IECGE 2024 Conference

The 2nd International Electronic Conference on Genes

11–13 December 2024 | Online

MDPI

Session: Human Genomics & Genetic Diseases

ACE I/D Polymorphism as a Potential Risk Factor for Congenital Heart Disease among North Indians: Insights from a Tertiary Cardiac Centre Study

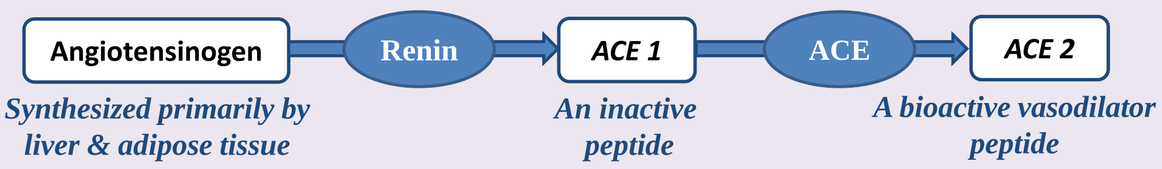
Shadab Ahamad[1], Prachi Kukshal[1], Ajay Kumar[1], Subramanian Chellappan[2], Yogesh Sathe[2], Prabhatha Rashmi Murthy[3]

[1]Sri Sathya Sai Sanjeevani Research Foundation, Palwal, Haryana, India
[2]Sri Sathya Sai Sanjeevani International Centre for Child Heart Care & Research, Palwal, Haryana, India
[3]Sri Sathya Sai Sanjeevani Centre for Child Heart Care & Training in Pediatric Cardiac Skills, Navi Mumbai, Maharashtra, India

INTRODUCTION

- ✓ **Congenital heart diseases (CHDs) account for *~28% of all birth defects*, affecting *1 in 100 live-births* & resulting ~*0.3 M cases annually in India.*[1]**
- ✓ ***Renin-angiotensin-aldosterone system (RAAS) is crucial in the pathogenesis of cardiovascular disorders & hypertension*, with angiotensin-converting enzyme insertion/deletion (ACE I/D) polymorphism being a key genetic factor.[2]**

Figure 1: The Renin-Angiotensin System



- ✓ **ACE I/D, located at *16th intron on chr17q23 of ACE 1*, induces *alternative splicing of 287 bp Alu elements*.**
- ✓ **So far, only three studies from China, Saudi Arabia, & Egypt have investigated the link between ACE I/D & CHD, but none found a conclusive relationship.[3]**

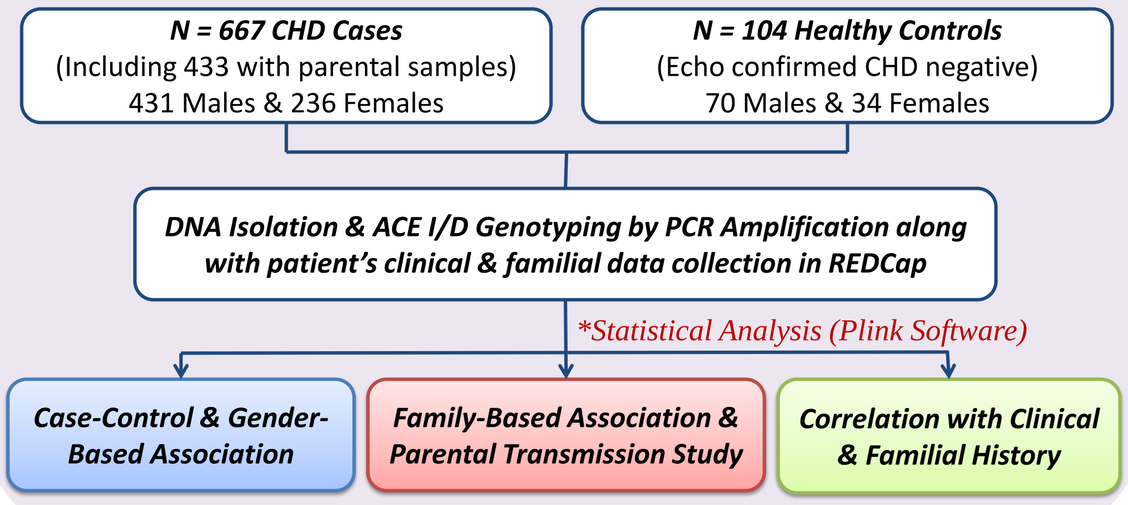
OBJECTIVE

To elucidate the genetic influence of ACE I/D polymorphism on CHD

METHODOLOGY

- ✓ **Study Design: *Case-Control and Family Based Association Study***
- ✓ **Study Participants: Patients who underwent cardiac treatment at *Sri Sathya Sai Sanjeevani Hospital- a Totally free of cost tertiary cardiac care centre***
- ✓ **IEC Approved with Written Informed Consent**
- ✓ **Exclusion: Patients showing *extra-cardiac anomalies, syndromic features, or any other neurodevelopmental and chronic disorders***

Figure 2: Study design



** Statistical Tests: $\chi 2$ test, parenTDT and Parent-of-origin (POO) test*

Table 4: Association of ACE I/D with Clinical, Familial & Environmental Factors

Factors (% Proportion)	*P* value compared within cases; OR (95 % CIs)			
	Genotypic	Allelic	Dominant	Recessive
CHD + PAH *(12.4 %)*	**0.050**	0.810	0.260	0.100*
Anemia in Patient *(43.7 %)*	0.130*	0.120*	**0.05**; 1.71 (1.04-2.79)	0.670
Early Diagnosis *(67.9 %)*	0.280	0.240	0.720	0.120*
Fast Heart Beat *(54.4 %)*	0.070*	0.600	0.098*	0.360
Pneumonia *(31.4 %)*	0.270	0.310	0.130*	0.980
Primi-Gravida *(29.5 %)*	0.083*	0.280	**0.05**; 0.71 (0.49-0.98)	0.760
Anemic Pregnancy *(24.5 %)*	0.170	0.097*	0.060*	0.450
Paternal Tobacco *(3.2 %)*	0.090*	0.091*	0.550	**0.03**; 2.59 (1.07-6.27)
Near Cell Tower *(31.9 %)*	0.280	0.104*	0.240	0.152

REFERENCES

[1] Saxena A. *Indian Pediatr.* **2018**; 55(12):1075-1082.
[2] Niu T, *et al. Drugs.* **2002**; 62(7):977-993.
[3] Ahamad S, *et al. Int. J. Sci. Rep.* **2024**; 10 (12): 422-431.
[4] Otte WM, *et al. PLoS Biol.* **2022**; 20 (2):e3001562.

Scan to access full study

RESULTS & DISCUSSION

Figure 3: Genotyping of ACE I/D Polymorphism

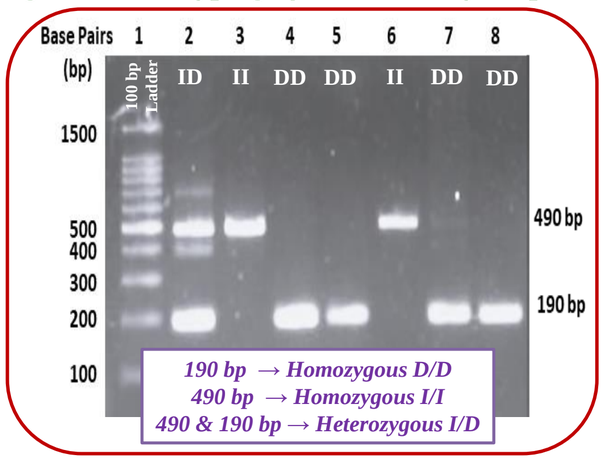


Table 1: Frequency Distribution

Genotype	Cases			Controls
	All	Male	Female	
DD	0.23	0.22	0.25	0.26
ID	0.47	0.47	0.48	0.36
II	0.30	0.31	0.27	0.38

Polymorphism was in Hardy-Weinberg equilibrium ($p > 0.001$)

Table 2: Case-Control & Gender-Based Association

Categories	*P* value w.r.t. controls in different models; OR (95 % CIs)			
	Genotypic	Allelic	Dominant	Recessive
CHD Cases (n = 667)	0.070*	0.430	0.070*	0.520
Acyanotic CHD (n = 446)	0.120*	0.510	0.120*	0.540
Cyanotic CHD (n = 221)	0.064*	0.370	0.059*	0.570
Acyn Vs Cyn CHD	0.780	0.680	0.520	0.990
CHD-Subphenotypic Association				
ASD *(n = 87)*	0.340	0.270	0.160	0.800
VSD *(n = 292)*	0.150*	0.510	0.140*	0.580
AV Canal *(n = 17)*	0.770	0.550	0.470	0.770
Single Ventricle *(n = 15)*	0.630	0.550	0.380	0.950
TOF *(n = 148)*	**0.024**	0.250	**0.022**; 1.86 (1.1-3.2)	0.590
TGA *(n = 12)*	0.470	0.230	0.360	0.810
TAPVC *(n = 32)*	0.140*	**0.03**; 0.50 (0.4-0.9)	0.075*	0.110*
Misc. CHD *(n = 64)*	**0.018**	0.890	0.110*	0.120*
CHD + Stenosis *(n = 268)*	**0.026**	0.290	**0.028**; 1.81 (1.1-3.1)	0.510
CHD + PAH *(n = 83)*	0.790	0.460	0.620	0.530
Gender-Based Association				
Males	0.120*	0.630	0.150*	0.420
Females	0.057*	0.230	**0.036**; 1.68 (1.0-2.7)	0.79
Males Vs Females	0.530	0.270	0.280	0.490

ASD: Atrial septal defect; AV Canal: Atrio-ventricular canal; CHD: Congenital heart disease; CIs: Confidence intervals; Misc.: Miscellaneous; OR: Odd ratio; PAH: Pulmonary artery hypertension; TAPVC: Total anomalous pulmonary venous connection; TGA: Transposition of great arteries; TOF: Tetralogy of fallot; VSD: Ventricular septal defect

*Significant P values ($p \leq 0.05$) are in **bold** font. * Trend of association ($0.05 < p \leq 0.15$)* [4]

Table 3: Family-Based Association & Parental Transmission Study

Categories	*P* value *(parenTDT)*	*P* value (Parent-of-origin Analysis)		
		Paternal	Maternal	POO
CHD Cases	0.260	0.530	**0.022**	**0.037**
Cyanotic CHD	0.400	0.880	0.300	0.530
Acyanotic CHD	0.420	0.390	**0.039**	**0.039**
ASD	0.096*	0.350	0.160	0.730
VSD	0.690	0.056*	0.170	**0.021**
TOF	1.000	0.860	0.860	0.800
TAPVC	**0.046**	0.160	0.160	1.000
TGA+ SV+ AV Canal+ Misc. CHD	0.330	0.680	0.300	0.580

CONCLUSION

- ✓ **This is the *first study from India and possibly the only study globally that reports a significant association between ACE I/D and CHD.***
- ✓ ***DD genotype increases the risk of CHD in females* and is linked to prognosis of anemia, stenosis & PAH, while *II genotype increases CHD risk in offspring of tobacco consuming father by 2.5-fold.***
- ✓ **Cyanotic cases exhibited a higher prevalence of ACE I/D mutations, with *TOF showing the strongest association* ($p = 0.024$).**
- ✓ **POO showed *maternal transmission of D allele in CHD & paternal transmission in VSD.***