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Biomarkers and Drug Responsive Genotypes in Long QT Syndrome

By

Dr. Pratibha Nallari

Professor & Coordinator, CAS II

Dept. of Genetics

Osmania University,

Hyderabad,

Telangana State,

India.

Background

- Fatal cardiovascular disorder
- QTc interval prolonged
  - >440 ms in males
  - >450 ms in females
- Propensity to ventricular tachyarrhythmias.
- QTc prolongation due to ion channel dysfunction.

Diagnostic features:

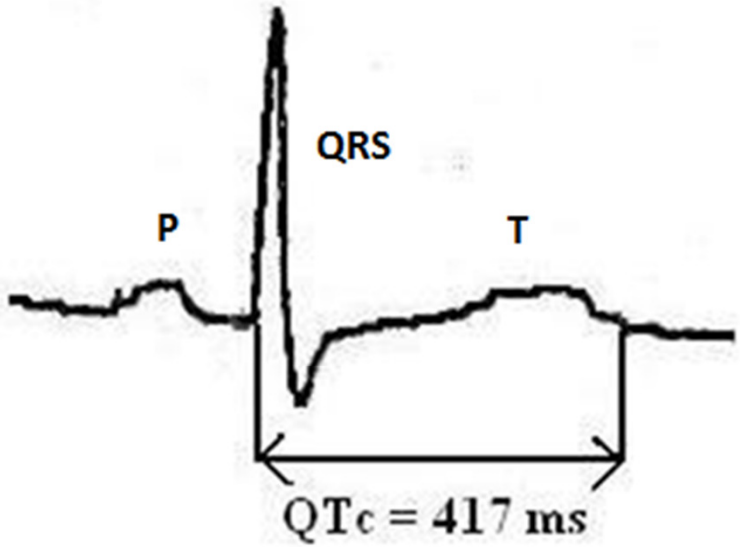
- Syncope, Prolonged QTc
- Siblings, or family members with unexplained syncope or sudden death

Classification: cLQTS and aLQTS

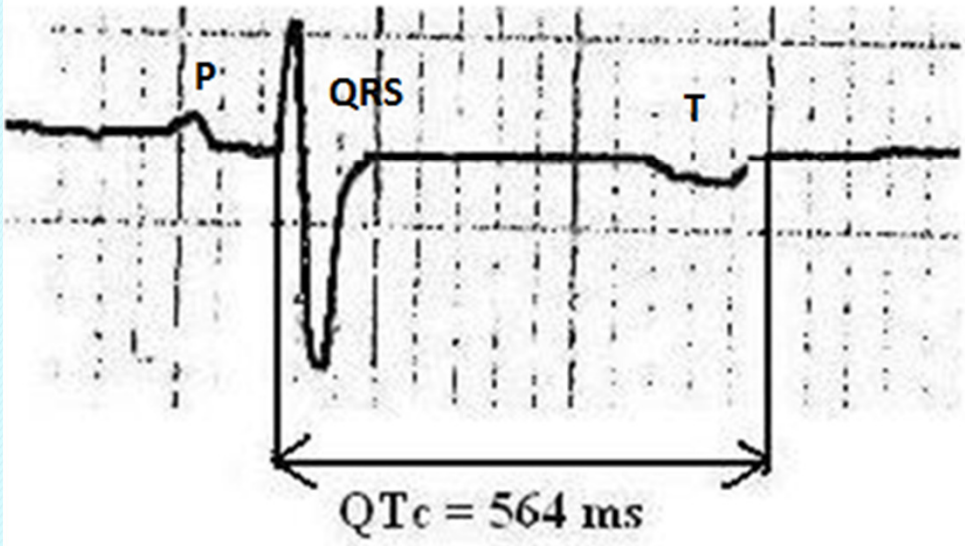
LQTS susceptibility proteins

- Cardiac ion channels (***KCNQ1, KCNE1, SCN5A, KCNH2, KCNE2***)
- Sodium / calcium channels localization to sarcolemma (***CAV3, ANK2***)
- Beta adrenergic receptor gene/s- adrenergic activation (***ADRB1, ADRB2***)
- Cytokine / hormone (***TNF-α and NPPA***)

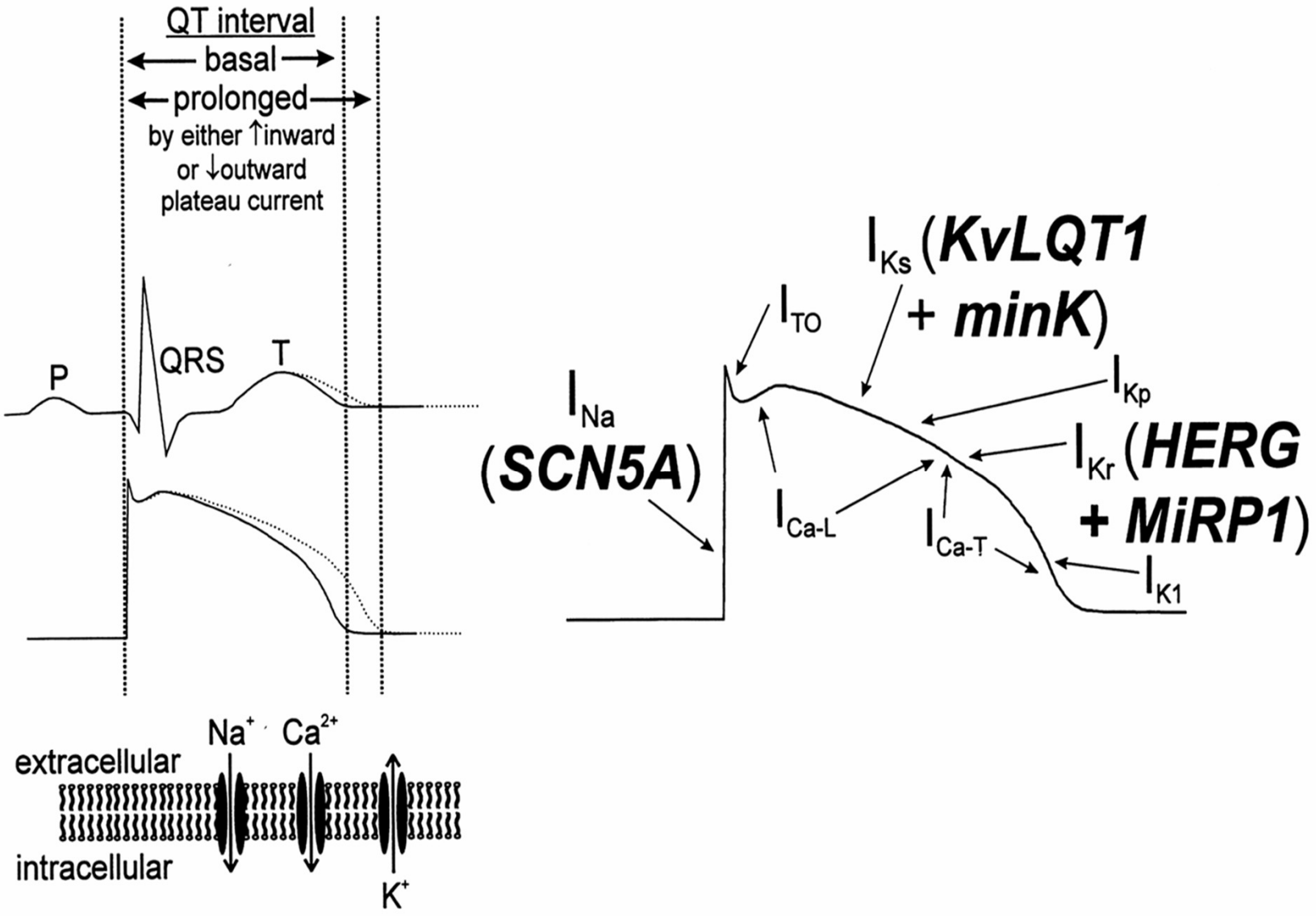
ECG pattern



ECG of a healthy individual



ECG of a patient with Long QT syndrome



Basis for the Long QT Syndrome

Focus of the Study

- Presently, the exact association of several SNPs with cardiac pathology is limited.
- Very few mutations have been functionally characterized to ascertain their potential severity.

- The main aim of our study was to examine the prevalence of LQTS in South-Indian population and the polymorphisms existing in this ethnically diverse population.
  - **Tumor necrosis factor-alpha** (*TNF-α*) gene polymorphisms to understand their **role** in LQTS.
  - **Atrial Natriuretic Peptide** (*NPPA*) gene implication as a possible **biomarker** in LQTS.
  - **Beta-1-adrenoceptor** (*ADRB1*) and **beta-2 adrenoceptor** (*ADRB2*) gene/s' polymorphisms for their **pharmacogenomic** implications

Methodology

Collection of the blood sample + familial and clinical information
(Controls 150 / LQTS n-46/ FDRs-69)

Controls-Osmania Hospital, Hyderabad; LQTS-Care hospitals, Hyderabad, Bengaluru, Calicut, Chennai.

↓

Genomic DNA isolation
(Lahiri et al, 1992; Saremi et al, 2007)

↓

PCR amplification

↓

Electrophoresis

↓

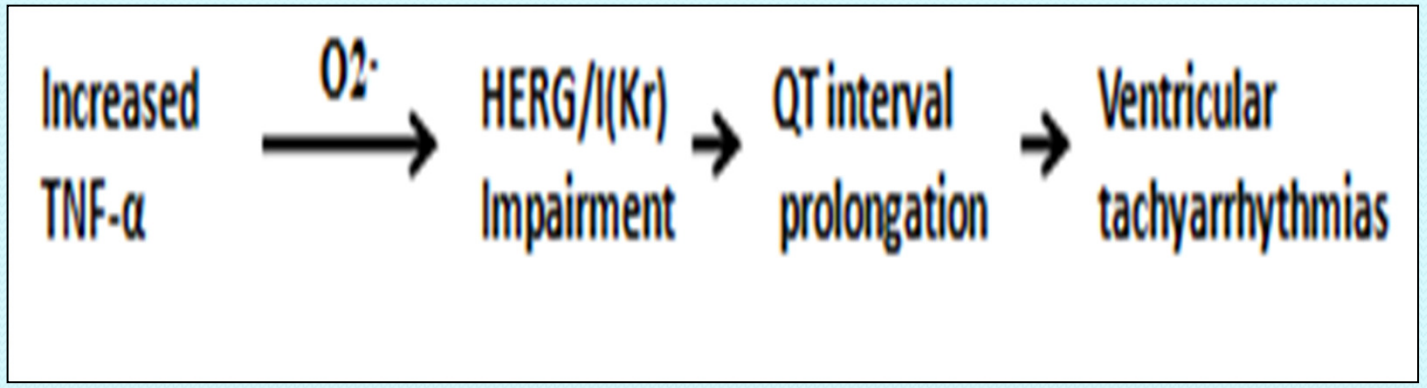
Allele-specific PCR
(Verjans et al, 1994)
(TNF-alpha -308G>A SNP)

RFLP **(Saiki et al, 1985)**
(*ADRB1, ADRB2, NPPA, TNF-alpha -1031T>C and -238 G>A SNPs*)

TNF-alpha(-308 G>A) rs1800629

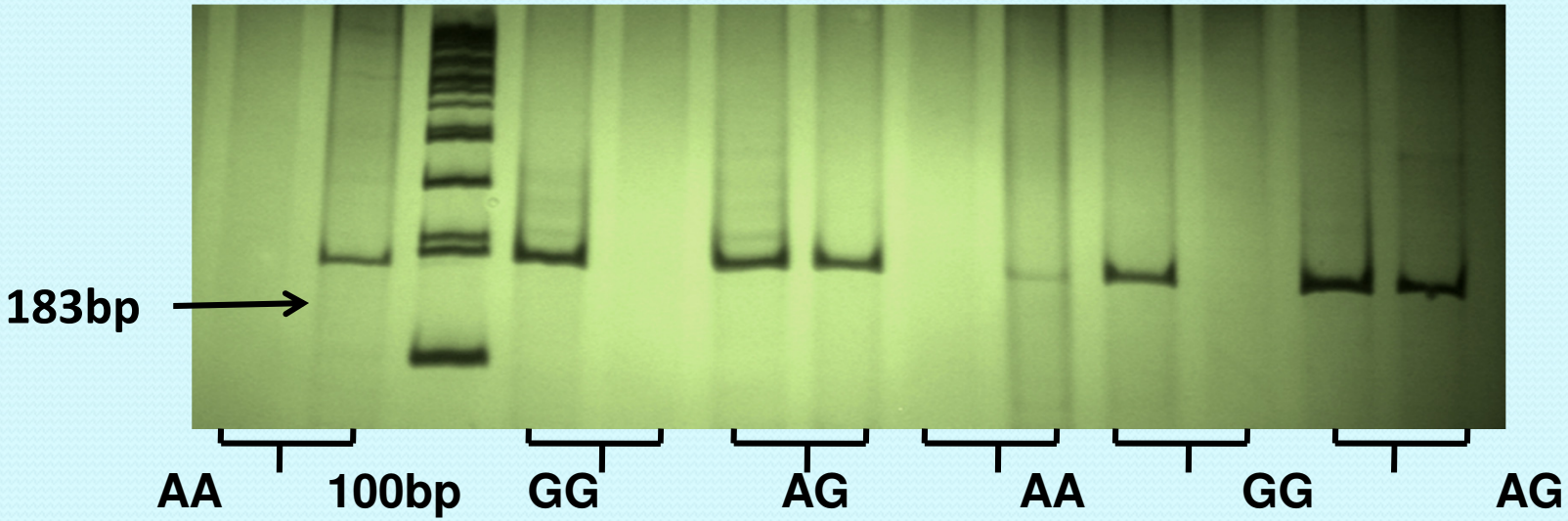
- TNF-*α* can modulate cardiac K+ channels.
- It influences HERG/*Ikr channels, leading to* repolarization defects.
- *IKr inhibition causes* early after depolarizations (*EADs)*
- Upregulated in transgenic mice with heart failure - prolonged APD.
- Inflammatory cytokines (TNF-*α*), triggers myocardial apoptosis - cardiac dysfunction and ventricular tachyarrhythmias.
- Role of TNF-*α* in LQTS may provide new insights into the potential molecular mechanisms of cardiac electrophysiology resulting in sudden cardiac death
- *TNF-alpha* is located at 6p21.3 – 4 exons.

Possible pathological events associated with TNF-*α:*



TNF-alpha -308 G>A (rs1800629)

Genotypes of *TNF-alpha* -308 G>A by Allele specific PCR



Genotypic and allelic frequency distribution

Genotype	Controls n (%)	LQTS n (%)	FDRs n (%)
AA	**18 (12)**	**9 (20)**	**15 (22)**
AG	82 (55)	22 (47)	33 (48)
GG	50 (33)	15(33)	21(30)
Allele			
G	0.61	0.57	0.54
A	**0.39**	**0.43**	**0.46**

The frequency of '**A**' allele and '**AA**' genotype was found to be predominant in LQTs

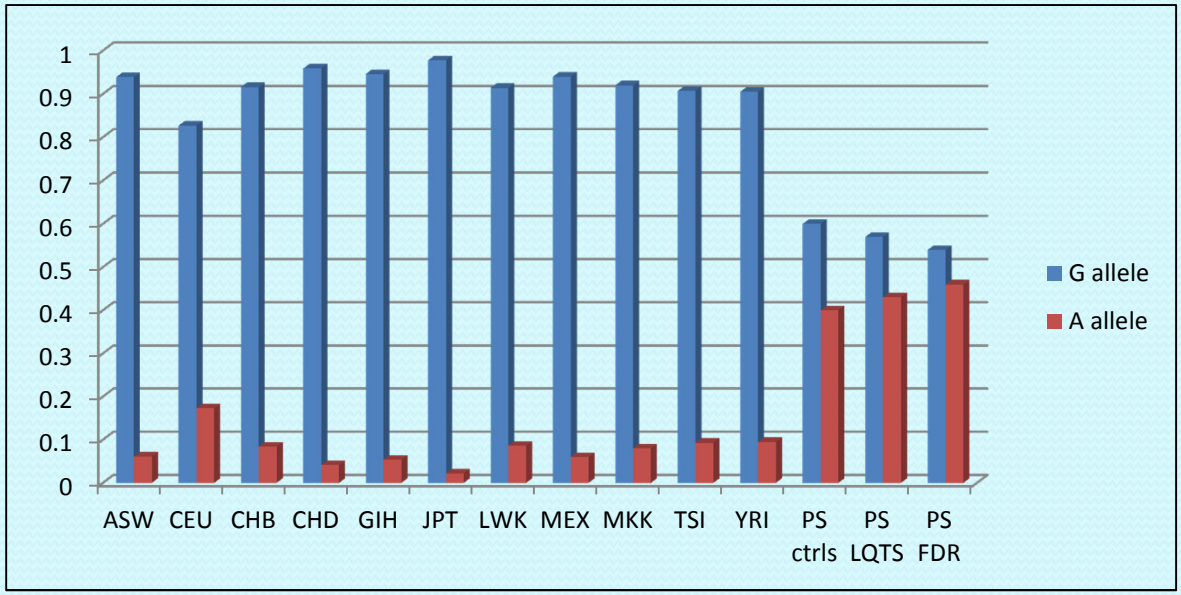
Risk stratification

Odds risk estimates of genotypes and alleles in LQTS and FDRs compared to controls of the *TNF-α* -308G/A polymorphism

TNF-α -308G/A							
Model	**Genotype**	**OR (95% CI) (LQTS Vs Ctrls)**	**p value**	**OR (95% CI) (LQTS Vs FDR)**	**p value**	**OR (95% CI) (FDR Vs Ctrls)**	**p value**
Codominant	GG AG AA	1.00 0.89 (0.42-1.88) 1.67 (0.62-4.47)	0.43	1.00 0.93 (0.40-2.19) 0.84 (0.29-2.42)	0.95	1.00 0.96 (0.50-1.84) 1.98 (0.84-4.66)	0.19
Dominant	GG AG/AA	1.00 1.03 (0.51-2.09)	0.93	1.00 0.90 (0.41-2.02)	0.81	1.00 1.14 (0.62-2.11)	0.67
Recessive	GG/AG AA	1.00 1.78 (0.74-4.3)	0.21	1.00 0.88 (0.35-2.21)	0.78	1.00 2.04 (0.96-4.33)	0.068
Overdominant	GG/AA AG	1.00 0.76 (0.39-1.47)	0.42	1.00 1.00 (0.47-2.11)	1.00	1.00 0.76 (0.43-1.35)	0.35
G vs A		1.17 (0.67-2.07)	0.56	1.12(0.64-1.97)	0.66	1.33(0.75-2.33)	0.31

None of the genotypes / alleles were found to be associated with the diseased phenotype.

Hapmap of TNF-alpha -308G>A polymorphism



- The 'A' allele frequency was considerably higher in South Indian population.

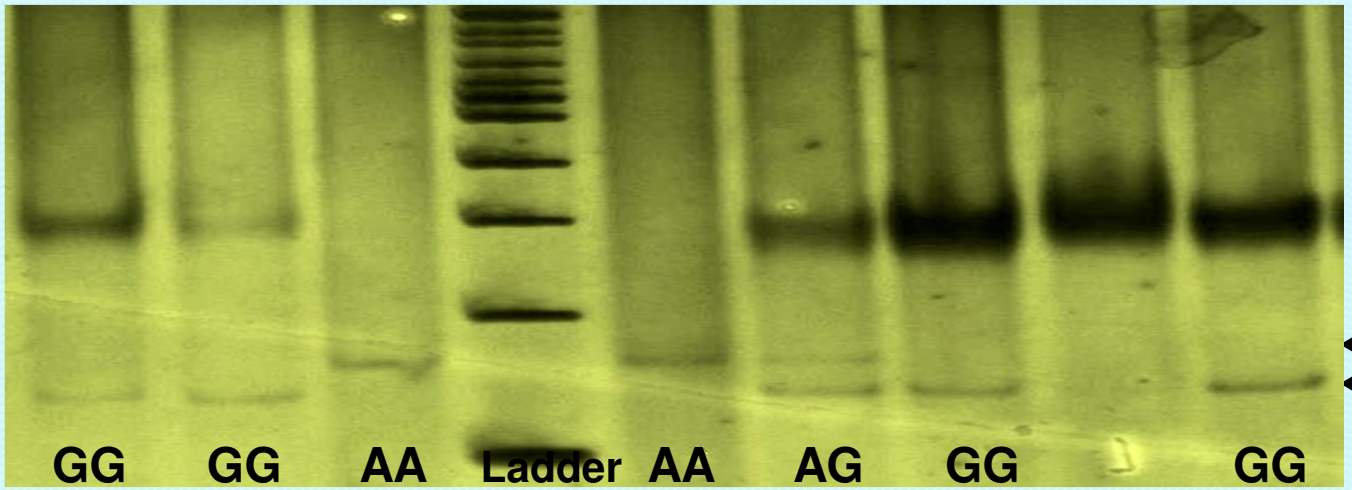
In-Silico Analysis:

- **TF Binding:** Deletion of **transcription regulators ADR1** [alcohol dehydrogenase (ADH) II synthesis regulator], **MZF1** (Myeloid zinc finger 1) - dysregulation of transcription and translation : influence downstream signalling.

- Parental consanguinity was reported to be high **(33%)** - 'A' allele – strengthening recessive nature of LQT.

TNF-alpha -238 G>A (rs361525)

Genotypes of *TNF-alpha* -238 G>A



Genotypic and allelic frequency distribution

Genotype	Controls n (%)	LQTS n (%)	FDRs n (%)
AA	**5 (3)**	**3 (7)**	**5 (7)**
AG	20 (13)	16 (35)	25 (36)
GG	125(84)	27 (58)	39 (57)
Allele			
G	0.9	0.76	0.75
A	**0.1**	**0.24**	**0.25**

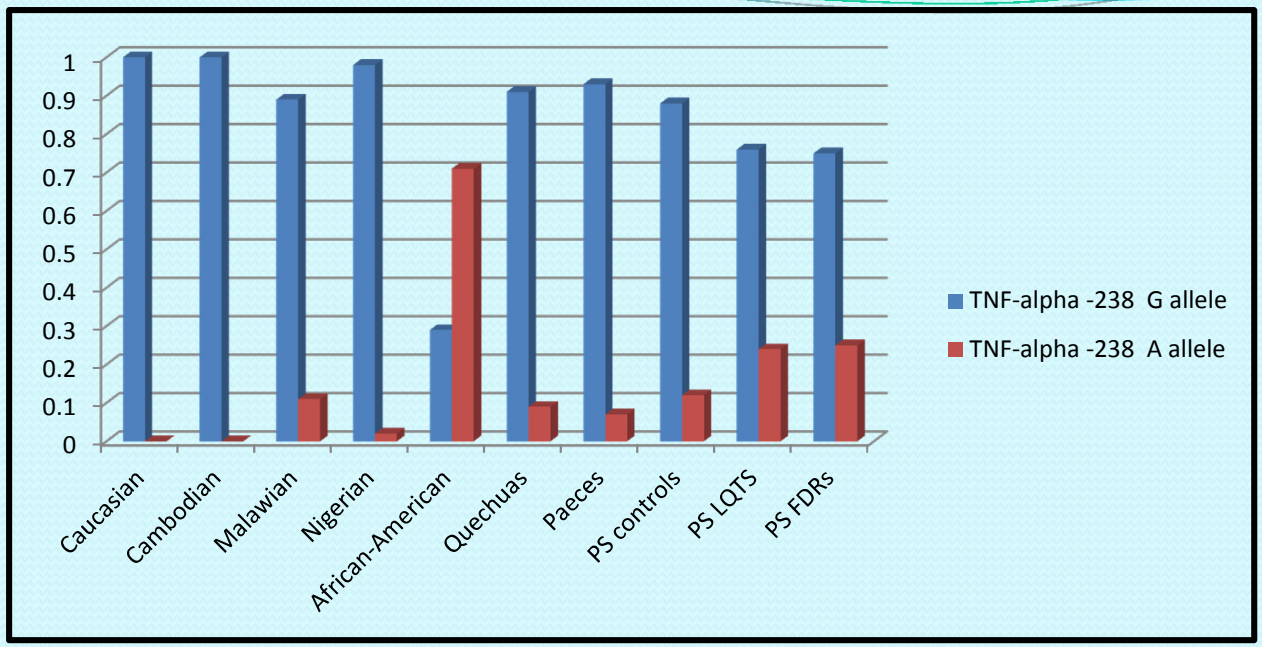
The 'A' allele and 'AA' genotype frequency : **two fold higher** in **LQTS** and **FDRs**

Risk stratification

TNF-α -238G/A					
Model	**Genotype**	**OR (95% CI) (LQTS Vs Ctrls)**	**p value**	**OR (95% CI) (FDR Vs Ctrls)**	**p value**
Codominant	GG	1.00		1.00	
	AG	**3.70 (1.70-8.06)**		**4.01 (2.01-7.98)**	
	AA	2.78 (0.63-12.33)	0.0034	3.21 (0.88-11.65)	0.0002
Dominant	GG	1.00		1.00	
	AG/AA	**3.52 (1.70-7.28)**	<0.0001	**3.85 (2.03-7.30)**	<0.0001
Recessive	GG/AG	1.00		1.00	
	AA	2.02 (0.46-8.81)	0.36	2.27 (0.63-8.10)	0.21
Overdominant	GG/AA	1.00		1.00	
	AG	**3.47 (1.61-7.47)**	0.0018	**3.69 (1.87-7.29)**	<0.0001
G vs A		**2.8(1.27-6.31)**	0.01	**3.0(1.35-6.64)**	0.0064

- The '**AG**' genotype : **4 fold risk** to LQTs.
- The '**A**' allele - **three-fold risk**.
- Implication the '**A**' allele in the etiopathogenesis of LQTS.

Hapmap of TNF-alpha -238 G>A polymorphism



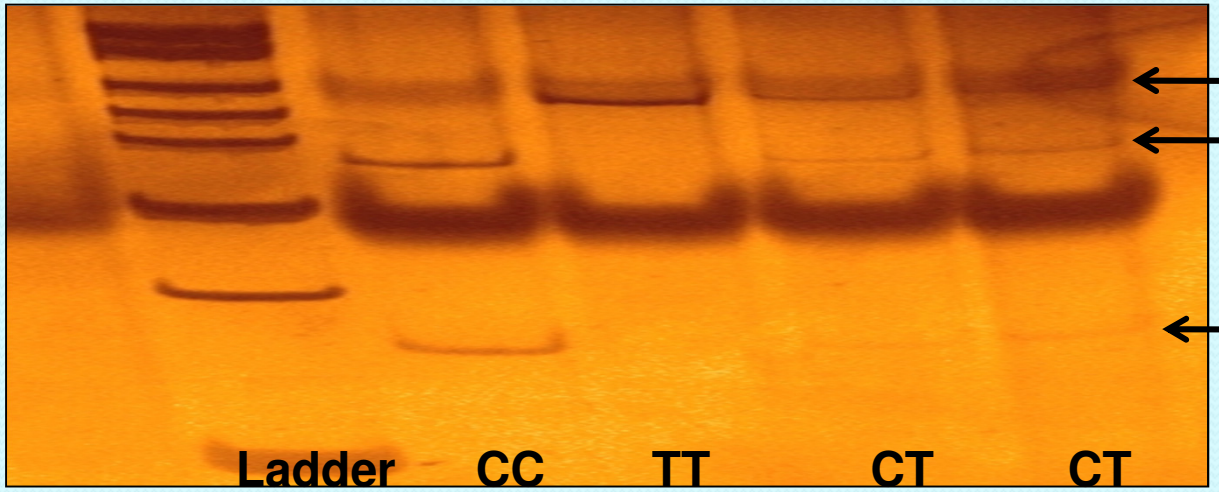
- The 'A' allele frequency was absent in Caucasian and Cambodian populations.
- Present in the South Indian population – **unique gene pool**.

In-silico Analysis:

- Transcription factor binding : loss of **HSF, NF-kB – binding sites :** variation in gene transcription and regulation leading to aberrant downstream signaling.
- Correlation to severity – higher **syncope** and **sudden cardiac death** episodes.

TNF-alpha -1031 C>T

Genotypes of *TNF-alpha* -1031 C>T



Genotypic and allelic frequency distribution

Genotype	Controls n (%)	LQTS n (%)	FDRs n (%)
CC	47 (31)	15 (33)	20 (29)
CT	75 (50)	23 (50)	37 (54)
TT	28 (19)	8 (17)	12 (17)
Allele			
C	0.56	0.58	0.56
T	0.44	0.42	0.44

The allelic and genotypic frequencies were similar in both controls and LQTs.

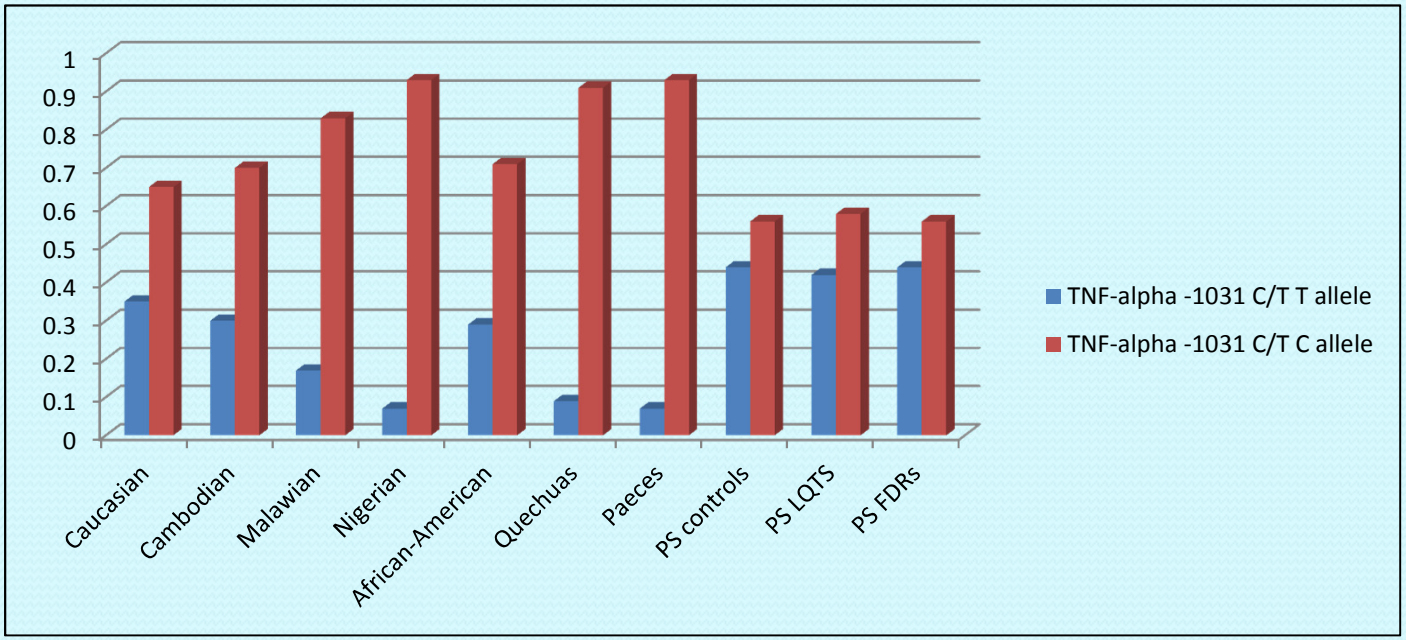
Risk stratification

Odds risk estimates of genotypes and alleles in LQTS and FDRs compared to control of the *TNF-α* -1031C/T polymorphism

TNF-α -1031 C/T							
Model	**Genotype**	**OR (95% CI) (LQTS Vs Ctrls)**	**p value**	**OR (95% CI) (LQTS Vs FDR)**	**p value**	**OR (95% CI) (FDR Vs Ctrls)**	**p value**
Codominant	CC CT TT	1.00 0.96 (0.46-2.03) 0.90 (0.34-2.38)	0.98	1.00 0.83 (0.35-1.94) 0.89 (0.29-2.72)	0.91	1.00 1.16 (0.60-2.23) 1.01 (0.43-2.37)	0.88
Dominant	CC CT/TT	1.00 0.94 (0.47-1.91)	0.87	1.00 0.84 (0.38-1.89)	0.68	1.00 1.12 (0.60-2.09)	0.73
Recessive	CC/CT TT	1.00 0.92 (0.39-2.18)	0.84	1.00 1.00 (0.37-2.68)	1.00	1.00 0.92 (0.44-1.93)	0.82
Overdominant	CC/CT TT	1.00 1.00 (0.52-1.94)	1.00	1.00 0.86 (0.41-1.83)	0.7	1.00 1.16 (0.65-2.05)	0.62
C vs T		0.92(0.52-1.61)	0.77	1.08(0.61-1.89)	0.77	1.00(0.57-1.74)	1.00

None of the genotypes / alleles were found to be associated with the disease phenotype.

Hapmap of TNF-alpha -1031 C>T polymorphism

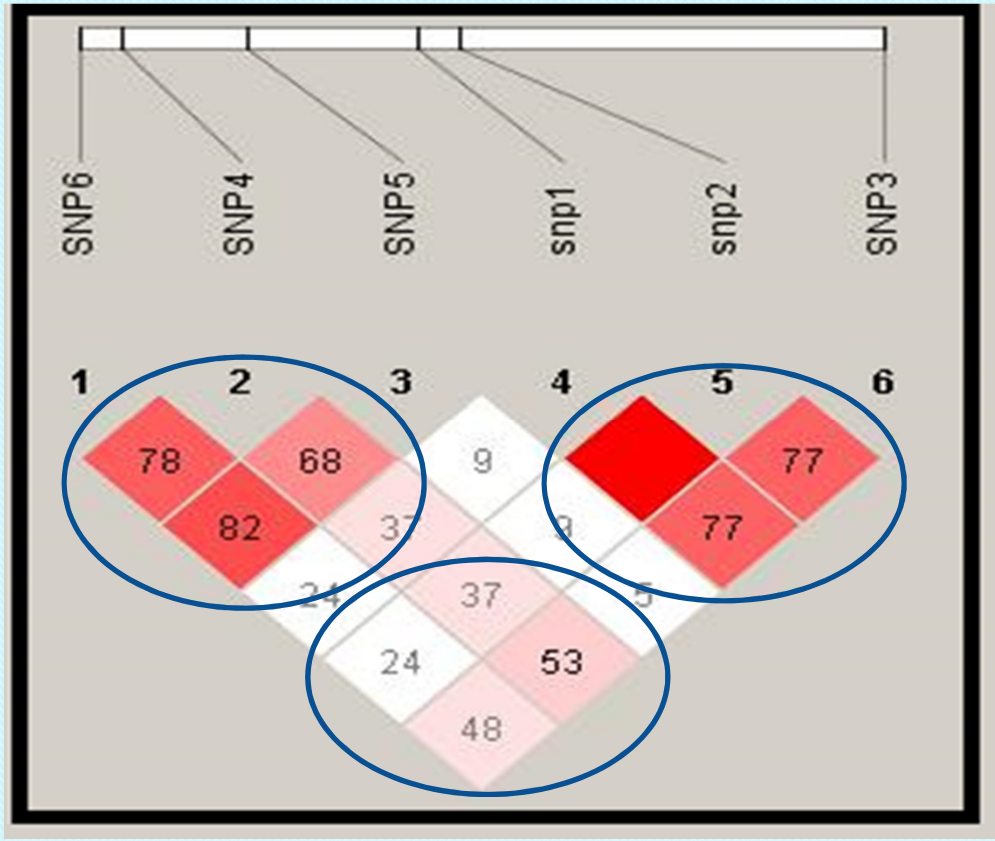


- The **'T' allele** frequency was higher in the South Indian population in comparison to other populations – Genetic Diversity.

In-silico analysis:

- **T allele** – deletion of TF site for **GCN4** : a negative regulator of transcription (RNA pol II).

Pairwise Linkage disequilibrium analysis of *KCNQ1*, *KCNE1* and *TNF-α* polymorphisms



SNP1- S546S (*KCNQ1*), SNP2-IVS13+36A>G (*KCNQ1*), SNP3-S38G (*KCNE1*), SNP4- -308G/A (*TNF-α*), SNP5- -1031C/T (*TNF-α*) & SNP6- -238G/A (*TNF-α*)

- A partial linkage disequilibrium was found between S38G (*KCNE1*) & -308G/A (*TNF-α*) (D'=0.53) and S38G (*KCNE1*) & -238G/A (*TNF-α*) (D'=0.48).

Haplotype frequencies - *KCNQ1, KCNE1* and *TNF-alpha* polymorphisms

Haplotype	Haplotype frequency	
	Controls	LQTS
GGGGCG	0.33	0.18
GAAATG	0.21	0.01
AGGGCG	0.14	0.03
GGGATG	0.04	0.14
GGGGTG	0.03	-
AGGATA	0.06	-
GAAGCG	0.03	0.03
GAAACG	-	0.15
AAAACG	0.02	0.05
AAAGCG	0.02	-
AGGGTA	0.02	0.11
AAAGCA	-	0.07
AAAATG	0.02	-
GGGATA	0.01	-
AGGATG	-	0.03
AGGGTG	0.01	-
AAAACA	-	0.01
GAAGTG	-	0.11

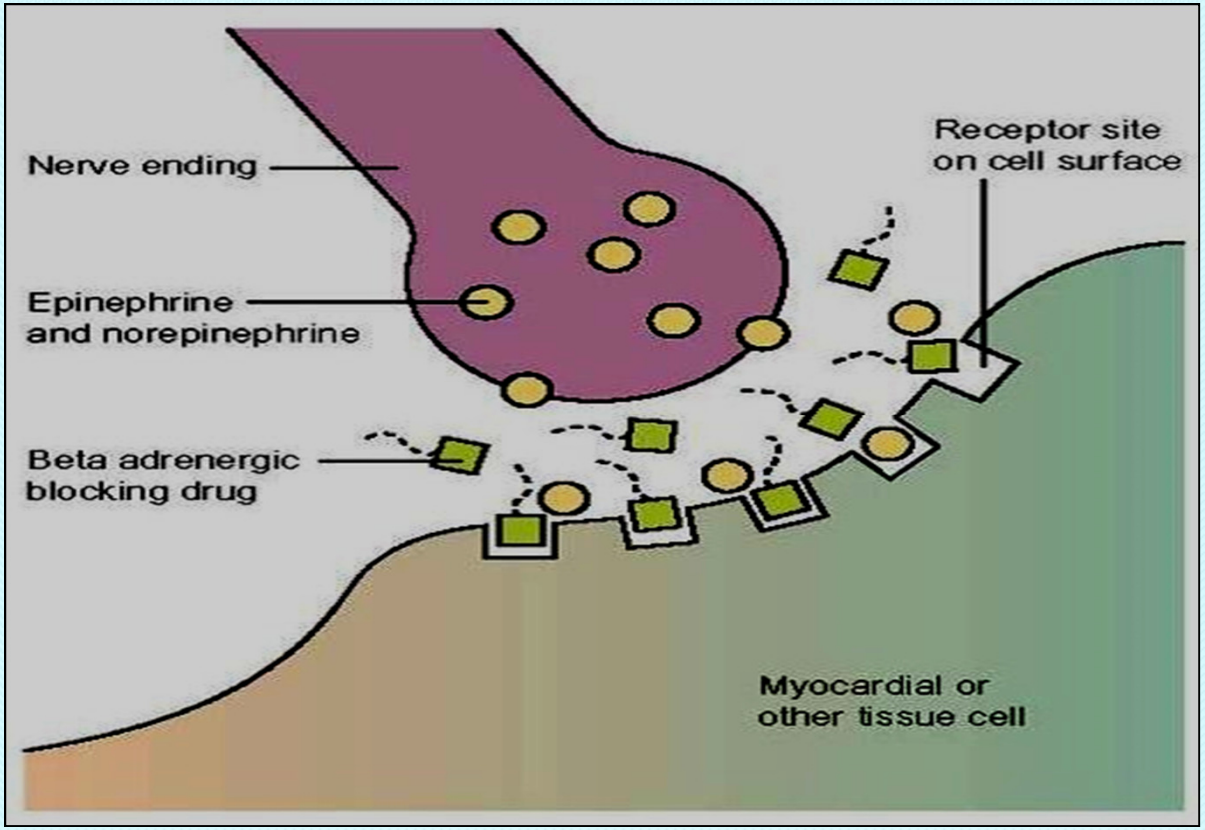
Compound Haplogroup: GGGATG, AAAACG, AGGGTA associated : role in LQTs etiology

Discussion:

- The multifaceted role of *TNF-α* in gene expression/regulation and its effects in cardiac events highlighted.
- Established a relationship between plasma TNF-α levels and the progression of left ventricular remodelling leading to heart failure.
- *TNF-α* promoter polymorphisms may influence gene expression
- Influence impairment of potassium and sodium channels causing prolonged APD.
- Etiology of LQTs elucidated.
- Hence can be implicated as a potential biomarker/diagnostic marker for LQTS.
- Compound Haplogroup : strengthens the gene-gene interactions

Beta-adrenergic receptor genes – *ADRB1* and *ADRB2*

- An imbalance of the parasympathetic and sympathetic nervous systems
- Fatal arrhythmia - ADRB1, ADRB2 gene/s
- Treatment with beta-blockers significantly reduces ventricular tachyarrhythmias and SCD.



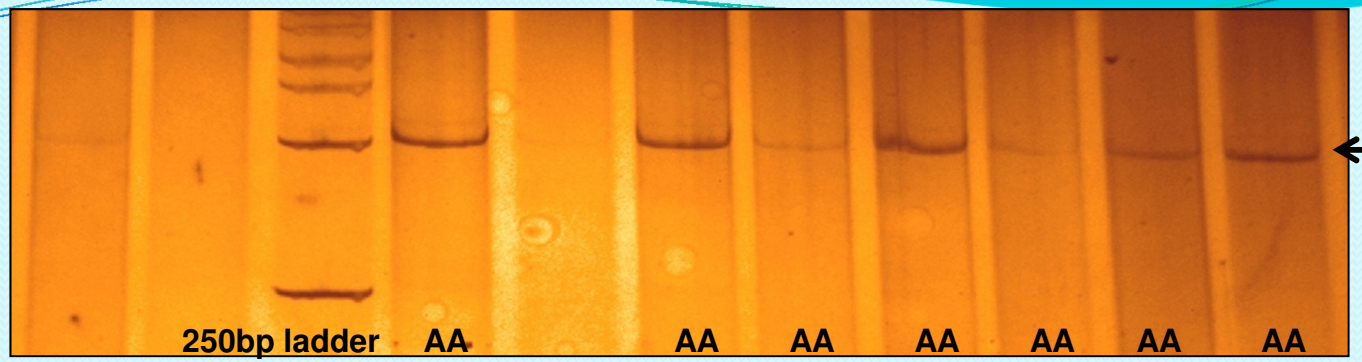
Beta-1-adrenoceptor gene (*ADRB1*):

- Localization - 10q24-26 - single exon
- **β**1-Adrenergic receptor – cardiomyocyte cell surface seven-transmembrane GPCRs
- β-adrenoceptor antagonists binding: reduces ventricular arrhythmias
- SNPs have differential effects : functional responses to adrenergic stimulation
- ***ADRB1* Ser49Gly and Arg389Gly genotypes –** increased risk to heart failure

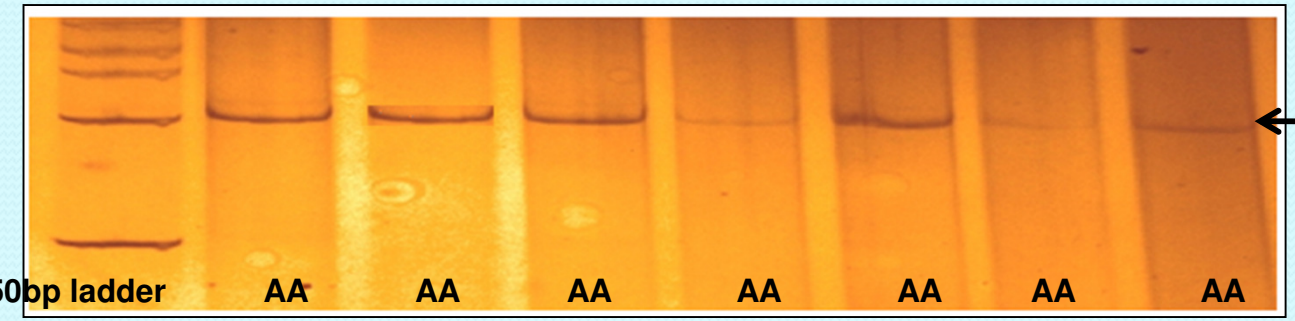
Beta-2 Adrenergic Receptor (*ADRB2*):

- Located at 5q31-q32 – single exon
- β2 adrenergic receptor (ADRB2) - member of the G-protein-coupled receptor (GPCR).
- Mediates vascular smooth muscle relaxation / vasodilation in response to sympathetic tone.
- Associated with signalling complex
- **Arg16Gly and Gln27Glu** are common variants
- Hence role of Beta-1,2 adrenergic receptor gene in LQTS was evaluated.

Genotypes of Beta-adrenoceptor-1 (S49G)



Genotypes of Beta-adrenoceptor-1 (R389G)

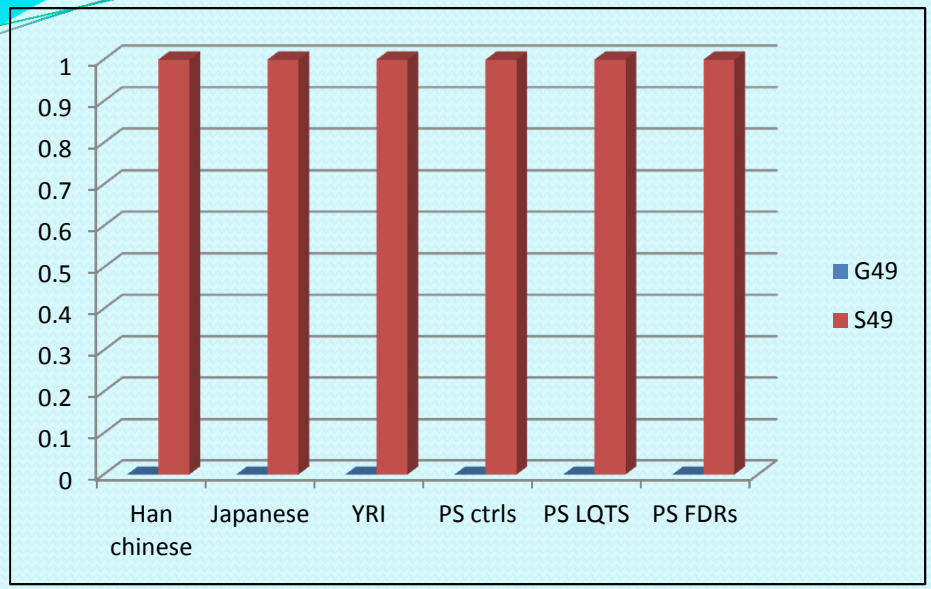


Genotypic frequency distribution

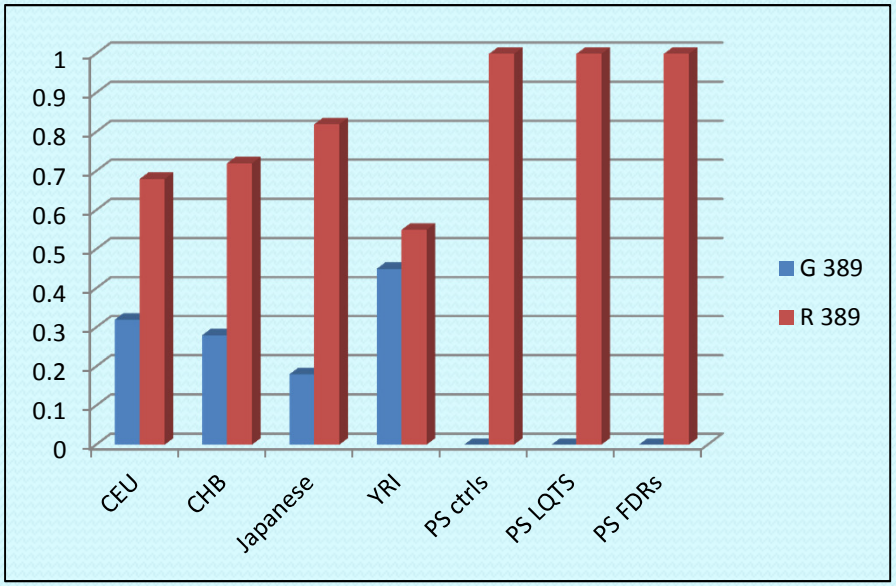
Gene	SNP	Genotype	Controls n (%)	LQTS patients n (%)	FDR n (%)
ADRB1	S49G	SS	150 (100)	46 (100)	69(100)
	R389G	RR	150 (100)	46 (100)	69(100)

Genotypes identified: **SS** of S49G and **RR** of R389G

Hapmap of Ser49Gly



Hapmap of Arg389Gly



Hapmap: Reflects **genetic diversity** of the South Indian population

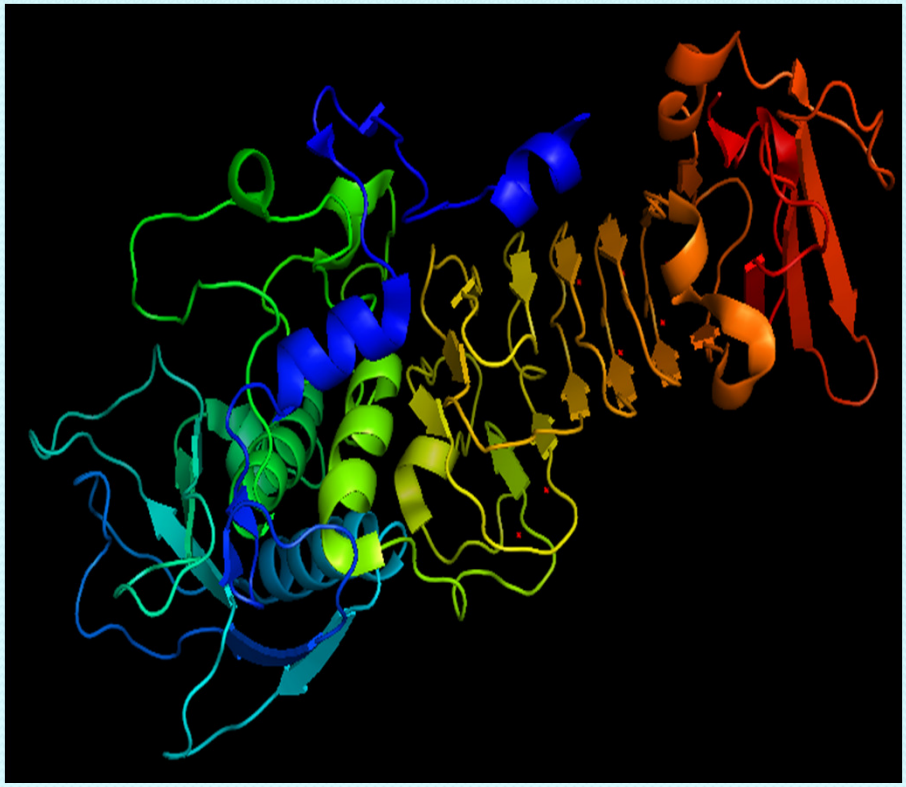
In-silico analysis:

- **S49G substitution of *ADRB1*** - altered secondary structure of beta-1 adrenergic receptor - loss of a beta sheet and decrease in the length of an alpha helix.

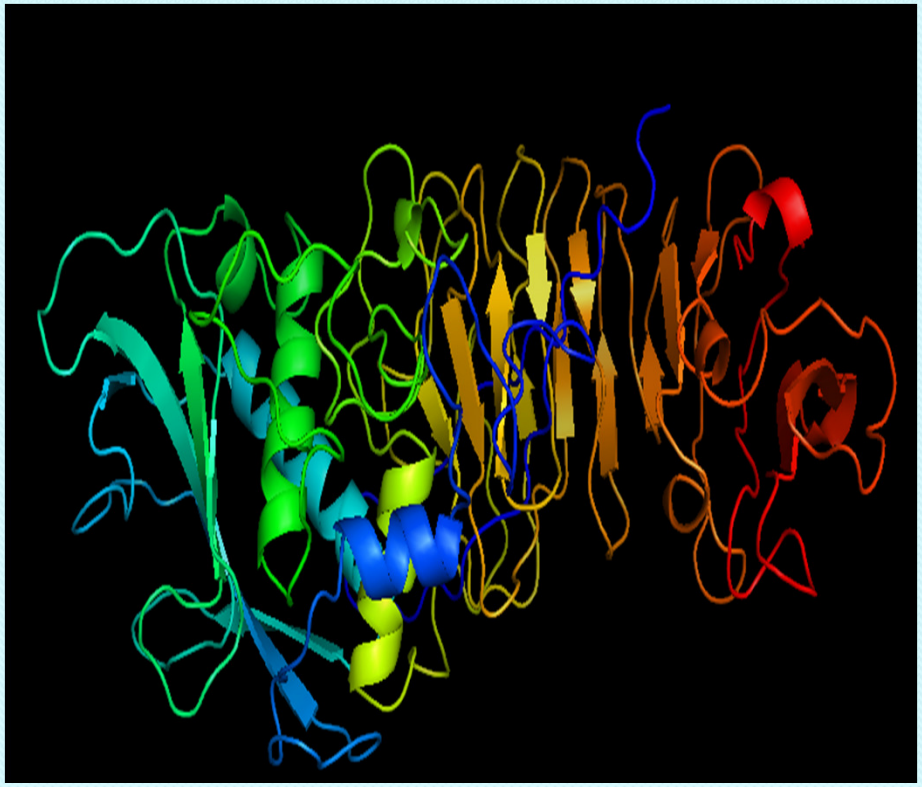
- **R389G:** secondary structure of ADRB1 protein altered - addition of a beta sheet, increase in length of an alpha helix - transmembrane structure of the protein altered.

Homology modelling

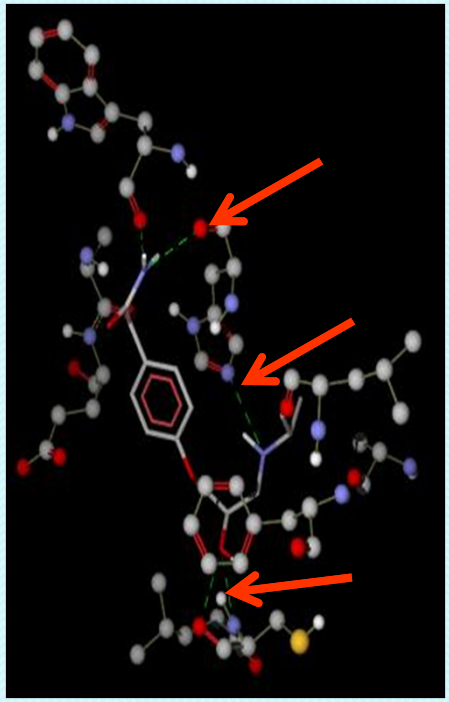
1K7G – Template Molecule

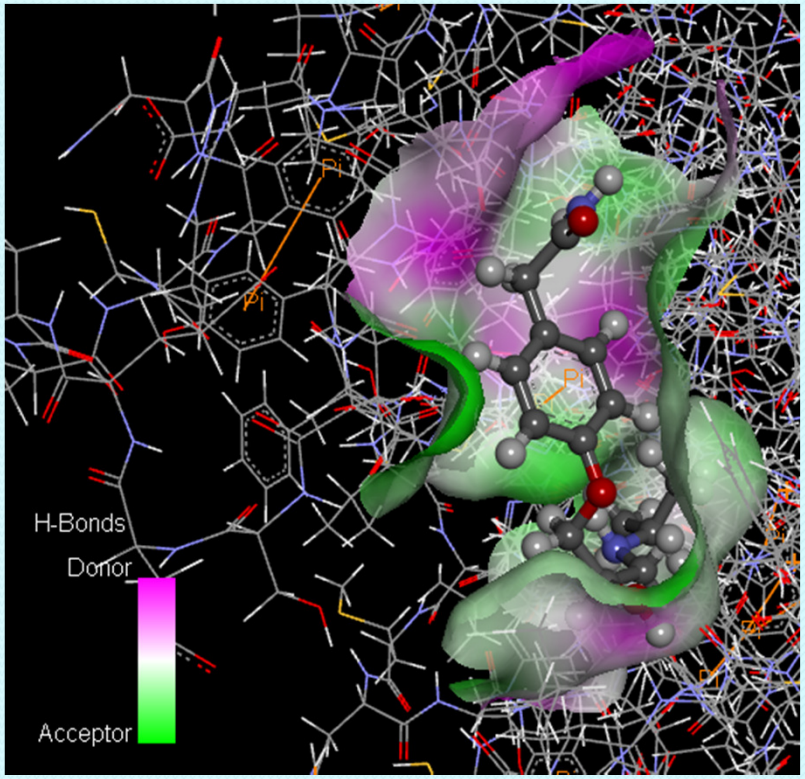


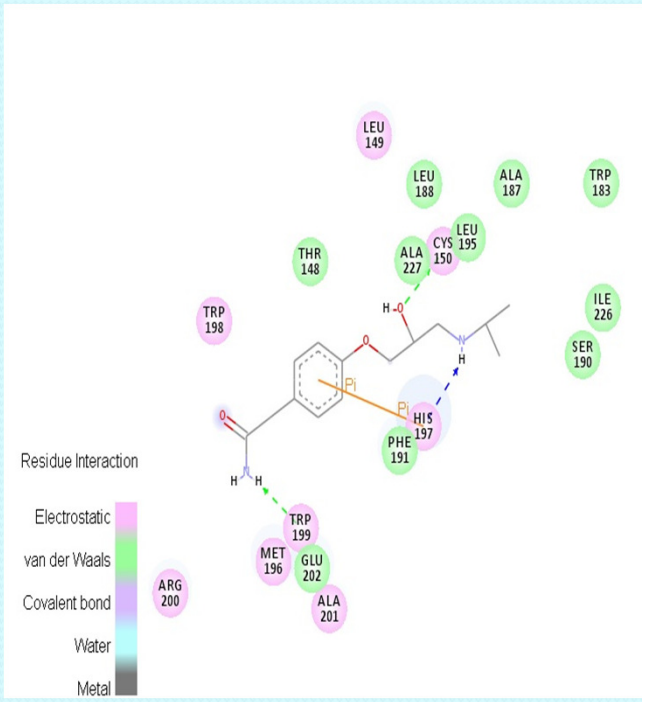
ADRB1 – Modelled molecule



Docking analyses – Wild Type

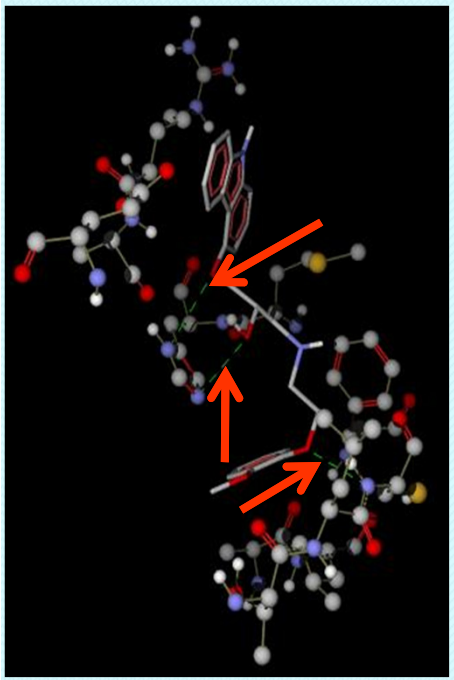


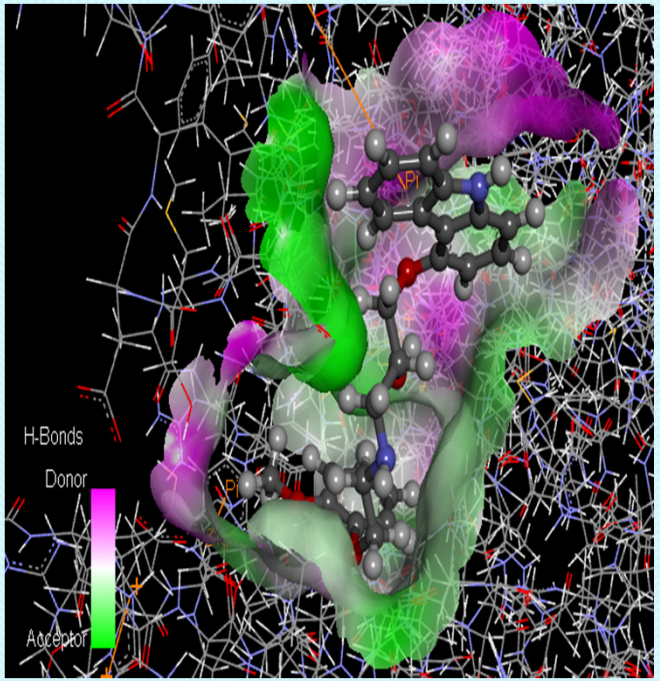


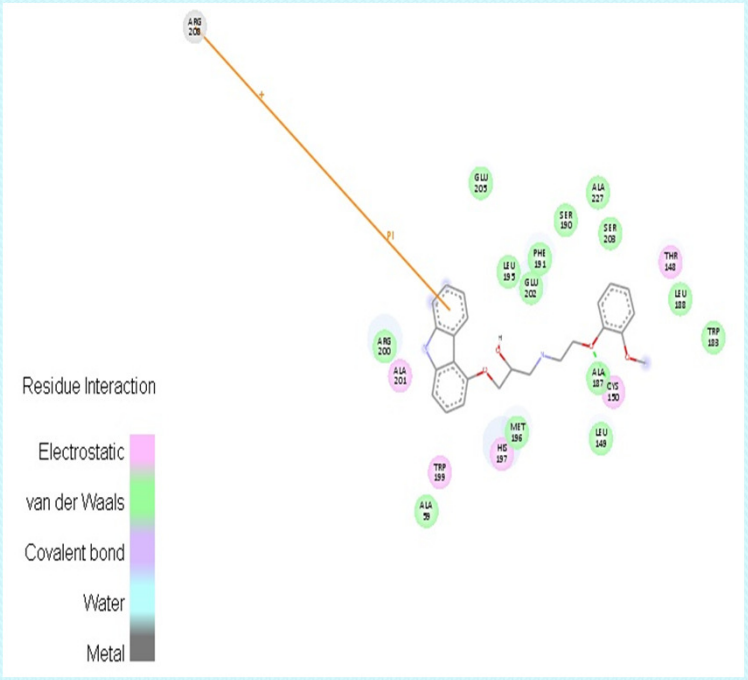


Drug – Atenolol – 4 hydrogen bonds

S49G – Variant

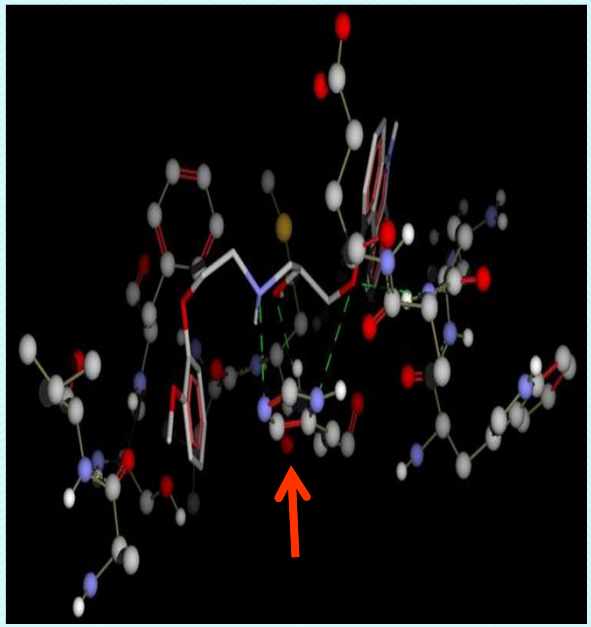


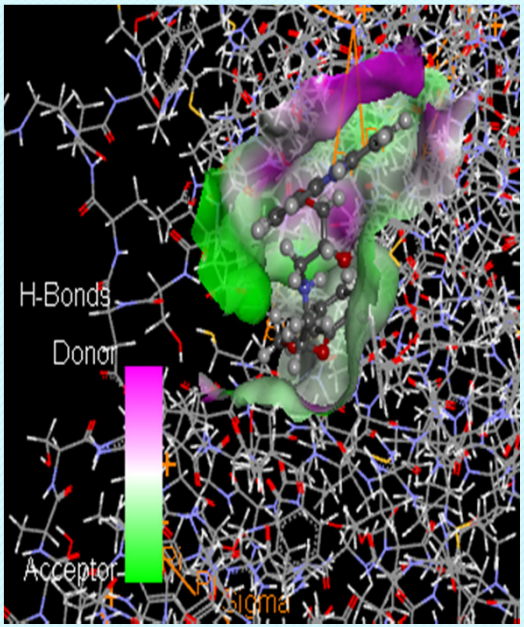


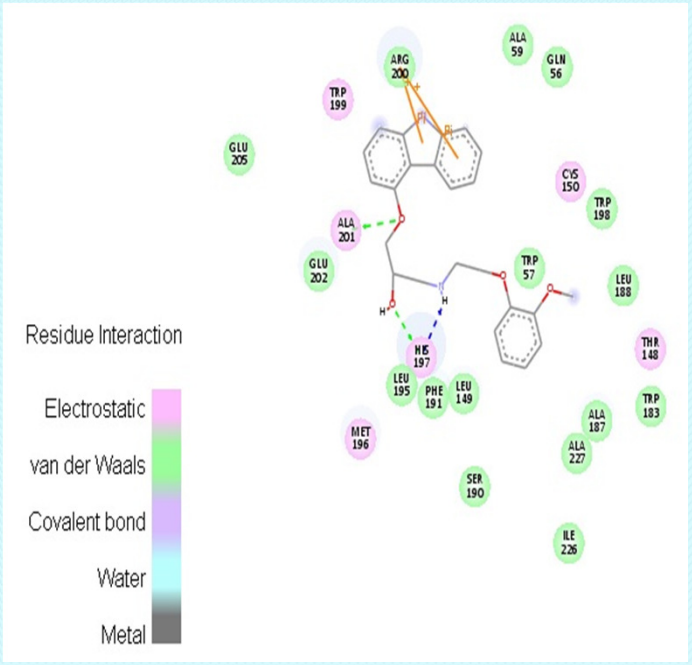


Drug – Carvedilol – 3 hydrogen bonds

R389G – Variant

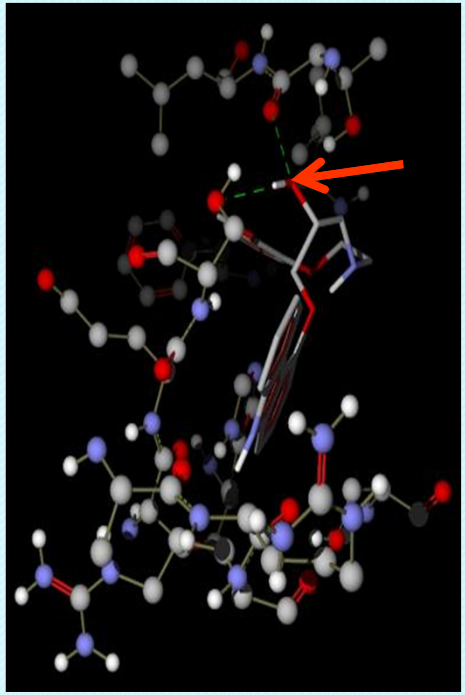


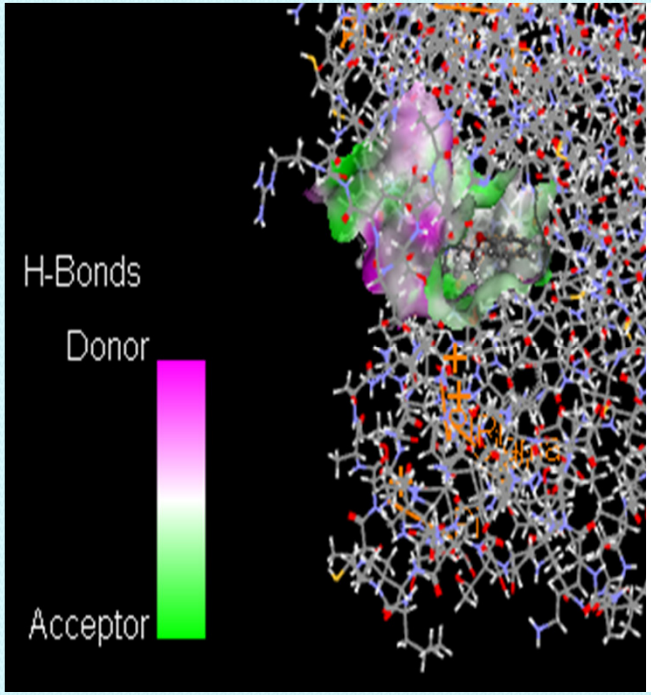


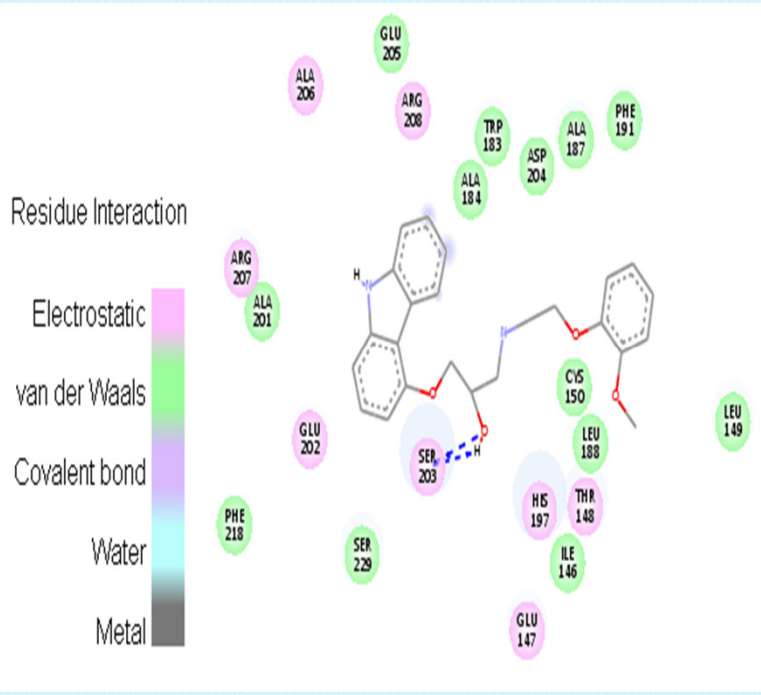


Drug – Coreg – 3 hydrogen bonds

S49G and R389G – Combined



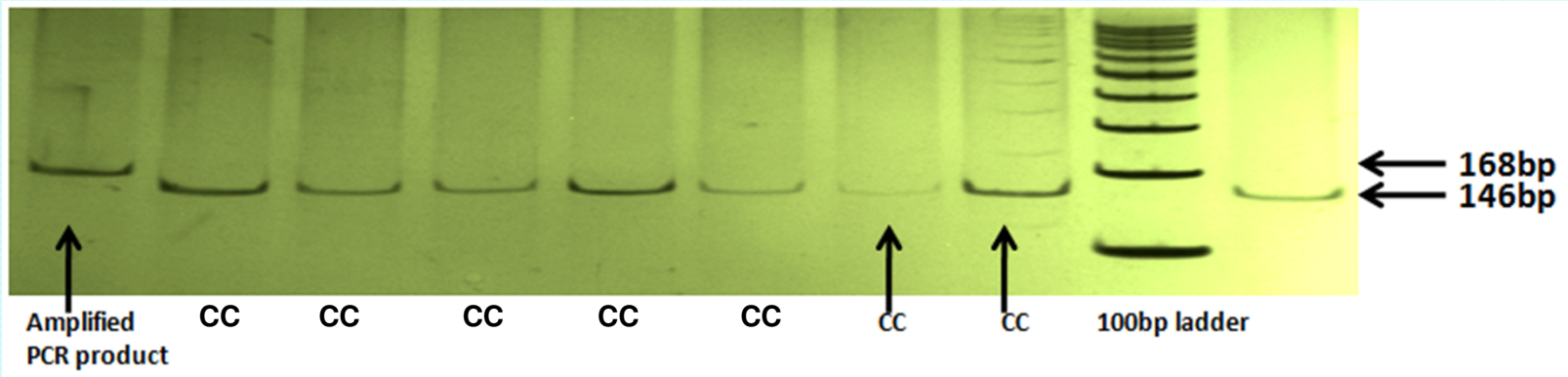




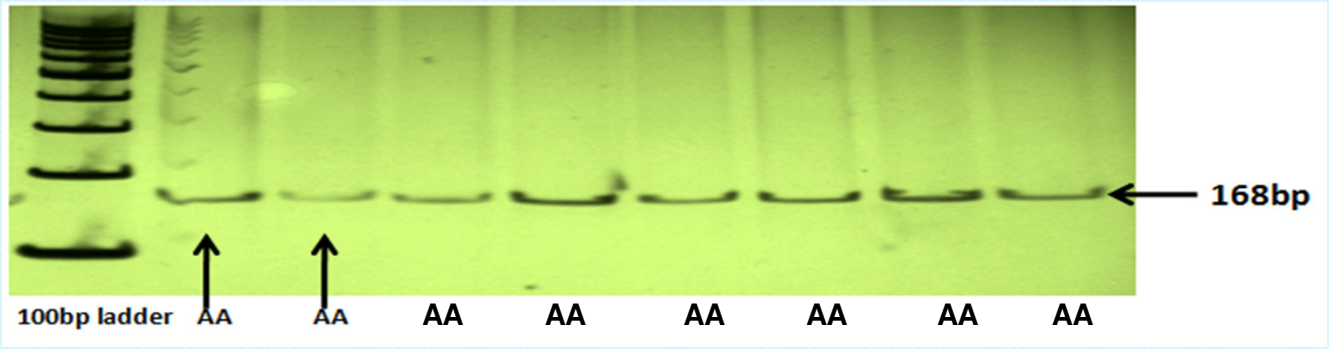
Drug – Coreg – 2 hydrogen bonds

BETA-ADRENOCEPTOR-2

Genotypes of *ADRB2* Arg16Gly (*NcoI*)



Genotypes of *ADRB2 Gln27Glu* (*BbvI*)

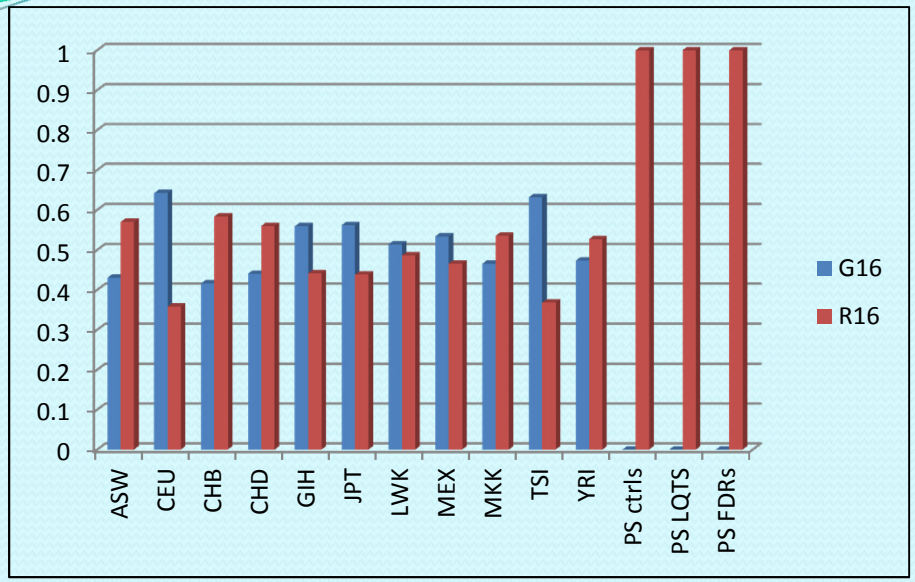


Genotypic frequency distribution

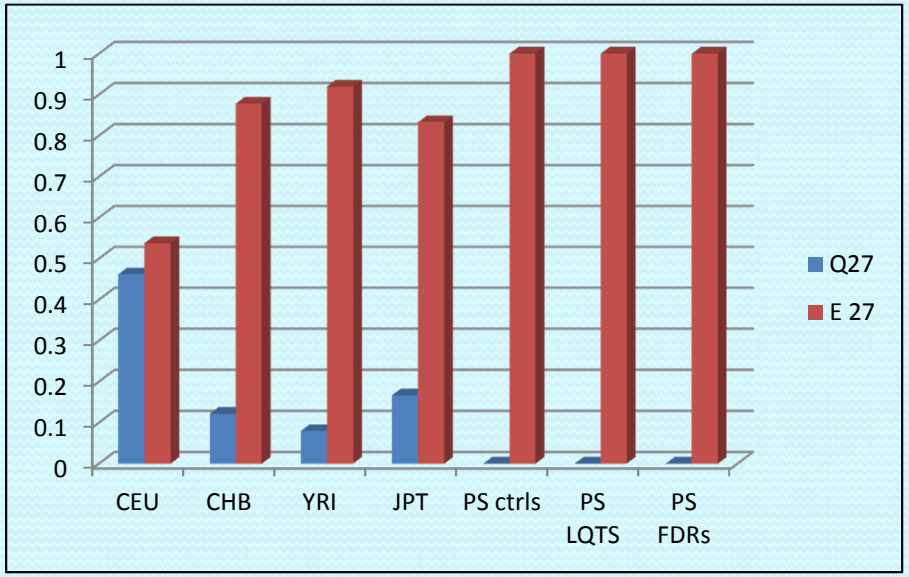
Gene	SNP	Genotype	Controls n (%)	LQTS patients n (%)	FDR n (%)
ADRB2	G16R	RR (CC)	150 (100)	46 (100)	69(100)
	Q27E	EE (AA)	150 (100)	46 (100)	69(100)

Genotypes identified: RR of G16R and EE of Q27E

Hapmap of Arg16Gly



Hapmap of Gln27Glu



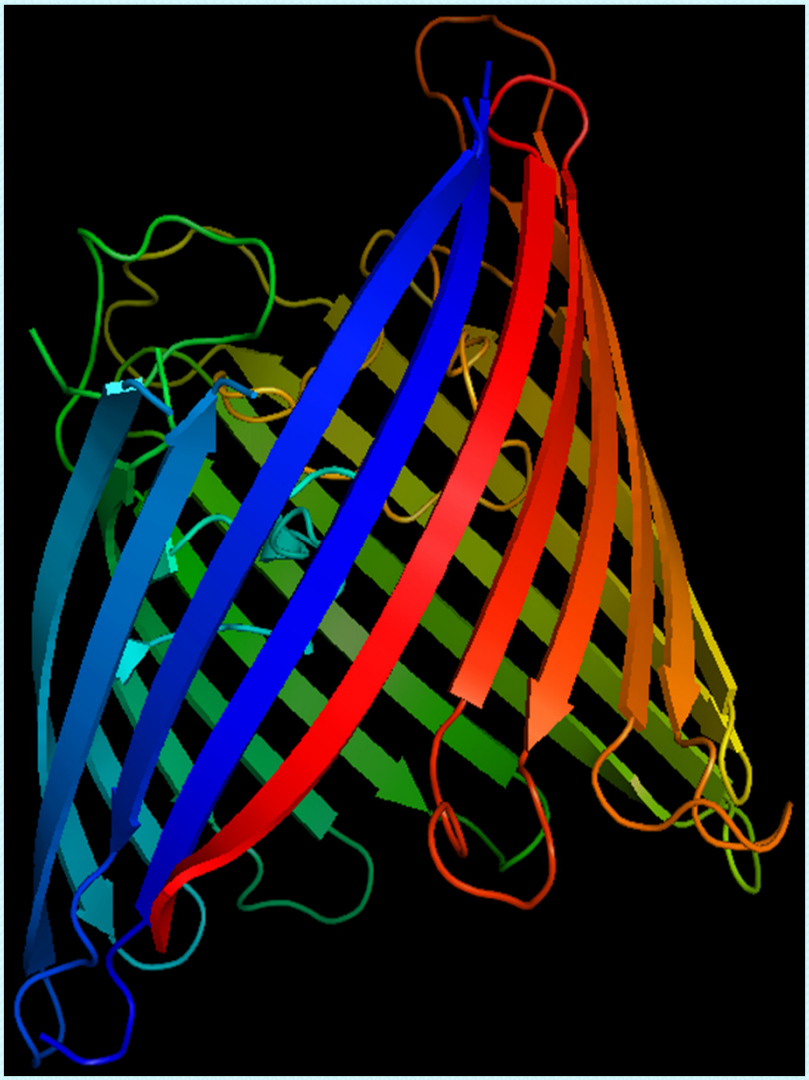
Hapmap: Highlights the genetic diversity – restricted to South Indian population

Insilico Analysis:

- G16R - Loss of a beta sheet and two alpha-helices.
- Q27E - alters the protein secondary structure : addition of two alpha helices and a beta sheet by the disruption of an alpha helix of ADRB2.
- Alterations in protein folding and signalling downstream.

Homology modelling

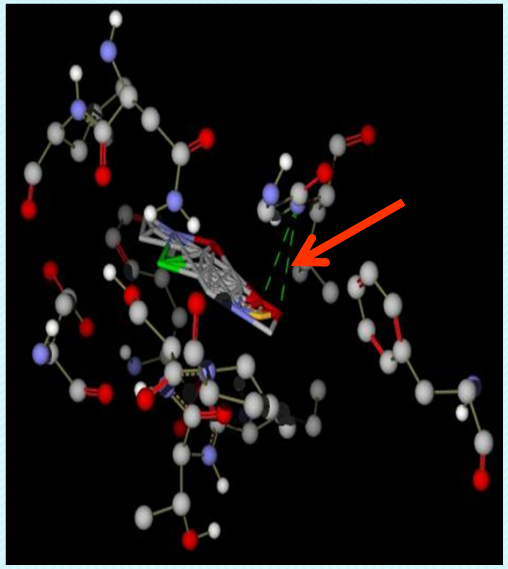
3TOS – Template Molecule

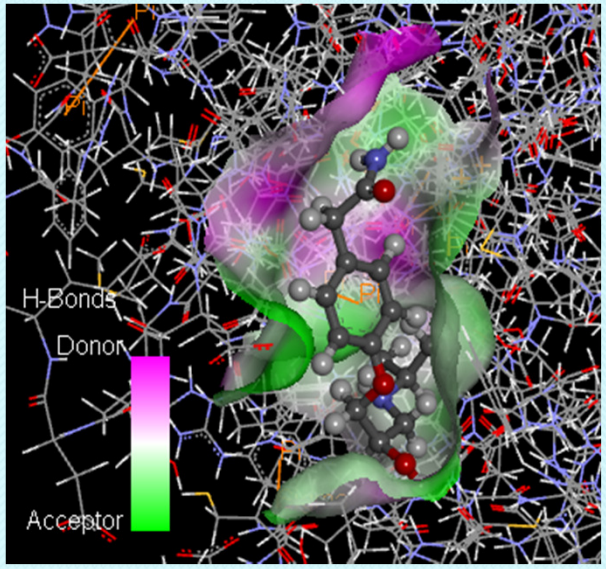


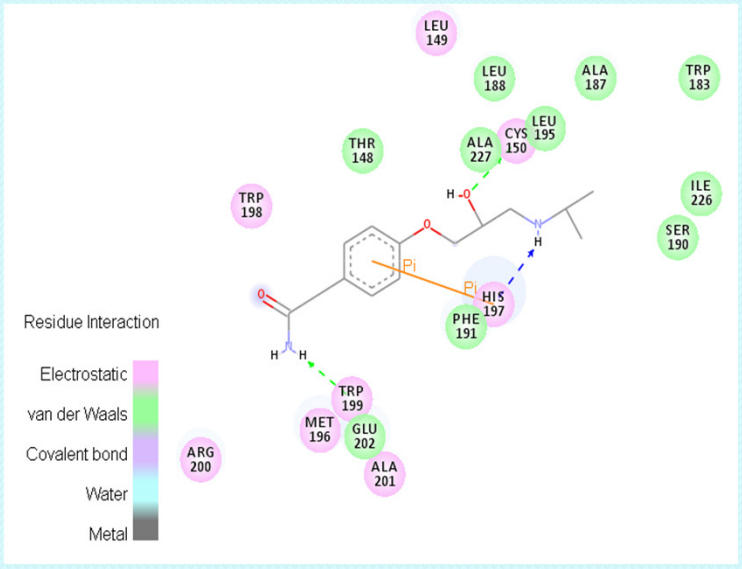
ADRB2 – Modelled molecule



Docking analyses
Wild Type protein, G16R and Q27E

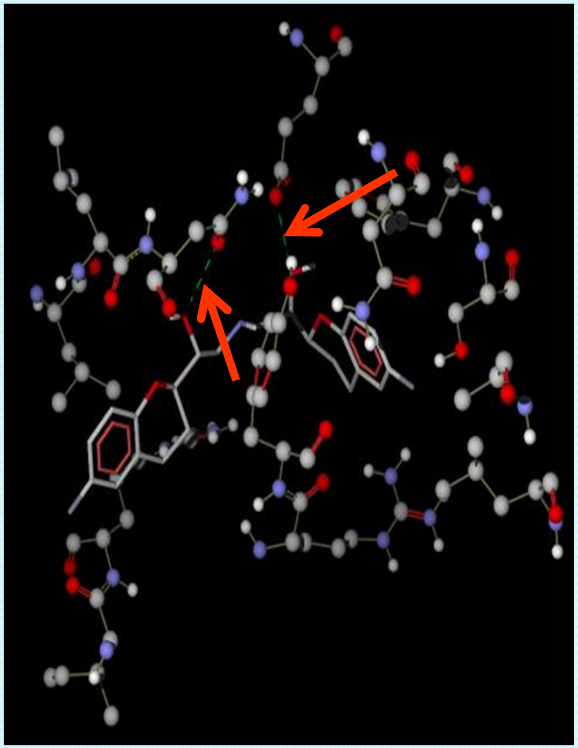


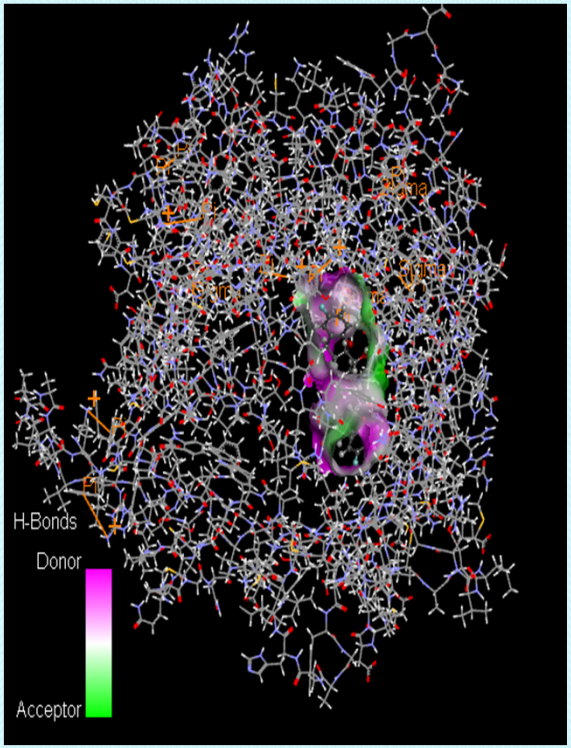


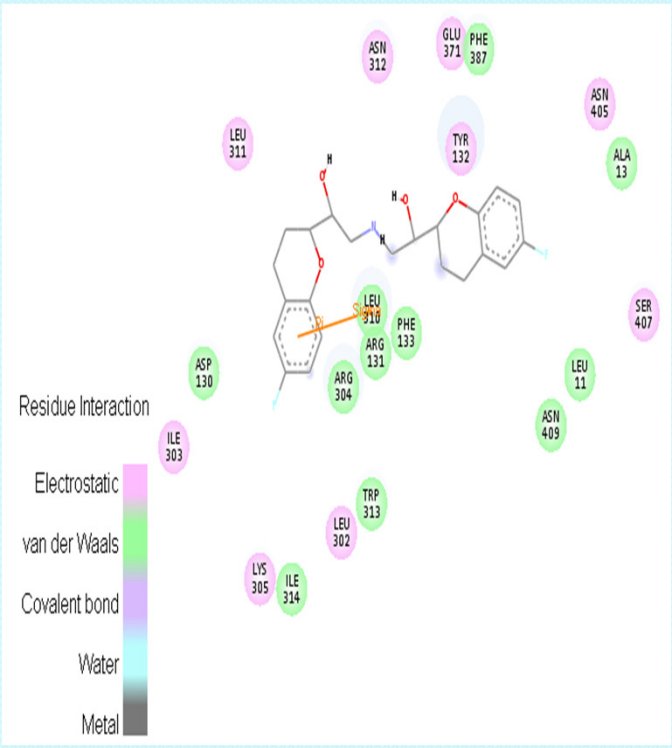


All three molecules showed interaction with the same drug molecule (Betapace) individually with 2 hydrogen bonds.

G16R and Q27E – combined







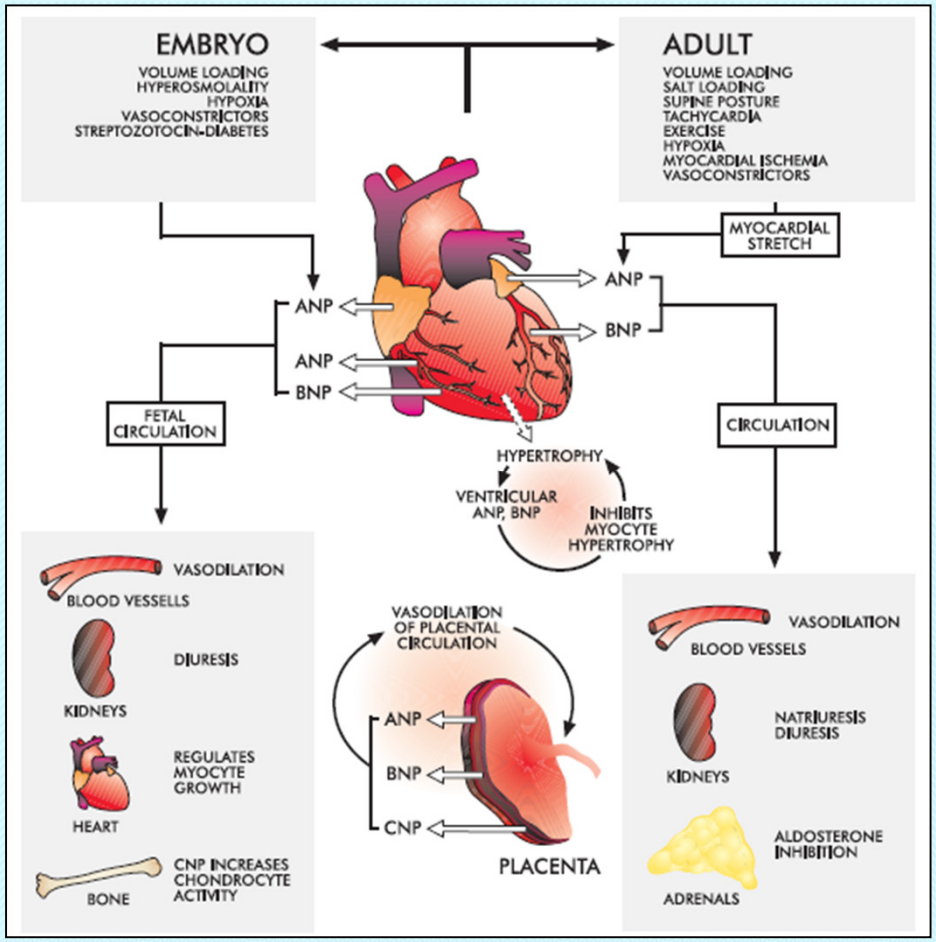
Drug – Nebivolol – 2 hydrogen bonds

Pharmacogenetic Implication:

- The S49G polymorphism localized to extracellular amino-terminal region of the receptor.
- S49 β_1-AR and R389 β_1-AR : good responders to agonist-evoked stimulation.
- G49 variant is associated with cardiomyopathy and heart failure.
- R389G is localized to the interface between transmembrane helix VII and the intracellular tail of the receptor
- A highly conserved region, critical to G-protein coupling and subsequent cell signalling.
- R16/E27 resistant to agonist-induced downregulation.
- Blockade of this receptor prevents myocardial infarction, prolongs life - SNPs.

Atrial Natriuretic Peptide (ANP)

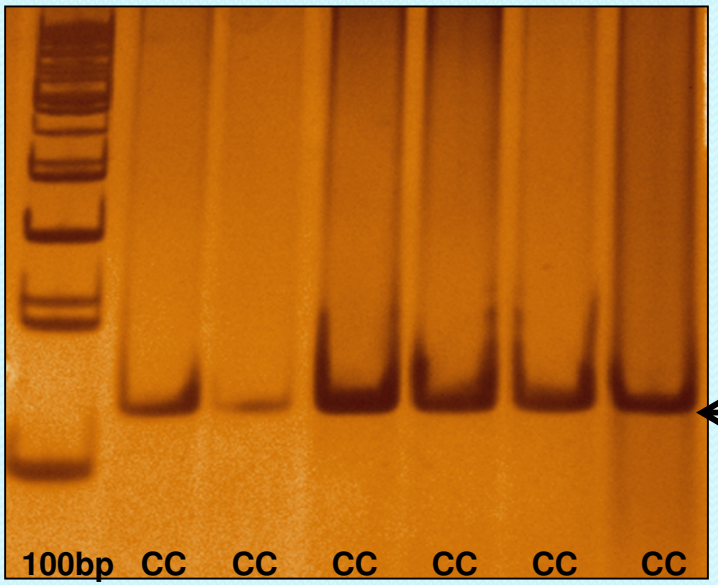
- Cardiac hormones secreted by endocrine heart
- Atrial natriuretic – 28 amino acid peptide
- Natriuretic, vasorelaxant, antihypertrophic, and antifibrotic
- Natriuretic peptide precursor A (*NPPA*) gene expression : transcriptional program in cardiogenesis
- ***NPPA* gene –** localized to 1p36.2 – 3 exons encodes the precursor of ANP
- NNPA – role in cardiogenesis



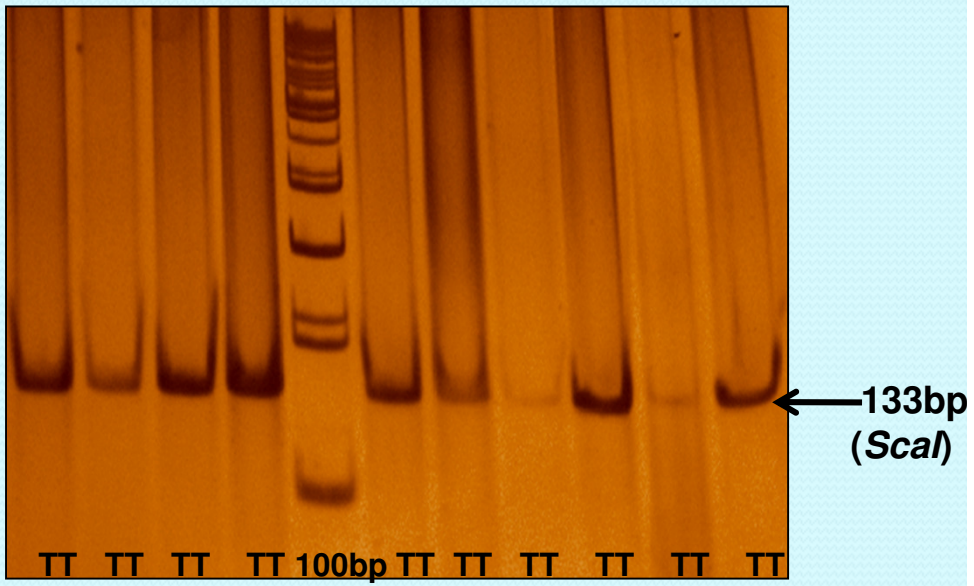
Three SNPs of *NPPA* analyzed-

- **promoter SNP: C-664G**
- **an intronic SNP: C1364A**
- **an exonic SNP: T1766C**

Genotypes of *NPPA* -664 C>G



Genotypes of *NPPA* 1766T>C

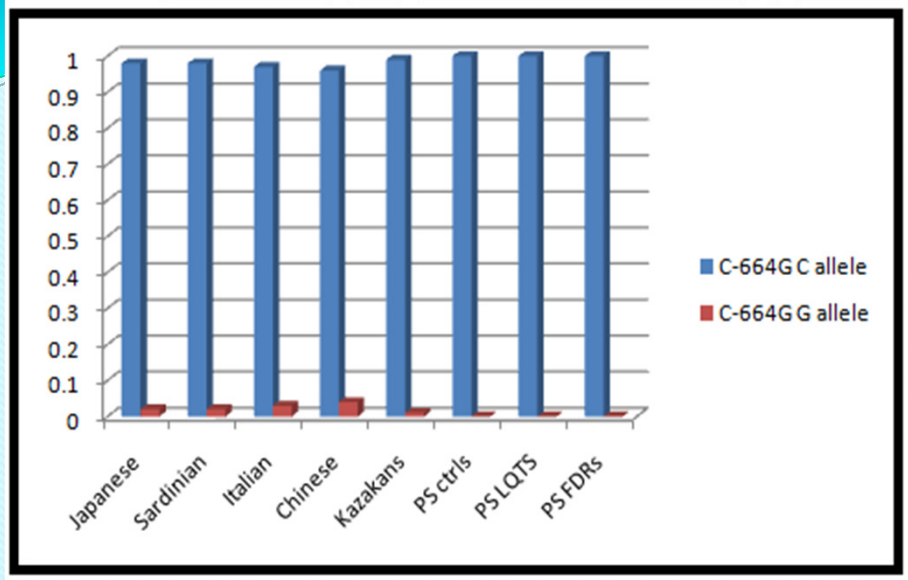


Genotypic and allelic frequency distribution of -664 C>G and 1766 T>Cpolymorphisms of *NPPA*

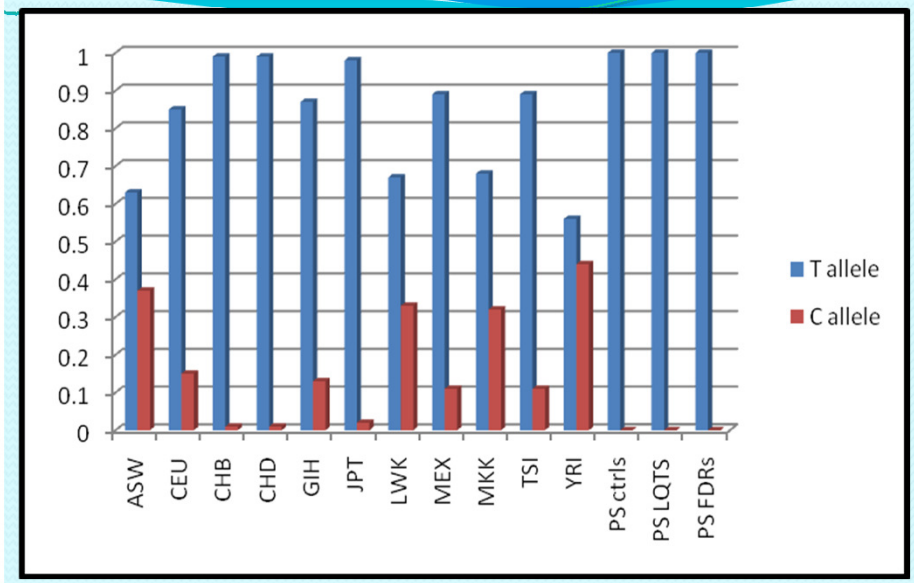
SNP	Genotype	Controls n (%)	LQTS n (%)	FDRs n(%)
C-664G	CC	150(100)	46(100)	69(100)
T1766C	TT	150(100)	46(100)	69(100)

C664G and T1766C genotype - monomorphic

NPPA -664C>G



NPPA 1766T>C



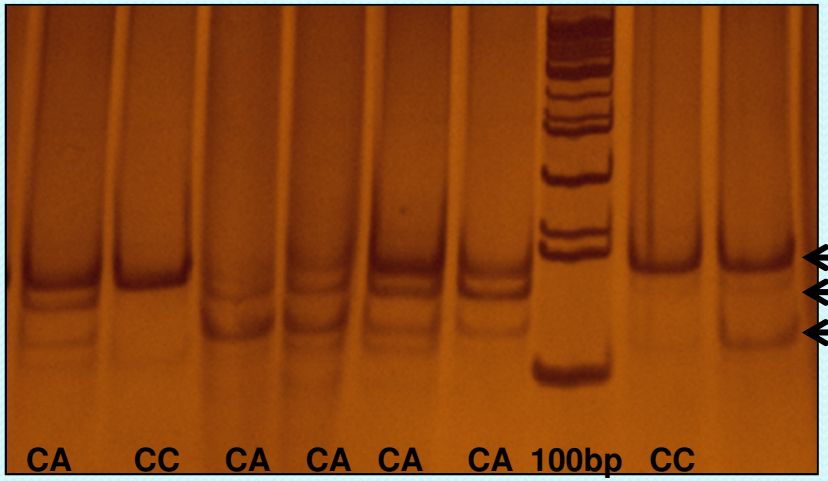
C-664G:

- Interestingly, only 'CC' genotype was identified.
- The *NPPA* -664 C>G promoter SNP : **creation of a new binding site for transcription regulators ADR1** [alcohol dehydrogenase (ADH) II synthesis regulator] : transcription and translation dysregulation.

T1766C:

- 'TT' genotype was identified : substitution of a stop codon by an arginine residue.
- Protein secondary structure prediction revealed an increase in helix length and coils.
- Protein folding alteration.

Genotypes of *NPPA* 1364 C>A

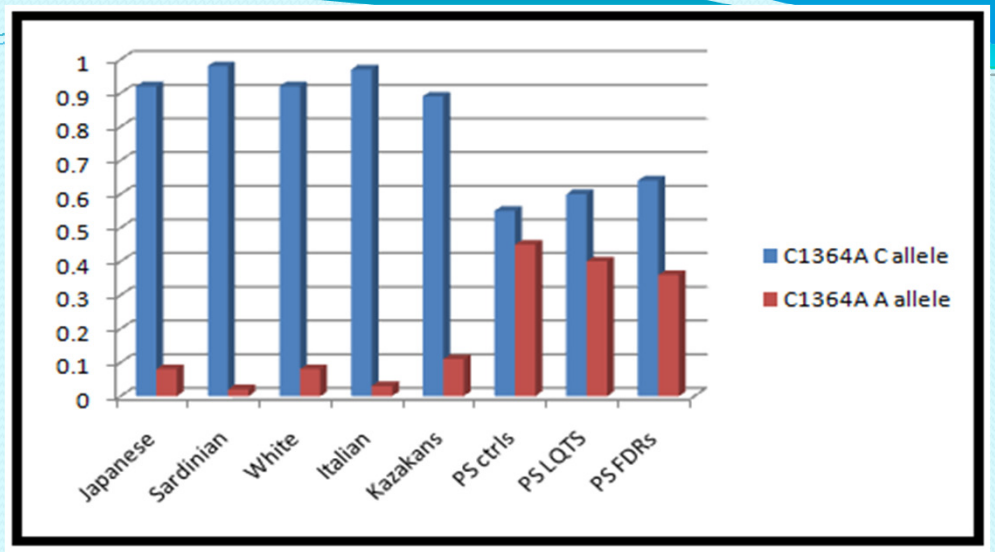


Genotypic and allelic frequency distribution of *NPPA* 1364 C>A

SNP	Genotype	Controls n (%)	LQTS n (%)	FDRs n(%)	Allele	Controls	LQTS	FDRs
C1364A	**CC**	**15 (10)**	**9 (20)**	**19(28)**	**C**	**0.55**	**0.6**	**0.64**
	CA	135 (90)	37 (80)	50(72)	A	0.45	0.4	0.36

'**CC**' genotype and '**C**' allele confer risk to LQTs

NPPA 1364C>A



Odds risk estimates for the C1364A polymorphisms

	Genotype	OR (95% CI)	p value
LQTS Vs Ctrls	CC	1.00	0.08
	CA	0.44 (0.18-1.10)	
	C Vs A	0.81 (0.21-3.06)	0.76
FDRs Vs Ctrls	CC	1.00	**0.0013**
	CA	**0.29 (0.14-0.62)**	
	C Vs A	0.68 (0.38-1.21)	0.19
LQTS Vs FDRs	CC	1.00	0.36
	CA	1.52 (0.62-3.74)	
	C Vs A	0.84 (0.47-1.49)	0.56

'CA' – risk genotype ; 'C' - risk allele - etiopathogenetic marker of LQTS

Insilico analysis:

- Intronic SNP 1364 C>A : increases free energy from **-110 Kcal/mol to -108 Kcal/mol** : a decrease in thermodynamic stability of mRNA secondary structure : cause variations in downstream signaling / splicing.
- The binding sites for exonic splicing silencers – **hnRNPA1, hnRNPA2B1, hnRNPF, hnRNPH1** and exonic splicing enhancers **- 9G8 and Tra2beta** were shifted.
- All of these modifications may influence downstream signalling influencing the ANP peptide synthesis.

- **It can be inferred that the 'C' allele encoded product may be playing a role in cardiogenesis regulation.**

- **Interestingly high parental consanguinity (67%) - recessive 'CC' - leads to SCDs in 44% of LQTS families.**

Haplotype frequencies of the 3 polymorphisms in controls and LQTS groups

	Haplotype	Haplotype frequency		Odds Ratio (95% CI)	p
		Controls	LQTS		
LQTS Vs Ctrls	CCT	0.55	**0.6**	1.00	-
	ACT	0.45	0.4	0.45 (0.18-1.11)	0.083
		Controls	**FDRs**		
FDRs Vs Ctrls	CCT	0.55	**0.64**	1.00	
	ACT	0.45	0.36	**0.29 (0.14-0.61)**	**0.0014**
		FDRs	**LQTS**		
LQTS Vs FDRs	CCT	0.64	0.6	1.00	
	ACT	0.36	0.4	1.48 (0.6-3.65)	0.4

- The **CCT** haplotype frequency was higher in LQTs **(0.6)** and FDRs **(0.64)** compared to controls **(0.55) -** susceptible haplotype/alleles
- **ACT** haplotype : protective **(p-0.0014)**.

Genotype-Phenotype correlations

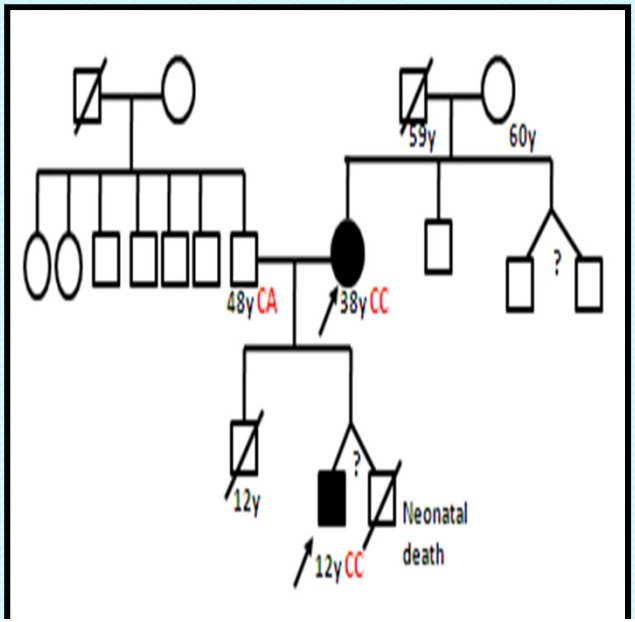
cLQTS (%)	Females n (%)	Deafness n (%)	F/h Sudden death n (%)	Consanguinity n (%)	Syncope n (%)
7 (77.7)	**7 (77.7)**	1 (11.1)	4 (44.4)	**6 (66.6)**	5 (55.5)

Clinical characteristics of 9 LQTS patients exhibiting CC genotype of *NPPA* 1364C>A polymorphism

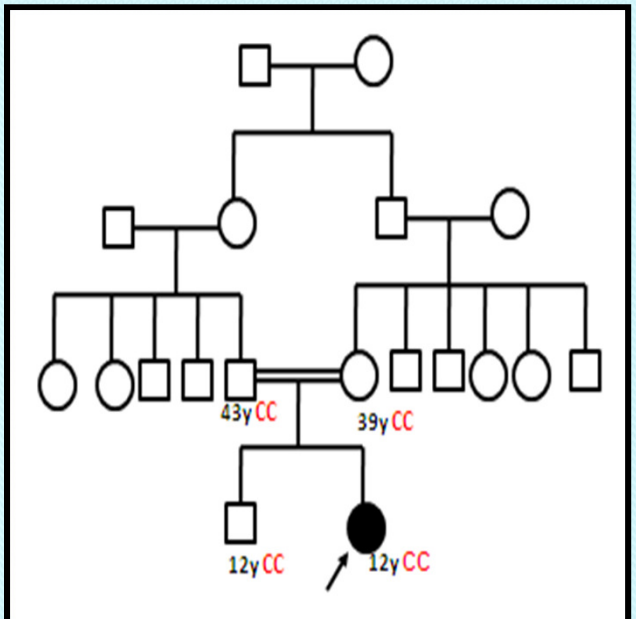
Comparison of characteristics in three LQTS families expressing 'CC' genotype of *NPPA* 1364 C>A SNP

	Family 1	Family 2	Family 3
CC genotype subjects	• Proband • Mother (also cLQTS patient)	• Proband (cLQTS) • Father • Mother • Sibling	• Proband • Mother • Sibling • Maternal uncle (mother's sibling)
Deafness	+	-	+
Consanguinity	-	+	-
Syncope in proband	+	+	+

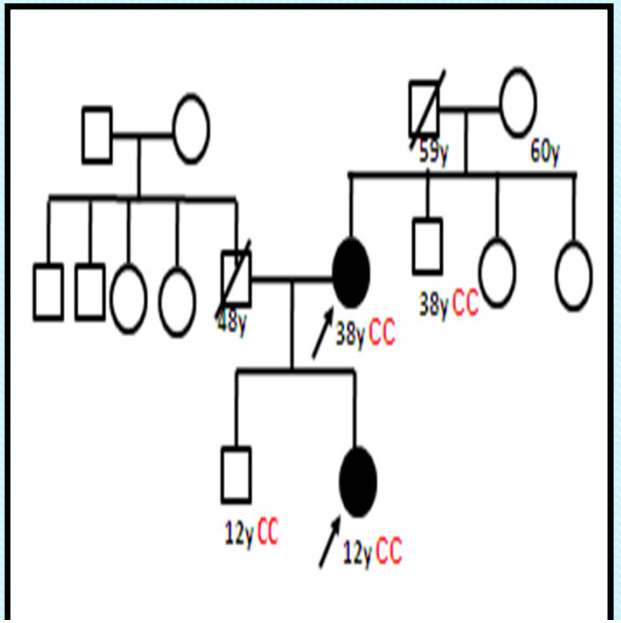
Family 1



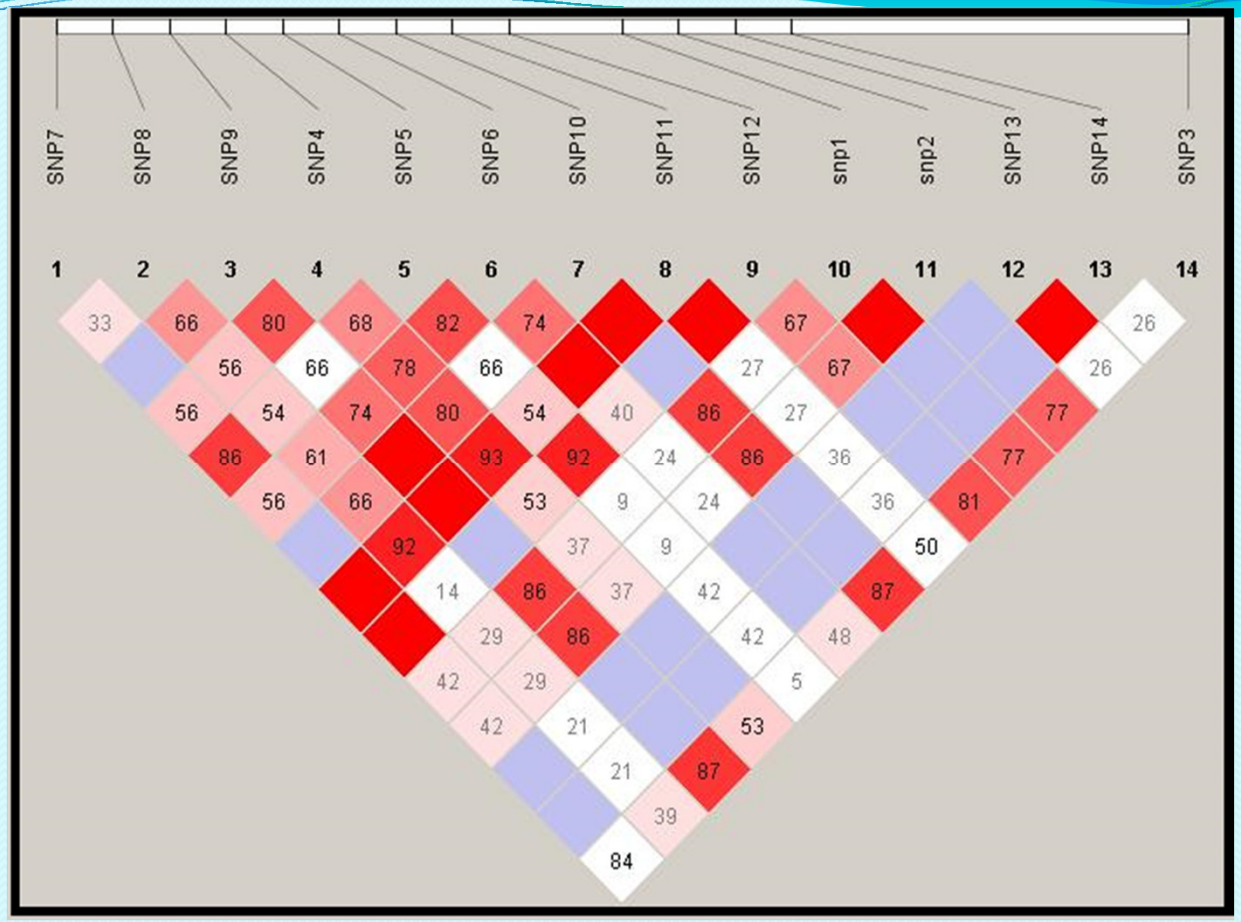
Family 2



Family 3



Gene- Gene interaction – LD Plot

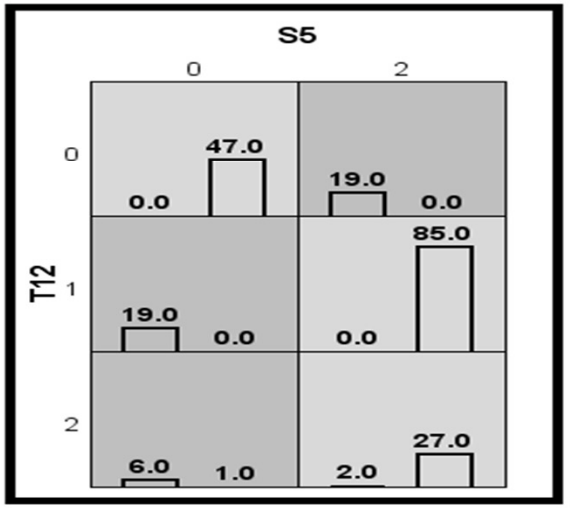


Strong LD was observed between

- ***NPPA and SCN5A and KCNE1,***
- ***TNF-α* and *NPPA* polymorphisms**

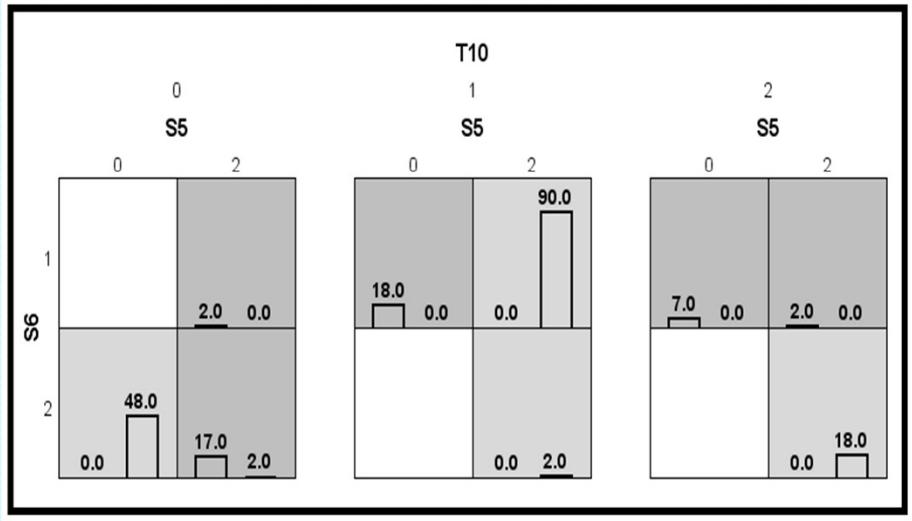
- **NPPA a developmental gene may influence IKs and INa currents & QTc interval during cardiogenesis.**

Gene- Gene interaction - MDR Analysis



Two loci model

S5 (SCN5A H558R) & T12 (TNF-α -238G>A)

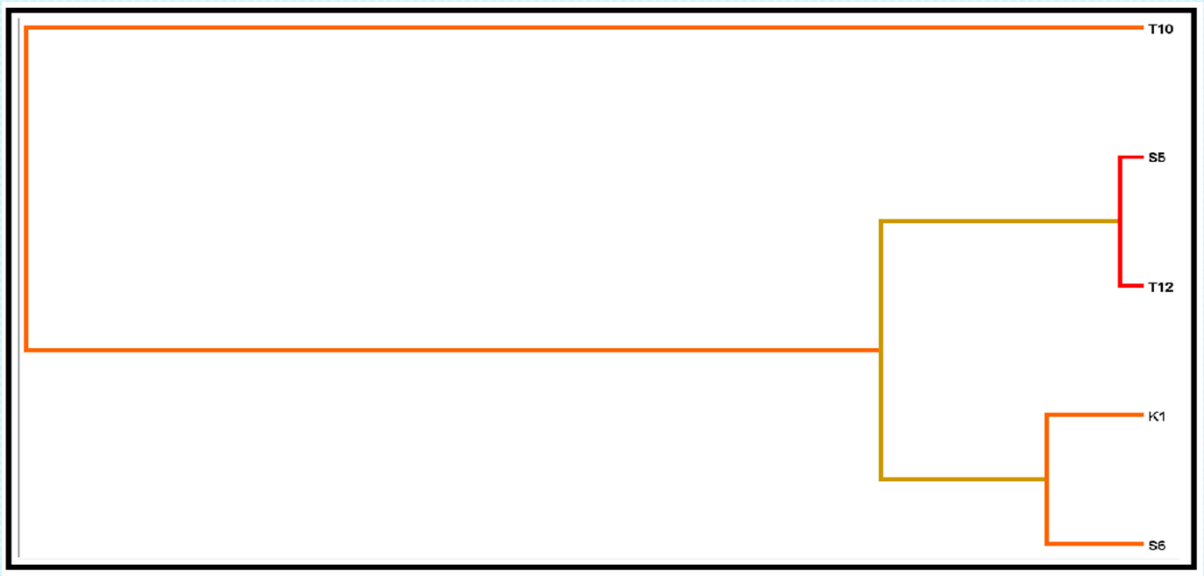


Three loci model interaction

(SCN5A H558R, SCN5A E1031E & TNF-α -308G>A)

- **High risk group:** SCN5A H558R : SCN5A E1031E
- **Low risk group:** SCN5A H558R : SCN5A E1031E : TNF-α -308G>A
- Variant genotypes – high risk to LQTS
- Heterozygous genotypes confer protection
- Strengthening the recessive pattern in LQTS.

Dendrogram

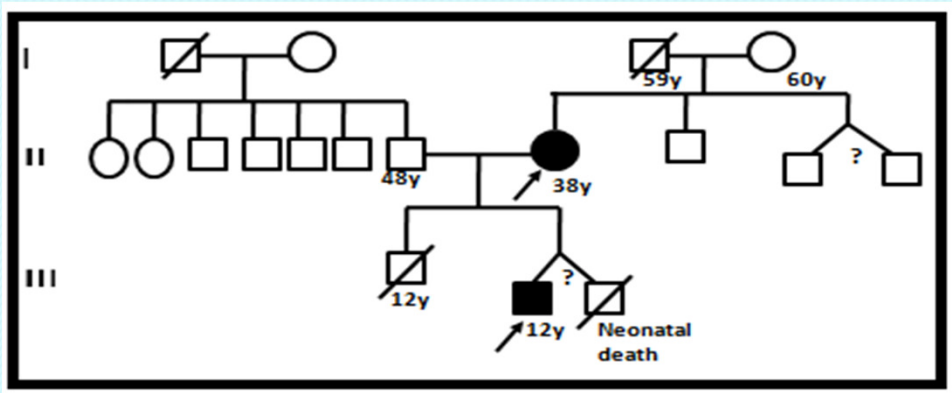


Dendrogram:

- Demonstrates the nature of the interactions between SNPs in a range of colours.
- Data suggests gene-gene interactions with respect to
- **KCNQ1 S546S, SCN5A H558R,**
- **TNF-α -308G>A and TNF-α -238G>A polymorphisms**
- **KCNQ1 S546S, SCN5A H558R and TNF-α -238G>A** belong to one phylogeny / cluster.

Family 5

- A 12 year old deaf boy presented with a history of syncope and prolonged QTc.
- F/H: Sudden neonatal death - twin brother and SCD of another sibling (12 yrs).
- The proband was diagnosed with cLQTS (JLNS)
- Compound heterozygosity identified.

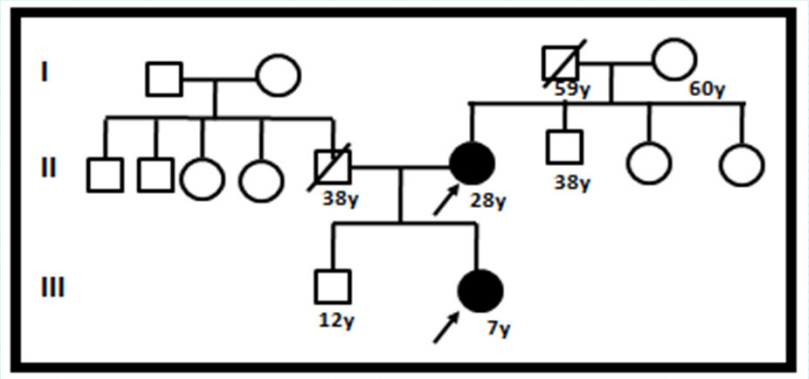


NPPA C1364A	*SCN5A* H558R	*SCN5A* 98297G>A	Identified
C	G	G	Proband (12y), Mother (38y)

- **Risk haplotype: CGG**
- **Genetic anticipation**
- **QTc >500 msec**
- **Sudden cardiac deaths in siblings**

Family 6

- Proband: 7 year old female and her 28 year old cLQTS mother.
- No family history of sudden deaths.

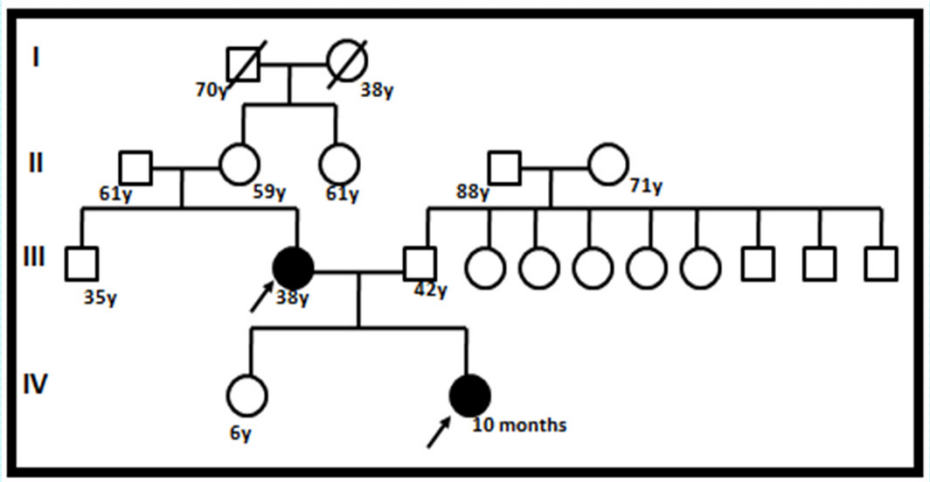


KCNQ1 S546S	*KCNQ1* IVS13+36A>G	*NPPA* C1364A	*SCN5A* 98297G>A	**Identified in**
A	A	C	G	Proband, Mother (cLQTS), sibling and maternal uncle

- Risk alleles - AACG in all affected members.
- Genetic compounds lead to impairment of potassium and sodium ion channels in LQTs.
- The developmental gene NPPA leads to malfunction during cardiogenesis causing cLQTs.
- Genetic anticipation and age related penetrance.

Family 7

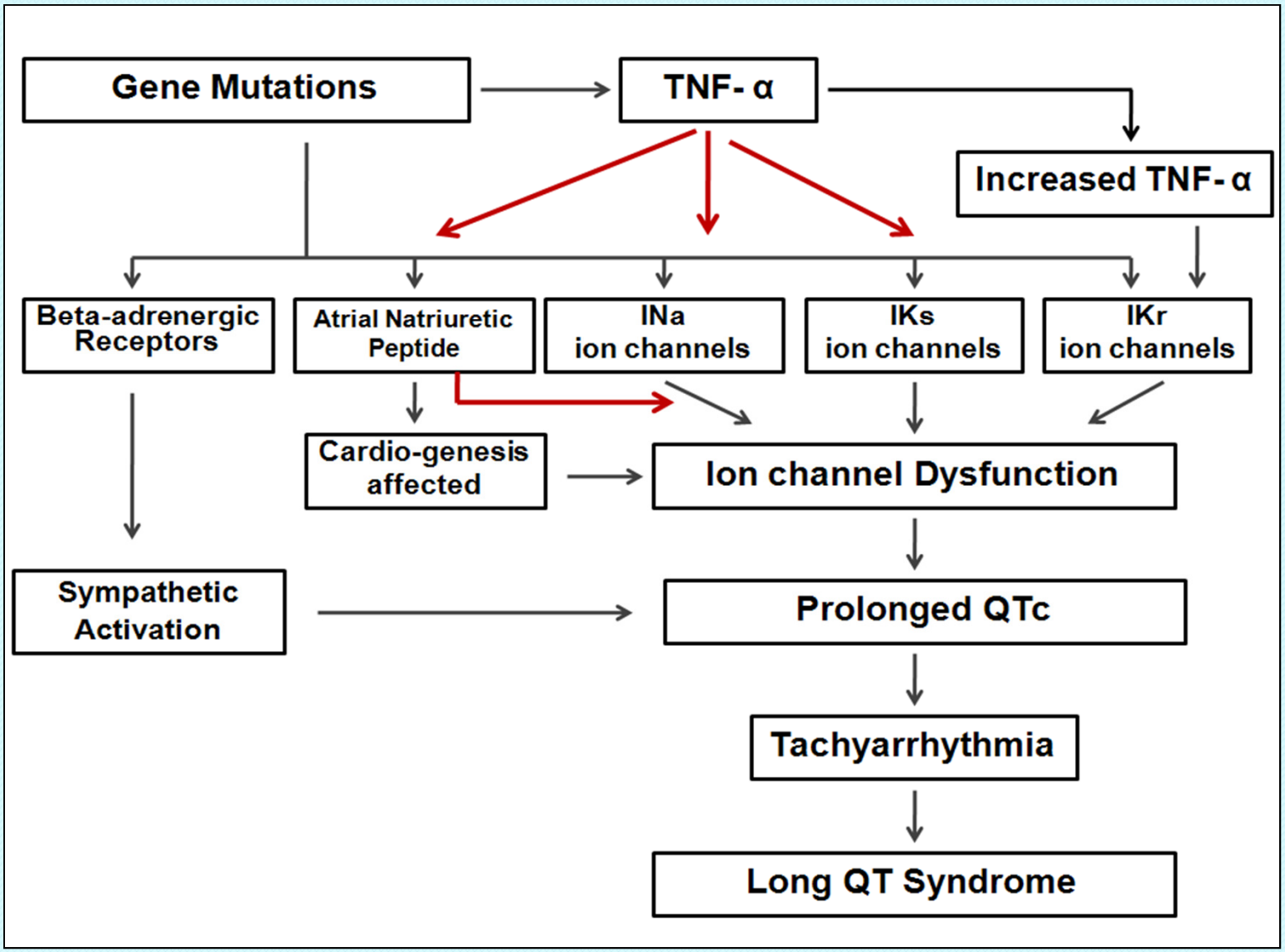
- Unique case of a 10 month female proband and her 38 year old mother
- Diagnosed with cLQTS/JLNS.



KCNQ1 S546S	KCNQ1 IVS13 +36A>G	SCN5A H558R	SCN5A E1061E	SCN5A S1074R	SCN5A 98297G>A	NPPA C1364A	Identified in
A	A	G	G	C	G	C	Proband
A	A	G	G	C	G	heterozygous	Mother

- Risk haplotype/alleles: AAGGCGC
- Genetic anticipation and age related penetrance.

Possible events involved in LQTS



Conclusion:

- The role of *TNF-α* influencing Na+ and K+ currents is elucidated.
- *TNF-α* exhibits pleiotropy with *NPPA* gene - involved in cardiogenesis/ aberrant/ defective ion channel.
- Strong association between *NPPA, SCN5A, KCNQ1* and *KCNE1* polymorphisms corroborated by family studies.
- Harbour the same haplotype carrying the risk alleles for these genes / genetic compounds.
- Emphasizes the interaction between the mentioned genes in the etiopathogenesis of LQTS.
- These interactions open new avenues in identifying the genetic interactions and genes implicated in LQTS.
- Elucidation of novel pathway and drug targets.

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THANK YOU

Thanks' for your kind attention!!!!!!



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