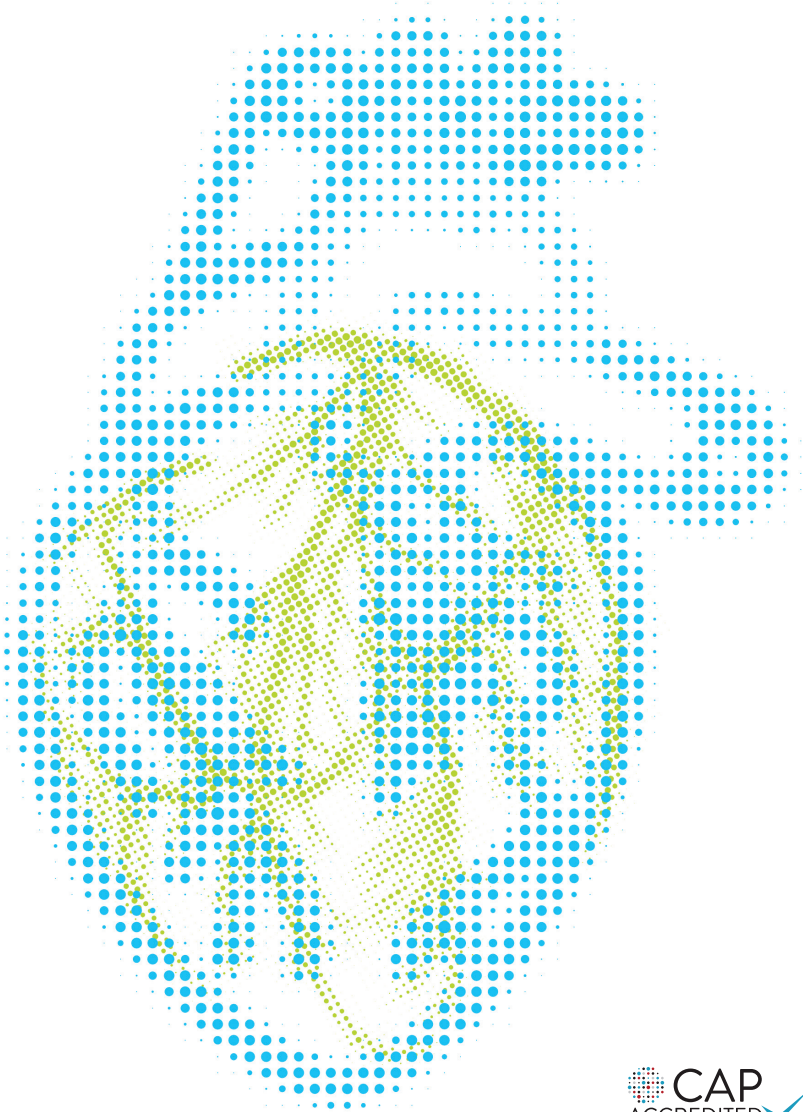


Cardio Genetics



Actia

Inherited Genetics

The understanding of pathology at a molecular level is critical for identification of many diseases and their subtypes. Precision in diagnosis, including the identification of disease subtypes directly influences treatment and patient outcomes.

Actia from MedGenome provides an end-to-end integrated solution to clinical genomics in India and is highly focused on the Indian population. Actia has been delivering actionable genetic insights for inherited genetic conditions enabling happier outcomes.

Cardio genetics

Many heart disorders are passed on through generations that affect people at any age and can be life-threatening. Heart disorders are genetically heterogeneous and have variable clinical presentations. Pathogenic variant(s) in a single gene may be associated with different cardiac conditions (clinical heterogeneity), and in different genes, it may cause a similar cardiac phenotype (genetic heterogeneity). The phenotypes can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner depending on the specific etiology. Cardiomyopathies can also be inherited in a mitochondrial manner. There is a strong genetic component in many of the commonly seen cardiac ailments.

Prevalence

- The estimated prevalence of cardiovascular disease in India is about 10.5% of the population which extrapolates to a burden of about 32 million affected individuals¹
- Risks in the Indian populations is 11% for non-diabetic patients and 21.4% for diabetic patients.^{1,2,3 & 4}
- The incidence of cardiac disorders have increased from 2% to 10.5% of the urban population¹
- Congenital Heart Disease has an estimated prevalence is 2-6 per 1000 live births
- Familial Hypercholesterolemia affects about 1 in 500 people in most countries.

1. Jayashree S., Arindam M. and Vijay K. V. 2015 Genetic epidemiology of coronary artery disease: an Asian Indian perspective. *J. Genet.* 94, 539–549
2. Mohan V, Deepa R, Rani SS, et al. Prevalence of coronary artery disease and its relationship to lipids in a selected population in South India: The Chennai Urban Population Study (CUPS No. 5). *J Am Coll Cardiol* 2001;38:682-7. 10.1016/S0735-1097(01)01415-2
3. Gupta, Rajeev. "Recent trends in coronary heart disease epidemiology in India." *Indian heart journal* 60.2 Suppl B (2008): B4-18.
4. Enas, Enas A., and A. Senthilkumar. "Coronary Artery Disease in Asian Indians: An Update and Review." (2001).

What are the common Cardiac disease that have a genetic component?

Congenital Heart Disease (CHD)

- The most common type of birth defect, representing an important cause of infant morbidity and mortality
- Refers to structural and functional heart defects present during birth, that include septal defects, valve defects, and outflow tract anomalies
- Syndromic CHD can be due aneuploidies, chromosomal deletions or translocations, or single-gene defects

Cardiac Channelopathies

- Cardiac channelopathies develop as a result of mutations in genes encoding ion channel proteins, involved in cardiac conduction, impairing channel function
- Most channelopathies follow an autosomal dominant pattern of inheritance

The major cardiac channelopathies are:

Long QT syndrome (LQTS)

- Most common cardiac channelopathy, estimated to occur in about 1 in 2500 persons and is characterized by prolongation of the QT interval on ECGs.
- It can be asymptomatic or characterised by symptoms like arrhythmias/heart flutters, syncope/fainting and sudden cardiac death.
- There are currently 13 types depending on the presence of the mutation in the various genes.
- Majority of LQTS follow autosomal dominant mode of inheritance.

Short QT syndrome (SQTS)

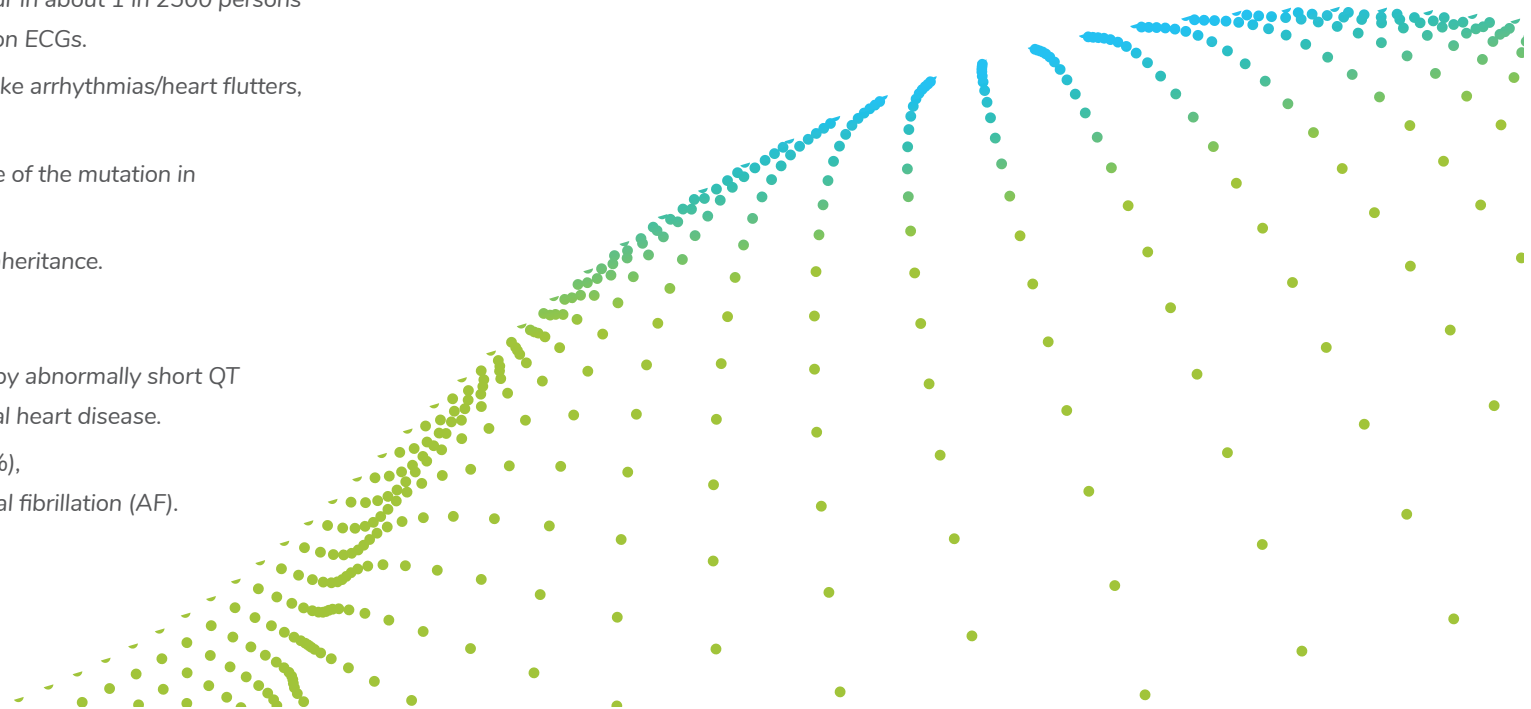
- A rare inheritable cardiac channelopathy characterized by abnormally short QT intervals and atrial fibrillation in the absence of structural heart disease.
- Cardiac arrest is the most frequent symptom (up to 40%), followed by palpitations (30%), syncope (25%) and atrial fibrillation (AF).

Brugada syndrome (BS)

- Characterized by ST segment elevation in leads V1–V3 of an electrocardiogram (ECG).
- Sudden cardiac death could be the first manifestation of the disease.
- Can occur from early infancy to late adulthood
- Affected Individuals develop a monomorphic ventricular tachycardia; often precipitated during sleep or rest, and especially fever.
- Accounts for 4-12% of sudden cardiac deaths.

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

- A pathological condition whereby intense physical exercise or acute emotional stress can trigger abnormal heartbeat - i.e., ventricular tachycardia—that can lead to dizziness, fainting (syncope) and in worst cases, cardiac arrest and sudden death.
- Affected individuals have normal resting ECGs with a structurally and functionally normal heart.
- It has an estimated prevalence of 1:10,000 and commonly manifests at an early age.



Cardiomyopathies

- Defined as disease of the heart muscle, characterized by the muscle becoming enlarged, thick or rigid
- Can lead to heart failure, arrhythmias, and/or sudden death
- Can also be a presenting feature of other genetic disorders, such as Noonan's syndrome, Danon disease, Fabry disease, mitochondrial myopathy, or muscular dystrophy

The different genetic cardiomyopathies are:

Hypertrophic cardiomyopathy (HCM)

- Also known as idiopathic hypertrophic subaortic stenosis (IHSS)
- Characterized by thickening, particularly of the left ventricle, which makes it very difficult for blood to flow through the heart and for the left ventricle to fully relax
- Children with HCM are also at increased risk for arrhythmias

Dilated cardiomyopathy (DCM)

- Also known as congestive cardiomyopathy, DCM is the most common form of cardiomyopathy in children, and ischemic cardiomyopathy is the most common type of dilated cardiomyopathy
- In DCM, the heart becomes enlarged and does not contract or squeezes poorly

Restrictive cardiomyopathy (RCM)

- In RCM, the ventricle is not able to relax properly. As a result, blood flows back into the atria, and they become enlarged, while the ventricles remain normal in size
- This is a rare form of cardiomyopathy that can occur anytime from childhood to adulthood

Arrhythmogenic Right Ventricular Dysplasia (ARVD)

- It is a disorder of the muscular wall of the heart where part of the myocardium breaks down over time, increasing the risk of an abnormal heartbeat (arrhythmia) and sudden death
- It usually appears after 10 years of age.

Left ventricular non-compaction (LVNC)

- The most recently classified form of cardiomyopathy, characterised by abnormal trabeculations in the left ventricle, most frequently at the apex
- Can be associated with left ventricular dilation, systolic or diastolic dysfunction, or both, or various forms of congenital heart disease
- A condition where the muscular wall of the left ventricle appears 'spongy'

Can affect the heart's ability to work efficiently as a pump, and affect the electrical signaling of the heart

Familial Hypercholesterolaemia (FH)

- A genetic condition with an abnormally high level of cholesterol in the blood.
- Deposition of cholesterol in the walls of arteries leads to atherosclerosis resulting in coronary artery disease and heart attack
- FH can be transmitted in both autosomal dominant and recessive inheritance patterns
- Inherited forms of hypercholesterolemia resulting from mutations in the LDLR, APOB, or PCSK9 gene have an autosomal dominant pattern, while mutations in the LDLRAP1 gene cause autosomal recessive form



Why do you need Genetic Testing for Cardiac Diseases?

- Genetic diagnosis can be life-saving as genetic test results can direct and improve patient treatment, management and target surveillance for cardiovascular complications
- They can help determine if an individual carries a disease-causing variant associated with a heritable risk to develop cardiomyopathy, providing valuable information to the patient and their family about future medical management
- Genetic testing can differentiate hereditary cardiomyopathy/channelopathy from other genetic and non-genetic heart conditions

Cardiovascular Pharmacogenomics

- Pharmacogenetics involves applying DNA sequence data to predict drug response, drug discovery and development
- It ensures right drug to the right patient in the right dose
- A significant interpatient variability in drug response has been observed much of which can be attributed to genetics
- A person's genotype can influence drug metabolism, drug transport, and sensitivity to a drug
- Sufficient guidelines are now available describing the use of genetic information to guide treatment with these therapies

When do you need to get tested?

1. Patients with heart defect present since birth
2. Unexplained cardiac arrest or sudden deaths in the family that might have been caused by an undiagnosed heart disease
3. Enlarged heart
4. Heart failure at less than 60 years of age
5. Irregular heartbeat
6. Early heart attack, coronary artery disease or stroke
7. Enlarged aorta or aortic aneurysm in the chest at less than 55 years of age
8. Sudden infant death syndrome (SIDS) in the family
9. Very high cholesterol level

Who needs to get tested?

- Individuals presenting with symptoms of cardiovascular disease
- Individuals with a family history of CAD or Familial Hypercholesterolemia or other Cardiovascular diseases
- Individuals with high lifestyle risk i.e. with hypertension, diabetes, smoking habits, alcohol consumption, stressful lifestyle, etc.
- All individuals above the age of 35 years, with comorbidities like hypertension, diabetes or elevated blood cholesterol



Why Recommend Actia for Patients ?

Actia offers a broad range of pre-designed gene mutation panels which have been developed with in-depth disease understanding of the genetic disorder incorporating the latest research in that particular domain.

New updated technologies, helpful customer service, and clear result interpretation along with counselling sessions with our expert genetic counsellors, make us equipped to provide you the best available support for your patients and families with Cardiovascular Disease.

ACTIA offers:

1. Actia Cardiac Channelopathy Panel: Includes sequence analysis of 50 genes which encode myocardial ion channels that regulate cation in influx/efflux, as well as channel-associated regulatory factors and interaction partners.
2. Actia Cardiomyopathy Panel: Includes sequence analysis of 154 genes associated with cardiomyopathies often encode proteins of the sarcomere.
3. Cardiomyopathy predisposition test: An additional testing option available is the where a 25bp deletion in the MYBPC3 gene is looked into.
4. Hypercholesterolemia gene panel: NGS panel with 23 genes associated with FH.
5. Clopidogrel dosage CYP2C19*2 & CYP2C19*3.
6. Statin-induced myopathy predisposition SLCO1B1 p.(Val174Ala) by RT-PCR.
7. Warfarin dosage-VKORC1 (c.-1639 G>A), CYP2C9*2,CYP2C9*3,CYP2C9*13 by RT-PCR.

What are the test methodology?

1. Next Generation Sequencing (NGS)

Using genomic DNA extracted from blood, the coding regions of all the genes are captured and sequenced simultaneously by NGS technology on an Illumina platform. The sequence data that is generated is aligned and analyzed for sequence variants.

2. Multiplex ligation-dependent probe amplification (MLPA)

Deletion and duplication analysis of genomic DNA is carried out by MLPA. This method allows for the amplification of multiple targets with only a single primer pair.

Test sample requirements

Blood (3-5ml in EDTA tubes)

Extracted DNA samples (1µg high quality DNA)

Required forms

- Relevant clinical information including all the clinical presentations and symptoms
- Test request form

Turn around time (TAT)

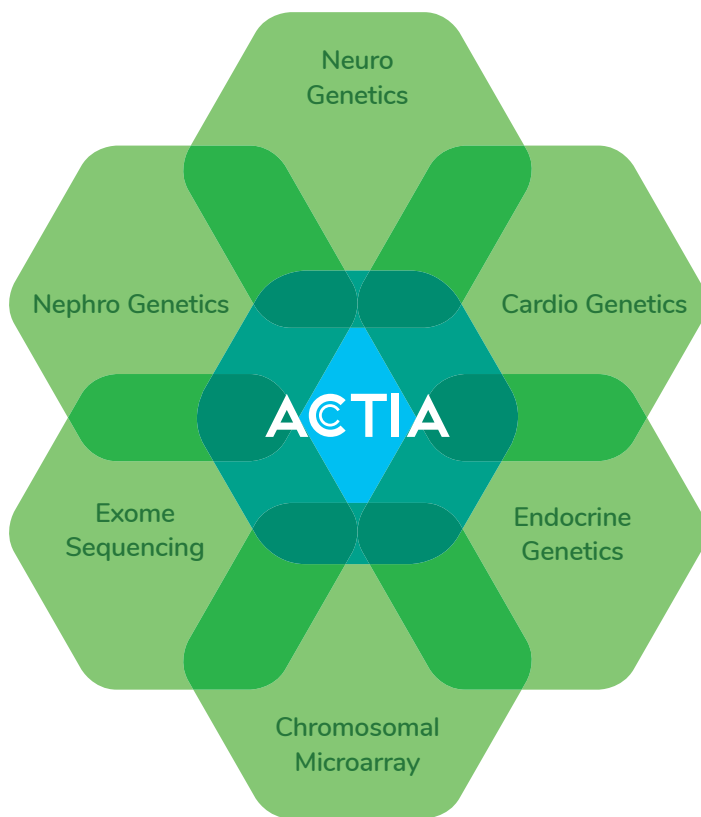
- 28 days for NGS
- 15 days for MLPA

FREE GENETIC COUNSELLING

Actia offers all your patients FREE pre & post-test genetic counselling with our expert and certified genetic counsellors.

Best available support for your patients and families via

- Latest technologies
- Helpful customer service
- Clear result interpretation
- Counselling sessions with our Genetic Counsellors



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