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Adults with Congenital Heart Disease: A Genetic Perspective

A thesis submitted to the Division of Graduate Studies
and Research at the University of Cincinnati

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Abstract

Successful treatment of children with congenital heart disease has led to a new age in the management of adults with congenital heart disease, who are now much more likely to survive and reproduce. Comprehensive treatment of the adult with congenital heart disease requires a thorough consideration of genetics by Cardiology professionals. In this thesis we examine clinical and laboratory aspects of genetics evaluation in the treatment of congenital heart disease. Research studies provide evidence that congenital heart disease can be inherited in both syndromic and non-syndromic forms. A clinical examination, along with close medical, developmental, and family history can provide clues to testing for such inherited conditions. Resources such as Online Mendelian Inheritance in Man (OMIM) and Genetests are available to aid in the identification of appropriate genetic tests. Once a test is identified it is important to pre-counsel a patient for all of the possible results since genetic testing can have implications for their management as well as for their family members. Current technologies for genetic testing can be grouped into traditional cytogenetic, molecular cytogenetic, and molecular genetic techniques. The choice of the correct test depends on the physician's level of suspicion for a specific causative genetic change. Genetics has already been integrated into the field of Cardiology and will only increase as the technology and understanding of genes and development improves. The incorporation of these new findings will ensure optimal treatment for patients and their families.

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Chapter 1.

Adults with Congenital Heart Disease: A Genetic Perspective*

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Introduction

As a result of the genetic revolution, most specialty clinics need to consider the impact of genetics on the diagnosis, management, and treatment of their patient population. Cardiology is no exception. In fact, it is likely that genetic information will eventually transform the definitions and taxonomy of congenital heart disease (CHD) used in daily practice. Further, as we learn to apply genetics to risk assessment and an understanding of pathogenesis of heart malformations, many of our diagnostic and therapeutic strategies will be impacted. A current challenge is to incorporate such information into the doctor's little black bag. As these times are already upon us, an understanding of basic genetics is necessary for top-notch care in Cardiology. The goal of this chapter is to identify and explain key implications of genetic testing for Adults with Congenital Heart Disease. At the conclusion of the chapter, the reader should be familiar with elements of the clinical session that can be used to diagnose a genetic condition, be able to identify resources available to investigate genetic diagnoses and sites for laboratory testing, and be prepared to develop a genetic testing strategy for an adult with CHD.

What is Congenital Heart Disease?

CHD refers to structural or functional abnormalities that are present at birth even if discovered much later. CHD comprises many forms of cardiovascular disease in the young including cardiac malformations, cardiomyopathies, vasculopathies and cardiac arrhythmias (reviewed in(1-4)). Cardiac malformations are an important component of

CHD and constitute a major portion of clinically significant birth defects with estimates of 4 to 50 per 1000 live births. For example, it has been estimated that 4 to 10 live born infants per 1000 have a cardiac malformation, 40% of which are diagnosed in the first year of life. However, bicuspid aortic valve, the most common cardiac malformation, is usually excluded from this estimate. Bicuspid aortic valve is associated with considerable morbidity and mortality in affected individuals, and by itself occurs in 10 to 20 per 1000 of the population. When isolated aneurysm of the atrial septum and persistent left superior vena cava, which each occurs in 5-10 per 1000 (1), are taken into account the incidence of cardiac malformations approaches 50 per 1000 live births. The incidence of cardiomyopathy, vasculopathy and arrhythmias, including channelopathies, are less well characterized, but in light of above considerations an incidence of CHD of 50 per 1000 live births is a conservative estimate. In this chapter, we will use CHD in a generic way to refer to all forms of pediatric heart disease or cardiovascular disease in the young.

Evidence Congenital Heart Disease is Genetic

There is a long-standing clinical view that most cases of CHD are isolated. Based on studies of recurrence and transmission risks, a hypothesis of multifactorial etiology has reigned for several decades. However, CHD is not purely multifactorial, since cytogenetic abnormalities such as Down syndrome have been identified, and other examples of families with multiple affected individuals exhibiting classical Mendelian transmission have been reported (2). In the past decade molecular genetic studies have exploited these observations and provided insight into the genetic basis of CHD

(reviewed in (1-4)). These insights have contributed to an impression that the genetic basis of pediatric heart disease has been underestimated. However, inheritance of nonsyndromic CHD is often complex.

From Phenotype to Genotype

On any given day, a cardiologist sees a variety of patients. What findings suggest a genetic etiology? Subtle clues obtained in clinic can point to a genetic cause. Here we focus on the importance of **medical history**, **family history** and **clinical exam** in the investigation of a genetic cause for adults with CHD.

Detailed assessment of the patient's medical history, and in some cases the pregnancy history, can provide a starting point for classification of genetic disease. Individuals with CHD are likely to have a history of cardiac surgery, previous visits to a cardiologist, and records containing past echocardiography (ECHO) or electrocardiogram (ECG) results. In some cases, clinical history will identify the presence of a characteristic trait that would not otherwise be found on clinical exam. One example is the individual who was born with polydactyly but had early surgical removal of extra fingers/toes. This type of information can be crucial for the classification of patients with syndromic versus non-syndromic phenotypes. A developmental assessment is also part of the medical history. Evaluation of past gross and fine motor skills as well as cognitive development will lead to the recognition of developmental delay which is more likely to be associated with certain CHD as part of a syndrome. Since this assessment may not have been done since childhood, it is particularly important to explore this aspect of past medical history with the adult patient.

Family history can distinguish genetic conditions that are not usually inherited (e.g. Down syndrome or trisomy 21) from genetic conditions that exhibit familial clustering (e.g. bicuspid aortic valve). The recognition of familial heart disease has been complicated by three genetic phenomena (Table 1) that obscure the familial nature- reduced penetrance, variable expressivity and genetic heterogeneity. Further, while most patients believe family history is important, many are unfamiliar with important clinical detail. Too often, in the hustle and bustle of a busy clinic, family history is asked on the initial visit, recorded and never revisited. This leads to a situation whereby **family history** is an under utilized tool in the recognition of genetic etiology (5). A precise recording of family history may require revisiting the questions on more than one occasion and obtaining information from more than one family member. In addition, family history, like other elements of the medical history, is dynamic and subject to change with the passage of time (6). Based on family history and clinical exam, the likelihood for a genetic etiology can be determined. If the condition appears to be inherited, a pedigree, a shorthand way to record family history, may give some indication as to the **mode of inheritance**. Such patterns of inheritance include autosomal dominant, autosomal recessive, X-linked, and mitochondrial. However, physicians should use caution not to rely ENTIRELY on family history because some genetic conditions are not hereditary, or do not display a family clustering on a pedigree. Figure 1 illustrates the types of simple inheritance and gives examples of genes that cause CHD.

A genetic condition may be identified by recognizing signature cardiac and/or noncardiac findings during the **clinical exam**. For example, tetralogy of Fallot is a

signature cardiac malformation for 22q11 deletion syndrome (del22q11), but a physician evaluating a patient with right ventricular outflow tract malformation may overlook dysmorphic facial features characteristic of del22q11. The presence of syndromic features is strongly supportive of a genetic condition and may be an indication for genetic testing. Even with what appears to be isolated CHD, typical features of the cardiac phenotype may suggest a genetic etiology with known inheritance. For example, electrocardiographic (ECG) findings of prolonged QT interval or echocardiographic (ECHO) findings of unexplained cardiac hypertrophy would be recognized by most cardiologists as conditions with a strong likelihood of genetic etiology and family clustering.

Online Mendelian Inheritance in Man (OMIM) is a reliable resource that can be used at the bedside as a tool to investigate conditions that may have a genetic etiology. OMIM can be accessed through the website for the National Center for Biotechnology Information (NCBI) (7). Users can enter patient phenotypic information and learn about genetic conditions to help them decide the appropriate testing scheme to pursue.

Clinical Utility of Genetic Testing

If completion of the personal medical history, family history and clinical exam suggests a genetic etiology of heart disease, genetic testing may be considered. A step-wise process for genetic testing identification, counseling and explanation of results as well as implications follows.

Choosing a Genetic Test

Decisions about the type of genetic test need careful consideration. If the physician has a strong index of suspicion for a specific genetic or cytogenetic abnormality, then karyotyping, Fluorescence In-Situ Hybridization (FISH), or gene-specific mutation analysis are indicated based on that suspicion. If the characteristics are not typical for a known condition, karyotyping or comparative genomic hybridization (CGH) may be necessary to identify a rare or novel genetic change. In addition to OMIM, Genetests, a resource supported by the National Institutes of Health (NIH), keeps up-to-date information on genetic conditions and clinical/research laboratory testing sites (8).

Figure 2 outlines a strategy for choosing an appropriate genetic test.

Preparing the Patient for Genetic Testing

Patients who decide to undergo genetic testing should be pre-counseled for possible test results. A cytogenetic abnormality that has been previously reported or that interrupts or deletes a biologically important gene(s) is likely to be involved with disease pathogenesis. Similarly, a sequence change that occurs in a highly conserved residue, changes the amino acid, and segregates with disease in a family is likely to affect gene function (especially during development) and could be expected to be deleterious. Such changes are considered to result in a **positive test**. Once they are identified, there are implications for patient management that extend to family care. If a deleterious change has been identified in a family, and an unaffected family member has a **negative result** during genetic testing, that person is considered to have a true negative result and does not have that specific genetic risk for heart disease. However, in a family where no one

has had a positive genetic test, a negative test means that the genetic cause has not been determined (it is neither good news nor bad news). That patient and his/her family members are still at risk and should be managed according to their personal/family history. Finally, a **variant of unknown significance (VUS)** is a genetic change that may or may not be a risk factor for CHD. This mutation may be a polymorphism or it may be disease causing. More information needs to be gathered before the doctor/patient incorporate this test result into clinical care.

Implications of Genetic Test Results

Once a genetic test result is obtained it can be used to make decisions about **management, screening, and prophylaxis**. Patients with isolated CHD are at risk for secondary phenotypes that can be caused by their gene mutation. For example, patients with an *NKX2.5* mutation may have undergone successful surgery for CHD, but they will continue to be at risk for atrioventricular block. They should receive regular ECG screenings to monitor that risk and encourage early treatment of any abnormal findings. Early detection of genetic status can improve screening and management, and as we come to understand the underlying pathogenesis, detection will be important for prophylactic treatment, such as the use of implantable cardiac defibrillator (ICD) in patients with channelopathies.

Implications for Family Members

Genetic information has health management and psychosocial implications for extended family members too. Individuals who have not previously had any symptoms

or risks for CHD may become candidates for intensified screening due to the genetic diagnosis of a family member. Families with a negative clinical history of CHD may think they are not at risk for hereditary heart conditions. Once a genetic cause has been identified, it can be advantageous to rule out individuals who are not at risk for a condition. This can prevent unnecessary, expensive and sometimes inconvenient screening practices. Information that has implications for family members must be managed cautiously as some family members may not be interested in sharing genetic information, getting genetic testing, or carrying out prophylactic measures that are available to them.

Describing Recurrence Risks

A **Recurrence risk** is a statistic that estimates the probability that a condition present in one or more family members will recur in another relative in the same or future generations (5). Improved survival of CHD in recent decades has led to more patients living to reproductive age, and renewed interest in recurrence risks. Ideally, recurrence risk is based on knowledge of the genetic nature of the CHD of interest and the family pedigree. When the disorder is known to have single gene inheritance, e.g. Marfan syndrome, the recurrence risk can be determined from known patterns of inheritance (Figure 1); this may become complicated when reduced penetrance or variable expressivity are present (Table 1). However, for most forms of CHD, the underlying patterns of inheritance are unknown; in this situation, recurrence risk is based on previous experience. Recurrence risks can be extended to include distant relatives, but adults with CHD are likely to be primarily concerned with risks to their siblings and their

children. One interesting finding of this data is that the risk for transmission appears to be higher when the affected parent is the mother compared to when the father has CHD. The genetic basis of this predilection is unknown, and the phenomenon has not been confirmed based on genetic diagnosis. As more information is published on this topic, clinicians will be able to provide more accurate information to adults with CHD who are concerned about the risks for their family members. Table 2 provides recurrence risks for several CHD types (2,9).

Reproductive Decision Making

Imaging studies (Ultrasound, MRI, Fetal Echocardiography), **chorionic villus sampling**, and **amniocentesis** are increasingly used for the evaluation of the fetus suspected of having CHD. For example, early, high resolution ultrasound measurements of nuchal translucency have been used to predict CHD in high risk families (10). Chorionic villus sampling and amniocentesis are invasive tests that involve the removal of placental tissue or amniotic fluid for genetic testing in the fetus (5). Genetic tests can also be used for **pre-implantation genetic diagnosis (PGD)** (5) in future pregnancies. This procedure involves external fertilization of embryos, as used for in-vitro fertilization (IVF), but adds a genetic screening step prior to reintroduction of the non-affected embryos to the uterus. Though PGD is infrequently used for non-life threatening conditions or adult onset disease, its use may be increased as the technology is improved and the cost decreases (11). PGD has already been used for Holt-Oram syndrome (12) and Marfan syndrome (13).

Current State of Genetic Technology

In the past two decades, there have been remarkable advances in the number and type of genetic tests that have become available for patient diagnoses as well as for prenatal and preimplantation genetic diagnosis. It seems safe to predict that this will continue to change given the pace of advances in technology. For purposes of our discussion, we have grouped clinically available genetic tests into three categories: cytogenetic, molecular cytogenetics and molecular genetic tests.

Traditional Cytogenetic investigations

Standard metaphase karyotype is used to analyze chromosomes with 450 to 550 bands in the case of many chromosomal disorders, especially those with variation in chromosomal number like trisomy (trisomy 18 or 21), monosomy (45,X or Turner syndrome) and gross chromosomal structural rearrangements like translocations, and large deletions (>5 Mb), duplications and inversions. However, in some cases a high resolution banding technique (3-5 Mb) is used to identify subtle chromosomal rearrangements such as some microdeletions and cryptic translocations that may go undetected by routine chromosomal analysis. Karyotyping is performed using peripheral blood lymphocytes, cord blood, skin fibroblasts, or bone marrow. In case of prenatal chromosomal diagnosis, cells from amniotic fluid or chorionic villi sampling are used (5). Cells are cultured; the chromosomes are arrested at metaphase stage and then used for karyotyping. In an adult patient or unborn fetus, indications for karyotype include suspicion of an undiagnosed syndrome that might result from recognition of dysmorphic facial features, developmental delay, mental retardation or other noncardiac anomalies.

Molecular cytogenetic investigations

Fluorescence in situ hybridization (FISH) is a molecular cytogenetic technique, which is used to identify aneuploidies and cryptic chromosomal translocations by localization of specific DNA sequences within interphase chromatin and metaphase chromosomes (5). This technique uses fluorescent probes that bind to specific sequence on a particular chromosome. Centromeric probes are used to identify aneuploidies, microdeletion probes used to identify microdeletion syndrome like CATCH 22q11.2, and telomeric probes are used to identify tiny deletions, duplications, or subtle translocations involving the distal ends of the chromosome (telomeres) as they are difficult to detect by standard or high-resolution karyotype techniques (14). One of the disadvantages of FISH is that since the probes are locus specific, a pretest decision must be made to determine which probe to use. This requires a high level of suspicion for a specific genetic condition on the part of the clinician. For example, the FISH probes used to identify Williams-Beuren syndrome are very different from those used to diagnose the 22q11 deletion syndrome. In addition to standard FISH, whole chromosome paint and multicolor FISH probes, which are actually a collection of probes, each of which hybridizes to different sequence along the length of the same chromosome are also used. Each chromosome is painted with different colors to help in the examination of structural chromosomal abnormalities, e.g. translocations.

Another molecular cytogenetic technique, **Comparative Genomic Hybridization (CGH)**, offers the opportunity to detect alterations in DNA copy number that result in smaller pieces of extra or missing DNA. Therefore, an increasing number of genetic

laboratories have introduced this technique as a diagnostic tool to detect copy number variants (CNVs). CNVs can vary in size from kilobases to megabases and occur in normal variation (comparable to single nucleotide polymorphisms- SNPs) as well as disease. Disease related CNVs are associated with aneuploidy, large and small deletions or duplications, and with unbalanced translocations. CNVs are most likely to be deleterious when they are large in size, homozygous, found in gene-rich regions and previously associated with disease. However, careful analysis of previously unreported microdeletions and microduplications is required on a case-by-case basis.

There are two types of CGH, chromosomal and array-based. In chromosomal CGH, differentially labeled test (i.e. patient) and reference (i.e. normal individual) genomic DNAs are cohybridized to normal metaphase chromosomes, and fluorescence ratios along the length of chromosomes provide a cytogenetic representation of the relative DNA copy-number variation. The resolution is limited to 10-20Mb. In array CGH, arrays of genomic BAC, P1, cosmid or cDNA clones are used for hybridization. Fluorescence ratios at arrayed DNA elements provide a locus-by-locus measure of DNA copy-number variation, and results in increased mapping resolution. Targeted arrays focus on chromosomal regions associated with known microdeletion or microduplication syndromes as well as all subtelomeric regions. Whole genome arrays permit analysis of deletions or duplications anywhere in the genome without requiring predetermination of a region of interest. As array CGH becomes more commonplace, it is serving an important role in gene discovery for causes of CHD. Studies have found cryptic chromosomal abnormalities in patients with CHD and additional birth defects, which could not be identified using standard cytogenetic technique (17). Several studies on

CNVs have resulted in the publication of maps of normal variation in the human genome as well as of disease-specific CNVs (18). These may be found in online catalogs such as the DECIPHER database (19) and the Toronto Database of Genomic Variants (20).

Molecular genetic investigations

Availability of mutation analysis by direct sequencing and comparative genomic hybridization (CGH) for clinical testing is relatively new. While cytogenetic techniques identify large changes in chromosome structure or number, mutation analysis by direct sequencing identifies small changes that occur at the level of a single nucleotide.

DNA mutation analysis is a technique used to identify small disease-causing changes. Ordering DNA mutation analysis requires knowledge of the gene(s) of interest. Mutation analysis identifies changes in the coding sequence of the gene including small deletions, insertions, or substitutions of nucleotides that alter the encoded amino acid and consequently protein structure. The most common method used to identify these DNA changes is by direct gene sequencing. Indirect screening methods, such as denaturing high-performance liquid chromatography or single-strand conformation polymorphism, have been used extensively. Additionally, newer, more cost-effective direct sequence analysis methods have become available (2). Mutation analysis is performed using DNA obtained from peripheral blood lymphocytes, but other tissues, such as skin, liver, muscle, buccal cells, or saliva, may also be used, depending on the availability. Once a sequence variation is identified, it is important to determine whether this variation is disease related. Basic criteria used to establish the disease-causing potential of a nucleotide change are that it (1) is predicted to alter the gene coding

sense, a gene splice site, or regulatory region of the encoded protein (2) segregates with disease in a kindred (3) is not found in unrelated, unaffected controls and (4) occurs in an evolutionarily conserved nucleotide. Although each of these criteria should be met by any disease-causing mutation, supporting evidence will come from the demonstration that affected individuals from unrelated families have mutations in the same gene. Another major problem is the interpretation of the biological importance of mutations. In many instances, little is known about the role of the normal gene product in cardiac development or function, and in some instances, genes were not known to have any role in the heart before mutation identification (e.g., Alagille syndrome). To date, a variety of mutations that cause CHD, including missense and frameshift mutations, have been identified, e.g. NKX2.5, TBX5, GATA4, JAG1, ZIC3, TFAP2B, TBX1 and FOG2 (15). Table 3 provides a summary of selected genes, their inheritance pattern, and their association with CHD. The extent and heterogeneity of the genes and the mutations identified thus far suggest that they are associated with a variety of pathogenic mechanisms, including loss of expression, inactivation, or loss/gain of function of the mutated products. These genetic findings have provided tools for studies in model systems, which have been informative for cardiac development and the pathogenesis studies of CHD.

Difference between genetic testing in research and clinical settings

The main differences between clinical genetic testing and research testing are the purpose of the test and the recipients of test results. The goals of research testing include identification of unknown genes and interpretation of gene function and

pathogenicity to advance our understanding of genetic conditions. The results of testing done as part of a research study are usually not available to patients or their healthcare providers. Clinical testing, on the other hand, is done to find out about an inherited disorder in an individual patient or family. Patients receive the results of a clinical test and can use these results to help them make decisions about medical care or reproductive issues. It is important for people considering genetic testing to know whether the test is available on a clinical or research basis. Clinical and research testing both involve a process of informed consent in which patients learn about the testing procedure, the risks and benefits of the test, and the potential consequences of testing.

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Tables

Table 1. Definition of genetic phenomena

Phenomenon	Attribute
Genetic heterogeneity	Similar phenotypes, different genetic cause.
Variable expressivity	Individuals with same disease gene have different phenotypes.
Reduced penetrance	Disease absence in some individuals with disease gene.

Table 2. Recurrence risks of CHD based on phenotype

Type of CHD	Recurrence Risk
Atrioventricular Septal Defect	3-4%
Tetralogy of Fallot	2.5-3%
Transposition of the Great Arteries	1-1.8%
Left Sided Obstructions	3%
Bicuspid Aortic Valve	8%
Hypoplastic Left Heart	3.8%
BAV risk in HLHS kindred	8%
Atrial Septal Defect	3%

Table 3. Mode of inheritance, and cardiac phenotype of selected CHD genes

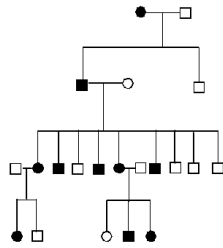
Gene	Inheritance	Associated with
NKX2.5	AD, Sporadic	ASD, AVB, VSD, TOF, HCM, TVA
TBX5	AD, Sporadic	Holt-Oram Syndrome, ASD, AVSD, AVB, TOF
GATA4	AD, Sporadic	ASD, VSD, AVSD, PV dysplasia
CRELD1	AD, Sporadic	AVSD
ZIC3	X-linked	Heterotaxy, TGA, DORV
SCN5A	AD, Sporadic	LQTS, Brugada Syndrome, SSS, AVB
JAG1	AD, Sporadic	Alagille Syndrome, TOF, PS/PPS
FBN1	AD, Sporadic	Marfan Syndrome, aortic root dilation
PTPN11	AD, Sporadic	Noonan Syndrome, PS, PV dysplasia, ASD, AVSD, HCM
EVC, EVC2	AR	Ellis van Creveld Syndrome, AVSD

AD: autosomal dominant, AR: autosomal recessive, ASD: atrial septal defect, AVB: atrioventricular block, AVSD: atrioventricular septal defect, DORV: double outlet right ventricle, HCM: hypertrophic cardiomyopathy, LQTS: long QT syndrome, PPS: peripheral pulmonary stenosis, PS: pulmonary stenosis, PV: pulmonary valve dysplasia, SSS: sick sinus syndrome, TA: tricuspid atresia, TAPVR: total anomalous pulmonary venous return, TGA: transposition of the great arteries, TOF: tetralogy of Fallot, TVA: tricuspid valve anomalies, VSD: ventricular septal defect

Figures

Figure 1. Illustration of classic Mendelian (simple) inheritance patterns. Examples of genes causing CHD associated with each mode of inheritance are shown.

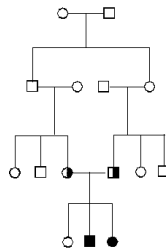
Dominant



- Disease in every generation
- Disease in males and females
- Gene Transmission = 50%

- *NKX2.5, TBX5, PTPN11, SCN5A*

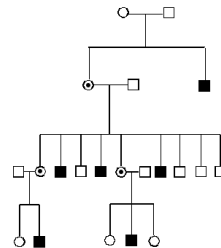
Recessive



- Disease may appear sporadic
- Disease in males and females
- Gene transmission = 25% if both parents are unaffected carriers

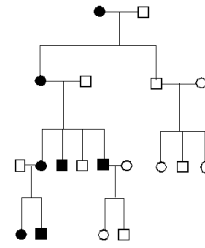
- *EVC, EVC2*

X-linked



- Disease in every generation
- Males are primarily affected with disease
- Female carriers may show symptoms
- Gene Transmission
 - Daughters of affected fathers will be carriers
 - Sons of affected fathers don't have disease
 - Female carriers have 50% chance of passing mutation to next generation- daughters are carriers, sons are affected
- *ZIC3, X-linked Cardiomyopathy*

Maternal



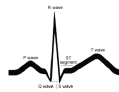
- Disease in every generation
- Disease in males and females
- Gene Transmission= 100% from mother, 0% from father
- Only passed through females

- *MT-TL1, Rare cardiomyopathies*

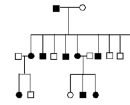
Figure 2. Strategy for selection of a genetic test in the cardiology clinic. Test selection may be specific, e.g. mutation analysis of a specific gene, or more general, e.g. karyotyping, if the genetic cause is unknown.

Phenotype to Genotype

CLINIC



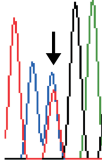
- Medical History: Developmental, Surgical
- Family History: Inheritance Pattern
- Clinical Exam: Syndromic, Non-Syndromic



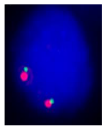
LABORATORY

High Suspicion of Specific Genetic Cause

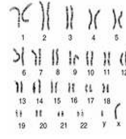
SYNDROMIC, NON-SYNDROMIC



Gene Sequencing: point mutations, small deletions or insertions

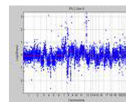


FISH: Alterations in chromosome number, deletions, and insertions



SYNDROMIC

Karyotyping: Structural chromosomal abnormalities- gross (>10Mb) deletions or insertions, rearrangements, and aneuploidy



CGH Array: Copy Number Variations

- Targeted: targeted to known microdeletion, microduplication syndromes
- Whole Genome: Spread throughout genome

Unknown Genetic Cause

NON-SYNDROMIC

Linkage Analysis Research

