CardioGene

GeneHealth UK

Inherited Cardiac Conditions (ICC)

Inherited Cardiac Conditions, or ICC, are a group of heart conditions that are due to a genetic cause. The most common types of inherited cardiac conditions are the cardiomyopathies and the inherited arrhythmia syndromes.

Cardiomyopathies

Cardiomyopathy is an umbrella term for a disease of the heart muscle. It is most commonly inherited and can affect people of all ages and both males and females. There are many different types of cardiomyopathy; the most common ones are Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), Dilated Cardiomyopathy (DCM) and Hypertrophic Cardiomyopathy (HCM). Left Ventricular Non Compaction (LVNC) is not yet an officially recognised type of cardiomyopathy and Restrictive Cardiomyopathy (RCM) remains a very rare condition.

HCM is the most common type of cardiomyopathy and occurs when the left ventricle of the heart becomes thickened. The thickness and how much of the muscle is affected can vary from person to person. There is often also scarring of the heart muscle. The incidence is between 1 in 200 and 1 in 500.

ARVC is an inherited heart muscle disorder where the heart muscle cells gradually become replaced by scar tissue and fat cells. ARVC generally affects the right side of the heart although the left ventricle can also be affected in ARVC. The incidence is between 1 in 2000- 1 in 5000.

DCM occurs when the pumping chambers of the heart become enlarged (dilated). When this happens, the heart muscle becomes weak and is unable to pump blood around the body efficiently. Approximately 25-50% of DCM cases are thought to be genetic. Incidence of DCM is approximately 1 in 5000. Non-genetic causes of DCM include viral infections, auto-immune disease and previous exposure to toxins or medications.

Inherited arrhythmia syndromes (IAS)
Inherited arrhythmia syndrome is an umbrella term that describes an inherited predisposition to abnormal heart rhythms. Usually there are no structural problems of the heart. The most common types of inherited arrhythmia syndrome are LQT, Brugada syndrome and Catecholaminergic polymorphic ventricular tachycardia (CPVT).

LQT Syndrome is the most common type of inherited arrhythmia syndrome. It is caused by mutations in genes which affect the way the electricity is conducted through the heart in the cells of the heart. The genes responsible for LQT are usually either potassium or sodium channel gene. LQT syndrome can sometimes be seen on an ECG as a lengthening of the time period of a particular part of the heartbeat cycle, known as the 'QT interval'. The incidence of LQT is approximately 1 in 2000.

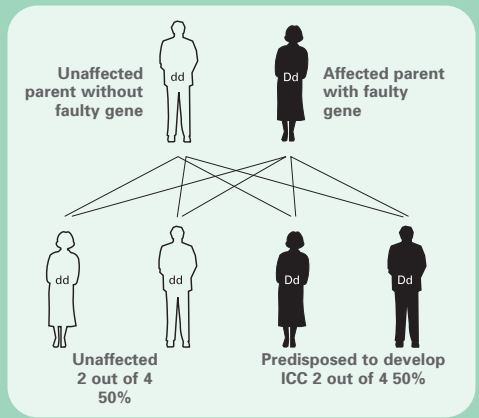
Brugada Syndrome is caused by mutations in genes that regulate the sodium channels of the heart, the results of which can be seen as a particular pattern on the ECG. However, these changes are not always seen on an ECG and a specific test is performed to evaluate for the presence of Brugada.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) causes a particular type of arrhythmia that is usually associated with exercise. It is usually caused by mutations in genes which affect the calcium channels of the heart. This can result in a specific type of arrhythmia.

What are genes?
Genes are the body's instructions which help to determine how the body forms, functions and is maintained. Different group of genes are responsible for causing different types of ICCs and there are presently over 200 different genes known to cause inherited cardiac disease, although it is likely that more will be discovered in the future.

Different genes cause different ICCs so the specific panel appropriate for your condition/family history will be discussed with you. A mutation in any one of these genes can lead to the development of an ICC in an individual, although some have more than one mutation as a cause of their condition.

How are ICCs inherited?
Genes come in pairs; one copy is inherited from our mother and one copy from our father. The majority of ICCs are inherited in an autosomal dominant (AD) manner, which means that there is a 1 in 2, or 50% chance, that an affected parent will pass the faulty gene onto each of their children (see diagram). However, there are some rarer types of heart conditions that are inherited in an X-linked pattern, where boys are more commonly affected than girls.



What is CardioGene?
CardioGene is a panel of specific cardiac genes that can be offered to you to determine what gene is causing your ICC. Depending on your/your family's particular type of ICC, the following panel of genes are tested. The appropriate panel will be discussed with you prior to testing.

CardioGene HCM	MYH7, MYBPC3, TNNT2, TNNi3, TPM1, TNNC1, MYL2,MYL3, ACTC1, PRKAG2, LAMP2, PTPN11, GLA, DES, TTR,FLNC, PLN, FHL1, CSRP3, ANKRD1 and ACTN2
CardioGene ARVC/DCM	ACTC1, BAG3, DES, DMD, DSP, FLNC, LMNA, MYBPC3, MYH7, PKP2, PLN, RBM20, TAZ, TNNC1, TNNI3, TNNT2, TPM1, TTN, ABCC9, ACTA1, ACTN2, ALMS1, ANKRD1, CAV3, CRYAB, CSRP3, DNAJC19, DOLK, DSC2, DSG2, EMD, EYA4, FHL2, FHOD3, FKRP, FKTN, FOXD4, GAA, GATA4, GATA6, GATAD1, GLB1, HFE, JUP, LAMA2, LAMA4, LAMP2, LDB3, MURC, MYH6, MYL2, MYL3, MYOT, MYPN, NEBL, NEXN, PRDM16, PSEN1, PSEN2, RAF1, RYR2, SCN5A, SGCD, SLC22A5, TBX20, TCAP, TMEM43, TMPO, TTR, TXNRD2, VCL, BRAF, CTF1, GLA, KCNJ2, KCNJ8,NKX2-5, PDLIM3, PTPN11, SGCA, and SGCB
CardioGene IAS	KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNAIC and RYR2
CardioGene ICD/SD	ACTA2, ACTC1, ACVRL1, APOB, BAG3, BMPR2, BRAF, CACNA1C, CALM1, CALM2, CASQ2, COL3A1, DES, DMD, DSC2, DSG2, DSP, EMD, ENG, FBN1, FLNC, GLA, JUP, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, KRAS, LAMP2, LDLR, LMNA, MYBPC3, MYH7, MYL2, MYL3, NKX2-5, PKP2, PLN, PRKAG2, PTPN11, RAF1, RBM20, RYR2, SCN10A, SCN5A, SOS1, TAZ, TGFBR1, TGFBR2, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, AARS2, ABCC9, ACAD9, ACADM, ACADVL, ACTA1, ACTN2, ADAMTSL4, AGK, AGL, AGPAT2, AKAP9, ALMS1, ANK2, ANKRD1, APOA5, APOC3, ATPAF2, BMPR1B, BSCL2, CACNA1D, CACNA2D1, CACNB2, CALR3, CAPN3, CAV1, CAV3, CBL, CBS, CETP, COL1A1, COL1A2, COL5A1, COL5A2, COQ2, COX15, COX6B1, CRELD1, CRYAB, CSRP3, CTNNA3, DLD, DNAJC19, DOLK, DTNA, ELN, EYA4, FAH, FBN2, FHL1, FHL2, FHOD3, FKRP, FKTN, FLNA, FOXD4, GAA, GATA4, GATA6, GATAD1, GDF2, GFM1, GJA1, GJA5, GLB1, GNPTAB, GPD1L, GUSB, HCN4, HFE, HRAS, JAG1, JPH2, KCNA5, KCND3, KCNE1L, KCNE3, KCNJ5, KCNJ8, KCNK3, LAMA2, LAMA4, LDB3, LIAS, LRP6, MAP2K1, MAP2K2, MIB1, MLYCD, MRPL3, MRPS22, MTO1, MURC, MYH11, MYH6, MYLK, MYOT, MYOZ2, MYPN, NEBL, NEXN, NOTCH1, NOTCH3, NPPA, NRAS, PCSK9, PDHA1, PHKA1, PITX2, PLOD1, PMM2, PRDM16, PRKG1, PSEN1, PSEN2, RANGRF, SCN1B, SCN2B, SCN3B, SCN4B, SGCA, SGCB, SGCD, SHOC2, SKI, SLC22A5, SLC25A4, SLC2A10, SLMAP, SMAD1, SMAD3, SMAD4, SMAD9, SNTA1, SPRED1, SURF1, TBX1, TBX20, TBX5, TCAP, TGFB2, TGFB3, TMEM70, TMPO, TRDN, TRIM63, TRPM4, TSFM, TNXRD2, VCL, ANK3, CTF1, KLF10, MYLK2, OBSL1, and PDLIM3

How does the test work?
As the detection rate is less than 100%*, testing is usually only performed on individuals who are affected with the condition. This is because the absence of a mutation in someone who is not affected would not be informative.

The test is performed on a blood or saliva sample and takes 4-6 weeks to obtain a result. Gene coverage is almost 100% for the most common genes for each ICC. This figure does vary between patients and is also affected by sample processing.

*current detection rates vary depending on the ICC

What will the test show?
There are 3 possible outcomes:

1. A mutation is identified in one of the genes known to cause ICC. Predictive genetic testing is possible for unaffected family members.

2. A genetic variation is identified, but the significance of whether or not it is disease-causing is not known (called a Variant of Uncertain Significance (VUS). Family studies will be suggested, where possible, to see who else carries the faulty gene and to try to determine the significance of the genetic variation. Predictive genetic testing may not be possible for unaffected family members.

3. No mutation is identified. It is possible that a mutation exists in an as yet unidentified gene. Further testing may be possible in the future with developments in research. In this instance, predictive genetic testing is presently not possible for other family members.

If a mutation is not identified, this does not mean that your ICC is not genetic, just that we have been unable to currently determine a genetic cause. Future genetic testing may be available depending on your condition.

CardioGene Predict
If a mutation has already previously been identified as a cause of the ICC in a family, then CardioGene Predict can offer testing for that specific mutation. This type of test is usually performed on an individual who is unaffected within a family and wishes to know whether or not they have inherited the mutation. The implications of a mutation identified in someone who is unaffected will be discussed with the client during the pre-test consultation.

What does it mean if I have a mutation?
If the test identifies a mutation in your sample, this means we have identified the cause of your/your family's ICC and that unaffected family members may benefit from a genetic test. It is unlikely that your clinical management will change upon the identification of a specific faulty gene; however for a few genes this may be the case.

Presently, it is not possible to predict the clinical course for most of the ICCs based on a particular gene or mutation as there generally is not a consistent correlation between the two. The specific gene identified will inform us how your ICC is inherited and will help us in determining which of your family members require clinical screening and who would benefit from genetic testing.

Screening
When an ICC has been identified in the family, it is advisable that all first degree family members undergo clinical screening by a cardiologist. This is regardless of whether a genetic mutation can be identified in the family and should also take place even in the absence of symptoms. The intervals and timings of screening should be discussed with your cardiologist and will be dependent on age and type of ICC.

Lifestyle factors
A good general health is important for cardiac health. Some gene mutations might require lifestyle changes. It is important that you maintain regular clinical screening for your heart condition, even in the absence of a genetic mutation being identified.

Financial issues
Some individuals may be concerned about the possibility of obtaining insurance coverage as a result of genetic testing. Currently, this not an issue in the United Kingdom as there presently exists a moratorium ensuring that individuals do not need to disclose genetic test results. This moratorium on genetic testing is in place until 2019. However, if you do have an ICC you may have difficulty in obtaining life insurance or a mortgage based on your condition. More information about this can be obtained at: **http://www.abi.org.uk**

Further information and support
http://www.cardiomyopathy.org/
http://www.sadsuk.org.uk/newsite/

Our knowledge of ICCs is rapidly growing and the information given is accurate to date. Please keep us informed of any significant changesin your diagnosis or family history as this may alter our advice to you.

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GeneHealth UK

Head office

GeneHealth UK
1 The Mill
Copley Hill Business Park
Cambridge Road
Cambridge
CB22 3GN

www.GeneHealthUK.com
Info@GeneHealthUK.com

Appointments

Call **0800 331 7177**
Mon-Fri 08.00-20.00
Sat 09.00-12.00

Clinics - Locations

Please visit our website **www.GeneHealthUK.com/Clinics** for an up-to-date list of clinic locations and directions. Please be aware that **most genetic counselling sessions are undertaken by phone** so a clinic appointment may not be needed.

GeneHealth UK is the leading provider of genetic tests and offers national and international counselling and testing services. We have designed our services to be comprehensive and to detect all of the clinically relevant mutations, however no genetic test will pick up all genetic mutations. If your results are abnormal you may be eligible for referral to an NHS clinic via your GP, or you could choose to see a consultant in one of our private clinics throughout the UK. This may be funded by either self-pay or private medical insurance.

Please visit **www.GeneHealthUK.com** *for more information and advice.*

GeneHealth UK is part of Check4Cancer Ltd.