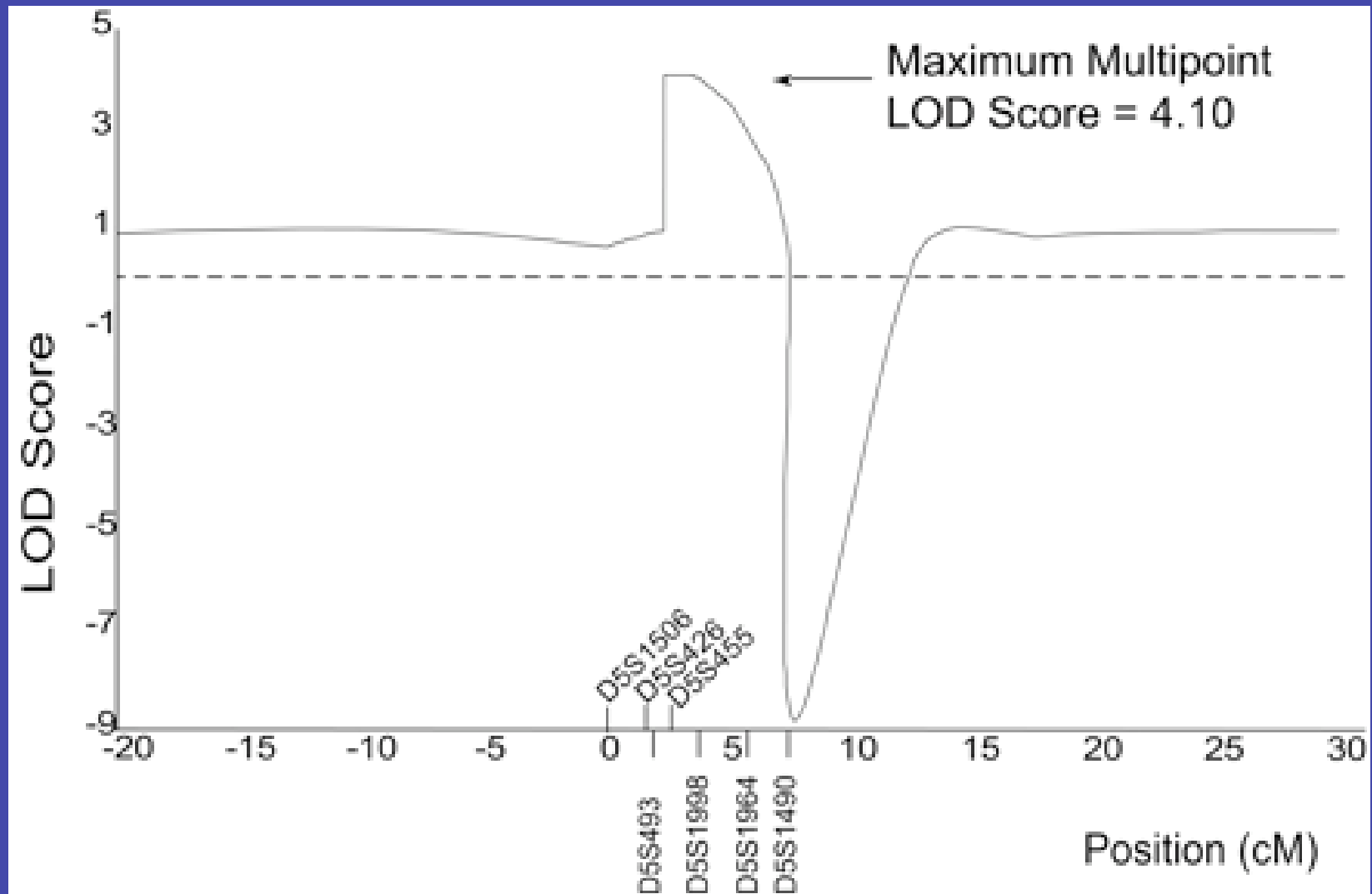
- **1. Study Subjects and Phenotyping**
 - Resting 12-lead ECG
 - Echocardiography
- **2. Isolation of Genomic DNA and Genotyping**
 - whole blood
 - DNA Isolation Kit for Mammalian Blood (Roche)
- **3. Linkage Analysis (LOD scores)**
 - Two-point linkage analysis (Fastlink software package)
 - Multipoint linkage analysis (Simwalk2 program)

Linkage of AF to Chromosome 5p13 Markers (Pairwise LOD Scores)

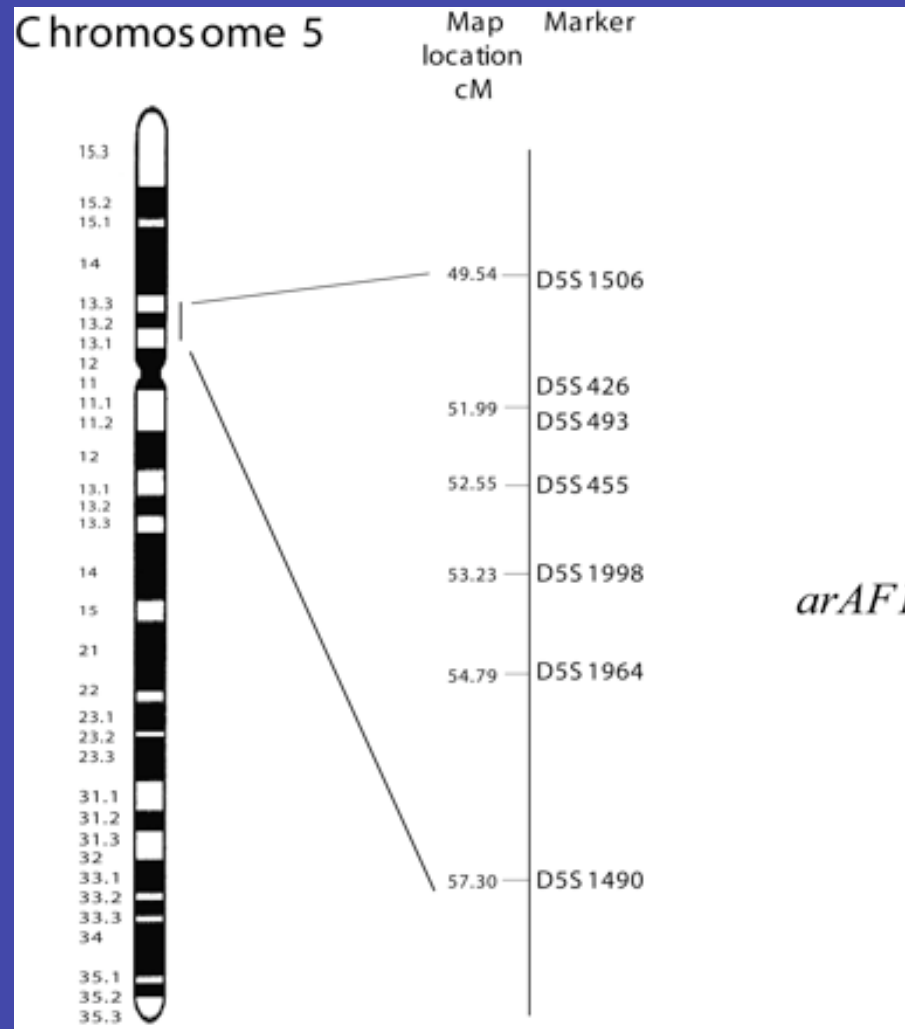
Recombination Fraction

Marker	0.00	0.05	0.10	0.20	0.30	0.40
D5S1506	-0.02	0.25	0.58	0.63	0.48	0.25
D5S493	0.22	0.08	-0.03	-0.17	-0.19	-0.13
D5S426	2.10	1.72	1.40	0.95	0.63	0.32
D5S455	3.05	2.61	2.17	1.39	0.84	0.43
D5S1998	2.23	1.98	1.74	1.26	0.81	0.39
D5S1964	1.91	1.77	1.60	1.20	0.78	0.37
DS51490	-3.24	-0.58	-0.11	0.20	0.24	0.16

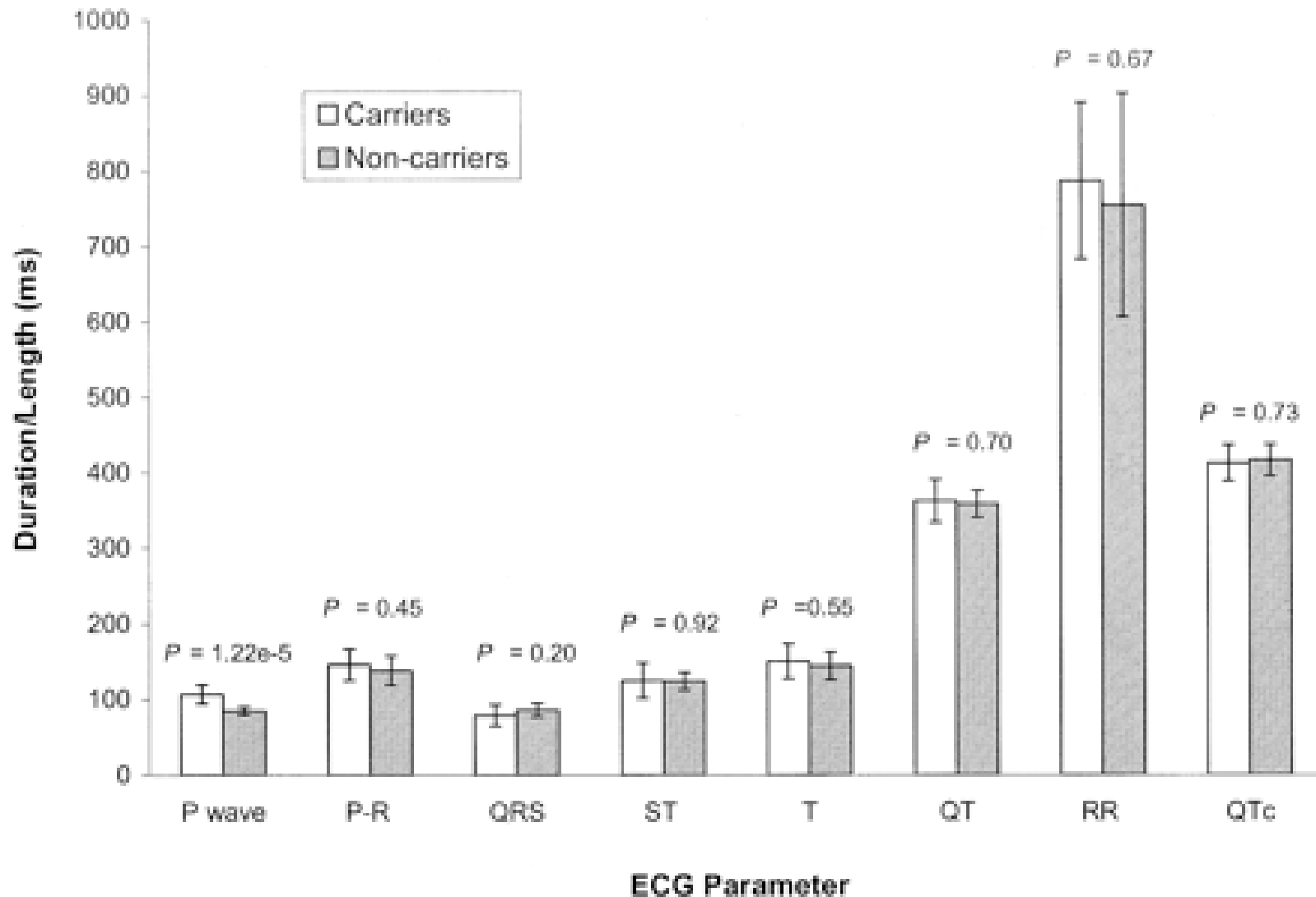
Linkage of AF to Chromosome 5p13 Markers



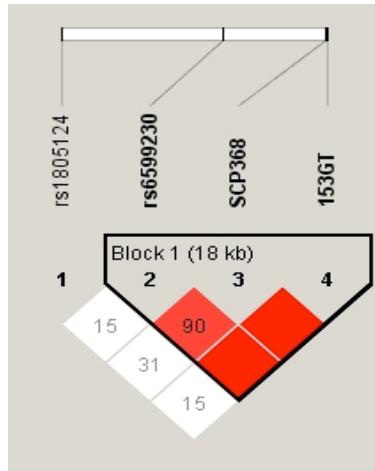
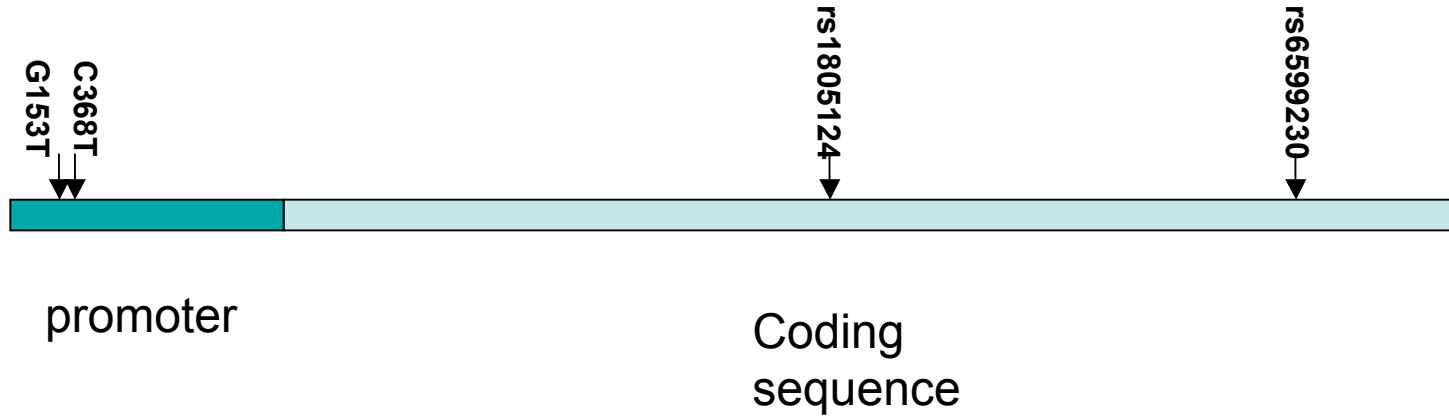
Linkage of AF to Chromosome 5p13 Markers



P-Wave Duration Is Significantly Prolonged in Heterozygous Carriers in the arAF1 Family



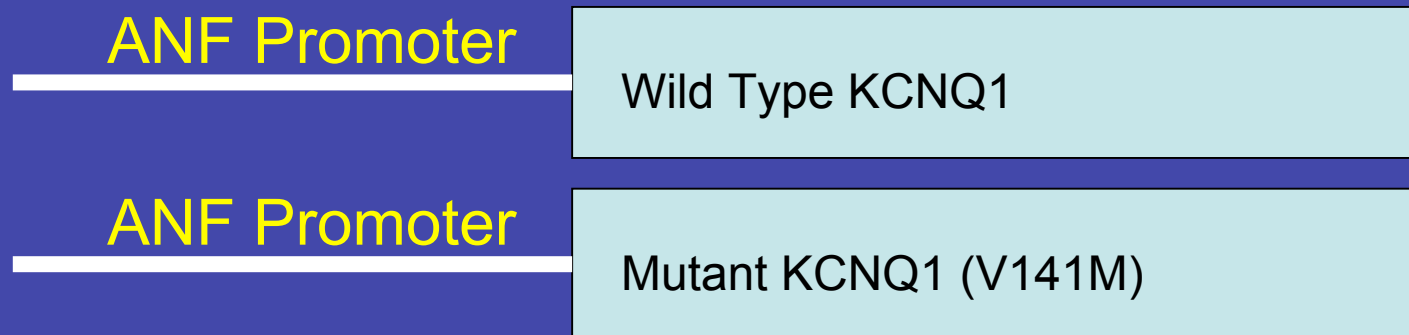
Typed SNPs in SCN5A



SNP	AF (Case=133; Control=428)					
	Risk Allele	Case (%)	Control (%)	OR	95% C.I.	<i>P</i> -value
rs1805124	A	76.0	74.6	1.077	0.773-1.503	0.660
rs6599230	C	82.8	82.0	1.053	0.722-1.535	0.788
SCP368	G	19.0	14.6	0.734	0.506-1.064	0.102
153GT	G	87.1	86.7	1.040	0.682-1.586	0.856

Creation of transgenic mouse model for AF

- 10 positive founders (6F 4M) for TG-WT KCNQ1
- 8 positive founders (7F 1M) for TG-MT KCNQ1 (V141M)



Acknowledgements

Postdoctoral Fellows

Shenghan Chen, M.D.

Xiaoli Tian, Ph.D.

Quansheng Xi, Ph.D.

Lin Li, Ph.D.

Tie Ke, Ph.D.

Shin Yoo, Ph.D.

Graduate student

Xianqin Zhang, B.S.

Technologist

Ying Ni, M.S.

Collaborators

Carlos Oberti, M.D. **CCF**

Mina Chung, M.D. **CCF**

Andrea Natale, M.D. **CCF**

Patrick Tchou, M.D. **CCF**

G. Michael Vincent, M.D.

University of Utah

Li Zhang, M.D.

University of Utah

Professor Yang Yanzong

Dalia Medical University, China