A Clinical Approach to Common Cardiovascular Disorders When There Is a Family History

The Implications of Inheritance for Clinical Management

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Since the advent of genotyping, recognition of heritable disease has been perceived as an opportunity for genetic diagnosis or new gene identification studies to advance understanding of pathogenesis. Until recently, however, clinical application of DNA-based testing was confined largely to Mendelian disorders. Even within this remit, predictive testing of relatives is cost-effective only in diseases in which the majority of families harbor mutations in known causal genes, such as adult polycystic kidney disease and hypertrophic cardiomyopathy, but not dilated cardiomyopathy. Confirmatory genetic testing of index cases with borderline clinical features may be economic in the still smaller subset of diseases with limited locus heterogeneity, such as Marfan syndrome. Furthermore, Mendelian diseases account for ≈5% of total disease burden.1 Genome-wide association studies have made headway in elucidating the genetic contribution to the more common, complex diseases, and high throughput techniques promise to facilitate integration of genetic analysis into clinical practice. Nevertheless, many genes remain to be identified and implementation of genomic profiling as a population screening tool would not be cost-effective at present. The implications of heredity, however, extend beyond serving as a platform for genetic analysis, influencing diagnosis, prognostication, and treatment of both index cases and relatives, and enabling rational targeting of genotyping resources. This review covers acquisition of a family history, evaluation of heritability and inheritance patterns, and the impact of inheritance on subsequent components of the clinical pathway.

Family History

Eliciting a family history is the first step to determining whether a known diagnosis is heritable or symptoms of unknown etiology have a hereditary basis. Both narrative and diagrammatic approaches are integral to data collection, the former including questioning for diseases that recur within the family and the latter involving construction of a pedigree or family tree. Incorporation of psychosocial and interactional data, such as emotional relationships (harmony, apathy, hostility, etc) upgrades the pictorial representation into a genogram.2

As a result of media coverage, internet access, and health promotion campaigns, many patients nowadays are medically literate and well aware of the impact of genetics on health. If the patient perceives this aspect of the interview as intrusive, however, it may be necessary to explain its relevance (eg, “Sometimes the health of a person’s family members may affect one’s own health”) and emphasize confidentiality.

For the narrative portion of the family history, various questioning styles may be appropriate, from an open-ended starter (“Do you know of any conditions that run in the family?”) to a checklist ranging from prostate cancer to osteoporosis. Just as medical students are encouraged to take a comprehensive screening history while experienced diagnosticians adopt a more tailored approach, the specialist tends to acquire a directed family history. Cardiologists will often concentrate on ischemic heart disease, the heritable risk factors thereof (viz., diabetes, hypertension, hyperlipidemia), cerebro- and peripheral vascular disease, and premature sudden cardiac death (SCD); shared environmental factors, such as passive smoking, also may be addressed. Extraneous details are thereby avoided, at the cost of potentially missing clues to multisystemic disorders, such as Anderson-Fabry disease, and historic misdiagnoses, such as apparent epilepsy or drowning in a family with long QT syndrome. Construction of a comprehensive pedigree should, however, rectify most of the omissions from directed family history acquisition, and has the added benefit of jogging the patient’s memory through the focus on specific relatives.

The Pedigree

At minimum, a pedigree covers 3 generations (typically subject, parents, and grandparents) and first- and second-degree relatives at each level on both sides of the family. The children of the subject’s generation are included from puberty onwards, although younger children and infants are also important if juvenile onset diseases are under survey. Ideally, the pedigree is expanded to include the details of as many generations and distant relatives as the subject is able to give; larger is better for diseases with low penetrance, for scrutiny of inheritance patterns, or as a guide for subsequent cosegregation on the disease or new gene identification studies to advance understanding of pathogenesis. Until recently, however, clinical application of DNA-based testing was confined largely to Mendelian disorders. Even within this remit, predictive testing of relatives is cost-effective only in diseases in which the majority of families harbor mutations in known causal genes, such as adult polycystic kidney disease and hypertrophic cardiomyopathy, but not dilated cardiomyopathy. Confirmatory genetic testing of index cases with borderline clinical features may be economic in the still smaller subset of diseases with limited locus heterogeneity, such as Marfan syndrome. Furthermore, Mendelian diseases account for ≈5% of total disease burden.1 Genome-wide association studies have made headway in elucidating the genetic contribution to the more common, complex diseases, and high throughput techniques promise to facilitate integration of genetic analysis into clinical practice. Nevertheless, many genes remain to be identified and implementation of genomic profiling as a population screening tool would not be cost-effective at present. The implications of heredity, however, extend beyond serving as a platform for genetic analysis, influencing diagnosis, prognostication, and treatment of both index cases and relatives, and enabling rational targeting of genotyping resources. This review covers acquisition of a family history, evaluation of heritability and inheritance patterns, and the impact of inheritance on subsequent components of the clinical pathway.

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Acquisition of an accurate family history depends on the reliability of both the patient and the clinician. The validity of patient reporting was assessed in a sample of 10 diabetic cases and 10 controls. The 20 index cases indicated the diabetic status of over 200 of their primary relatives, the majority of whom were subsequently interviewed. There were no discrepancies between the family histories provided by the index cases and the information obtained from their relatives. Although the sample number was small, these results suggest that patient reporting of family history is generally reliable.3

The extent to which healthcare workers request and record these details is also pertinent. In a study of family medicine studies. Standardized notation for pedigrees is summarized in Figure 1; examples from families with Mendelian and complex diseases are shown in Figure 2 and online-only Data Supplement Figure III.

There are 2 common strategies for acquisition of the pedigree. The first is to compile it in the presence of the patient, which has the advantage of allowing immediate discussion of pertinent findings. Completion of the task at the initial consultation is often not feasible, because a single subject may not be familiar with the medical history of all maternal and paternal relatives. This possible drawback is offset in consultations attended by several relatives together, as is practice (with mutual consent) at some centers specializing in inherited disease. The alternative approach is to mail questionnaires to patients well in advance of the consultation, to enable them to research their family history. A draft pedigree is constructed from the responses and subsequently modified through clarification and further exploration during the interview.

The Specialist Family History
The specialist family history usually entails deliberate omission of general screening questions in favor of detailed, tailored questioning. Rheumatological and renal disorders, for example, arguably influence cardiovascular health, but questioning for a family history thereof is not requisite, although a personal history is noteworthy. On the other hand, it is not sufficient for the tailored family history to be limited to cardiovascular disease, risk factors, and instances of SCD. Deaths from progressive heart failure should be distinguished from SCD. Coronary intervention and bypass surgery are worth specific queries, as are device implants, radiofrequency ablations, and transplantation if the focus is a cardiomyopathy or arrhythmic disorder. Undiagnosed symptoms, such as palpitation and syncope, also may be relevant, particularly in relatives who subsequently suffered SCD. The age of the relative at symptom onset and at the time of clinical diagnosis, intervention, or events merits documentation.

The circumstances of SCD also warrant exploration and may stratify the differential diagnosis in cases where autopsy was not performed or inconclusive; for example, SCD during sleep in a Southeast Asian man with noncontributory postmortem raises suspicion of Brugada syndrome. For the same reason, it may be worth exploring the background to apparently accidental deaths, to determine whether loss of consciousness might have preceded and precipitated trauma, as in fatal road traffic accidents and drowning. If a specific inherited disorder is under investigation, the clinician will often enquire about extracardiac symptoms that point to a syndromic form, such as congenital deafness in a family with suspected long QT (autosomal recessive Jervell-Lange-Nielsen syndrome) or kidney disease and neuropathy in the setting of hypertrophic cardiomyopathy (X-linked recessive Anderson-Fabry disease).

Integration Into Clinical Practice
The extent to which healthcare workers request and record these details is also pertinent. In a study of family medicine
residents interviewing model patients, the average time to obtain and document a family history was 16 (range 9–30) minutes, with ≈83% of available information typically elicited.4 Perhaps owing to time constraints, audits of clinical practice among primary care physicians suggest that the family history is of low priority. Research nurses observing 4454 patient visits to 138 family practitioners reported that family history was discussed during 51% of new patient interviews and 22% of visits by established patients, with the average duration of the discussion being under 2 1/2 minutes; a pedigree was present in 11% of patient records.5 The quality of the information obtained also may be limited. A separate investigation reviewed 53 charts from 15 randomly selected primary care physicians, collected from 223 consultations (mean 4.2 per patient) over a 5-year period. Although 39 patients self-reported a family history of at least 1 common disease, the case records reflected this in only 14 (36%). Study patients identified 115 first-degree and 213 second-degree relatives with 1 of the diseases under survey; the physicians documented this family history in only 23 (20%) and 4 (2%) of cases, respectively.6

The task of obtaining an adequate family history therefore may fall to specialists. At centers with a major interest in hereditary diseases, acquisition of a detailed pedigree often is integral to the work-up, with sharing of responsibility between physicians, nurses, and genetic counselors. As a consequence of variable and age-related expression, affected relatives of index cases with a genetically determined disease often have mild clinical manifestations and few, if any, symptoms. Unfortunately, limited disease expression may belie significant risk of events in some genetic diseases, including arrhythmogenic cardiomyopathy and the inherited arrhythmia syndromes, such as long QT and Brugada syndrome.7,8 Prospective clinical evaluation of relatives, sometimes on a periodic basis, is indicated in many scenarios. Compilation of a pedigree, therefore, is best viewed as a dynamic process, with periodic need for revision of earlier drafts to reflect the clinical status of family members as they age and undergo repeated examination. Further information also may become available on deceased relatives; in the field of inherited cardiovascular disease, obtaining postmortem reports and, if available, retained blocks for re-examination, frequently is invaluable. Electronic storage of family data facilitates updating; dedicated software packages are now available for pedigree construction and analysis.

Implications of Family History
Recurrence of a trait within a family may be a corollary of genetic transmission, shared environment (“household effects”), or common behaviors. Evidence of genetic contribution is sought at the family level through examination of the pedigree for inheritance patterns and at the population level through heritability studies.

Inheritance Patterns
If the prevalent mode of inheritance for a trait is well-established, the clinician may merely seek assurance that the pedigree is consistent with it. The downside of this common, time-saving approach may be a tendency to overlook more unusual inheritance patterns. Like most structural cardiovascular disorders, dilated cardiomyopathy is transmitted predominantly as autosomal dominant, and in this form accounted for 56% of a series of 39 affected families.9 A number of other subtypes, however, also were identified, including an autosomal recessive form in 16%, characterized by adverse prognosis, and X-linked recessive in 10%, associated with mutations in the dystrophin gene. Without meticulous scrutiny of the pedigree, it is possible to overlook departures from autosomal dominant transmission, such as skipping of generations and male-only disease; small, nuclear families further obscure inheritance patterns, underscoring the importance of recruiting and evaluating distant relatives. Pointers to different modes of Mendelian inheritance, summarized in Table 1, also are potentially explicable by incomplete penetrance or coincidence, further compounding the difficulties.

Simple Versus Complex Traits
The incomplete penetrance and variable expressivity that accompany many autosomal dominant traits implies the influence of genetic background and environmental factors on expression of the causal mutation. Recognition of the role of modifiers challenges the traditional dichotomy between “simple” Mendelian and “complex” multifactorial traits as artificial: a representation of perception rather than biological reality. Based on the multi-hit premise, the genetic contribution to complex diseases is attributable to interaction of 2 or more independently inherited alleles; the primacy of any individual gene is not discernible, but that is the sole distinction from a Mendelian model. It can therefore be argued that heritable traits represent a continuum from a discernible primary (causal) gene interacting with modifiers to increasingly shared influence by multiple genes and environmental effects.10 Awareness of this concept is important because of the practical constraints it imposes on genetic diagnosis. If penetrance and expression within a family are variable to the point of complexity, a single genetic variant identified in an index case cannot be presumed a primary mutation. In isolation, the variant may not be sufficient for clinical expression, limiting its predictive capacity among proven carriers. At the same time, the variant may not be necessary for clinical expression, precluding reassurance of relatives who do not carry it. Arrhythmogenic cardiomyopathy serves as a real-world example of this scenario. Autosomal dominant transmission predominate and penetrance is near complete in some kindreds. Conversely, in other families penetrance may be as low as 20% and the pedigrees reminiscent of multifactorial traits. A number of studies have now demonstrated that variants previously presumed to be independently pathogenic occur at low frequency in healthy control subjects, and that 2 or more variants frequently are necessary for clinical disease expression.11–13 The emerging genetic complexity of arrhythmogenic cardiomyopathy poses an obstacle to commercialization of predictive testing.

Non-Mendelian Inheritance Patterns
Allele-allele interactions, allele-dose effects, and environmental triggers are but 3 of the factors that may contribute to
variable penetrance and expressivity. Variations may arise at every stage at which gene products undergo regulation: transcription, splicing, translation, protein folding, oligomerization, translocation, compartmentalization within the cell or export from it, and turnover. Molecular chaperones, which double as heat shock proteins, assist in the correct assembly, folding, and localization of proteins. Noncoding RNA derived from both introns and extrons is also processed into micro RNA, small nuclear RNA, and other small regulatory RNAs. The resulting RNA regulatory networks control multiple facets of gene expression, including chromatin architecture, transcription, RNA splicing, editing, translation, and turnover.

Worthy of further discussion are epigenetic marks, defined as heritable alterations of genome function that are extrinsic to the primary DNA nucleotide sequence. DNA methylation, small regulatory RNAs, covalent modification of histone proteins, and chromatin conformation all fall under the umbrella of epigenetics. Normal epigenetic patterns are essential for growth and development. For example, the modification of histone acetylation and methylation, which is controlled by families of histone acetylases/deacetylases and methyltransferases/demethylases, regulates stem cell maintenance, differentiation, and function.

Genomic imprinting (Table 2) refers to an epigenetic mark that is specific for the parent-of-origin and results in preferential expression of only 1 of the 2 parental alleles, while the other is “switched off”. Placental mammals may have evolved imprinting to fine tune the growth and development.

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**Table 1. Mendelian Inheritance Patterns**

<table>
<thead>
<tr>
<th>Inheritance Pattern</th>
<th>Characteristic Features on Pedigree*</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Autosomal dominant  | • Every affected individual has at least 1 affected parent  
• Affected individuals who mate with unaffected individuals have a 50% chance of transmitting the trait to each child  
• 2 affected individuals may have unaffected children | Marfan syndrome  
Hypertrophic cardiomyopathy |
| Autosomal recessive | • An individual who is affected may have parents who are not affected (but both will be heterozygotic “silent” carriers of the recessive allele)  
• If 1 parent is heterozygotic for the recessive allele and the other a homozygote for the dominant allele, no offspring will be affected, but each child will have a 50% chance of being a heterozygotic carrier  
• The children of 2 heterozygotic carriers have a 50% chance of being heterozygotic carriers themselves, a 25% chance of being affected, and a 25% chance of being homozygotic for the dominant allele  
• If 1 parent is a homozygote for the recessive allele and the other a homozygote for the dominant allele, no offspring will be affected, but all will be heterozygotic carriers  
• All the children of 2 affected individuals will be affected | Naxos disease  
Cystic fibrosis |
| X-linked dominant   | • No father to son transmission  
• If the mother is affected, and the father is unaffected, each child will have a 50% chance of being affected (independent of sex)  
• If the father is affected, but the mother is unaffected, all daughters will be affected but sons will not  
• If both parents are affected, all daughters will be affected and sons will have a 50% chance of being affected | Rett syndrome  
Familial partial lipodystrophy |
| X-linked recessive  | • No father to son transmission  
• Only women can be silent carriers; men either have the trait or do not carry the gene  
• If the mother is a heterozygotic carrier, and the father is unaffected, daughters have a 50% chance of being affected and sons have a 50% chance of being affected  
• If the mother is a heterozygotic carrier, and the father is affected, then daughters have a 50% chance of being affected and a 50% chance of being carriers, while sons have a 50% chance of being affected  
• If the mother is affected, and the father is unaffected, then all sons will be affected and all daughters will be heterozygotic carriers  
• All the children of 2 affected individuals will be affected | Anderson-Fabry disease |
| Y-linked            | • Affected men transmit the trait to all their sons  
• Women cannot carry the gene | Non-syndromic hearing impairment |

* Assumes full penetrance.
of the fetus. In general, paternally inherited genes are associated with enhanced fetal growth through increased demands on the mother, while maternally inherited genes favor conservation of the mother’s resources for her future offspring as well as her own survival. Imbalances in imprinted gene expression appear to underlie key complications of pregnancy, such as gestational trophoblastic disease, and various congenital syndromes.16–21

As an example, hypomethylation of the imprinting control region 1 at 11p15 and maternal duplication of 11p15 are associated with the intrauterine and postnatal growth retardation of the Silver-Russell syndrome. Conversely, hypermethylation of the same region and paternal uniparental disomy of 11p15 result in the overgrowth and organomegaly of Beckwith-Wiedemann syndrome.22,23

Imprinting anomalies usually arise sporadically.

When familial clustering is observed, however, the inheritance pattern is not Mendelian; heritable genetic defects reveal effects only when inherited from the appropriate parent.14

**Heritability**

A phenotypic trait is considered heritable, in common parlance, when at least 1 of its determinants is transmissible between generations. Heritable need not mean inherited. Bilateral anophthalmia, for example, is caused by de novo loss of function mutations in the SOX2 gene in a significant proportion of cases.24 Index cases have unaffected parents because the mutations arise sporadically at germ-line level, but are capable of passing the defect on to their offspring. Furthermore, describing a trait as heritable gives no indication of the mechanism or pattern of intergenerational transmission, or the extent to which genetic and epigenetic factors contribute to the phenotype. If the scope of the term heritable appears restrictive, then the definition of heritability is still more specific. Heritability is the proportion of total phenotypic variance (σp2) in a given population that is due to variation in genetic factors (σg2).25 Estimation of heritability is discussed further in the online-only Data Supplement.26,27

**Limitations of Heritability**

Estimating heritability has long been an integral first step to elucidating the etiology of traits with evidence of familial recurrence but unknown or indistinct inheritance pattern. More recently, it has been argued that the heritability is anachronistic, an oversimplification of intricate biological systems, limited in scope and hence limited in use.28 The opposing school of thought holds that heritability retains its relevance in the genomics era, but the limitations of the concept must be understood to enable profitable application.29

First, the partitioning of phenotypic variance that forms the basis of heritability calculations assumes the absence of genetic–environmental covariance. This is not always a safe assumption. Dairy cattle, for example, may be fed according to the milk production capacity of their particular lines, leading to positive covariance.25

Second, heritability is a measure of the genetic and environmental contributions not to the phenotype itself, but to its variance around the mean for a given population. Thus, a low heritability implies that only a small proportion of the total phenotypic variation is due to genetic variation, not that the additive genetic variance itself is trivial. Nor does high heritability necessarily indicate predominant genetic determination. If a trait is highly heritable, then the phenotype of an individual in the current status quo should be a good predictor of its absolute phenotype, which may be influenced by changing environmental factors. The 150-year trend toward increasing height in successive generations in most European countries is probably attributable to improved nutrition, which in no way contravenes the reported heritability of 0.8 (80%).25,28,30

Third, heritability estimates provide no insight into the cause of differences between populations. In the mid-19th century, Caucasian men in the United States were, on average, 9 cm taller than their Dutch counterparts, but by the end of the 20th century, the Dutch had overtaken them by ~5 cm.

**Table 2. Non-Mendelian Inheritance Patterns**

<table>
<thead>
<tr>
<th>Inheritance Pattern</th>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondrial</td>
<td>Mitochondrial DNA is predominantly maternal in origin; therefore transmission is largely maternal</td>
<td>MELAS</td>
</tr>
<tr>
<td></td>
<td>Sons and daughters are equally likely to be affected</td>
<td></td>
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<tr>
<td></td>
<td>Affected men are significantly less likely than women to transmit the trait to their children</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phenotypic predictions are complicated by heteroplasmy (mixture of normal and abnormal mitochondrial DNA)</td>
<td></td>
</tr>
<tr>
<td>Apparently sporadic occurrence, no vertical transmission</td>
<td>Recurrent de novo mutation, unable to reproduce</td>
<td>Apert syndrome, FGFR2, anophthalmia</td>
</tr>
<tr>
<td>Complex</td>
<td>Interaction between multiple genetic and environmental factors</td>
<td>Type 2 diabetes, hypertension</td>
</tr>
<tr>
<td>Imprinting diseases</td>
<td>Rare inherited variants: only give rise to phenotype when inherited from the appropriate parent; alteration in epigenetic organization</td>
<td>Beckwith-Wiedemann, Prader-Willi syndrome, Angelman, transient neonatal diabetes</td>
</tr>
<tr>
<td>Paradoxical inheritance</td>
<td>Heterozygotes most severely affected</td>
<td>Myocilin glaucoma</td>
</tr>
<tr>
<td></td>
<td>? Homozygotes able to form functional dimers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormalities more severe in women with random X-inactivation</td>
<td>Craniofrontonasal syndrome</td>
</tr>
<tr>
<td></td>
<td>where mutant and wild-type ligand-bearing tissues are adjacent</td>
<td></td>
</tr>
<tr>
<td>Anticipation through generations</td>
<td>Triplet repeat expansion; telomere shortening</td>
<td>Myotonic dystrophy</td>
</tr>
</tbody>
</table>

In spite of the high heritability of adult height, this reversal is most likely environmental rather than genetic in etiology.25,29

Fourth, the heritability estimate is strictly applicable only to the original population under test conditions. Age and sex, for example, are recognized covariates in heritability calculations. Theoretically, the heritability of a trait may vary by population and environment, although in practice it is often similar in other populations of the same species and even across species.25,28,30

Contemporary Role of Heritability

Couched in the above caveats, the contemporary role of heritability estimation can be revisited. The rationale for genome-wide association studies is the “common disease/common variant” hypothesis: that the genetic contribution to complex traits is due to alleles occurring at high population frequency but exerting modest effects on phenotype in the individual. More than 300 replicated associations now have been reported between common variants and complex traits, ranging from height to type-2 diabetes, obesity, atrial fibrillation, cardiac conduction, and renal function.31-36 Yet, the variance explained by the validated single nucleotide polymorphisms is usually only a fraction of the narrow-sense heritability. For example, with genome-wide association studies, an estimated 50 variants associated with adult height, they appear to account for a mere 5% of the total phenotypic variance.31 Among the potential sources of this “missing heritability” are gene–environment interactions, inherited epigenetic factors, copy number variants, such as insertions and deletions, copy number neutral variation, such as inversions and translocations, and the “common disease/rare variant” (or “genetic heterogeneity”) hypothesis.37,38 The “missing heritability” of complex traits is discussed in more detail in the online-only Data Supplement.37,39-42

Application of Heritability to Mendelian Traits

Heritability, therefore, remains a valuable benchmark for monitoring progress in the elucidation of common, complex traits. Both the principles and methods of heritability analysis also are applicable to the phenotypes associated with Mendelian diseases. Nested analysis of variance (ANOVA) further allows evaluation of inter- and intrafamilial differences. The combination of heritability estimation and nested ANOVA enables dissection of the relative contribution of mutational heterogeneity, modifier genes, and environmental factors to continuous phenotypic measures. The original test sample for this analysis comprised >300 relatives from type 1 autosomal dominant polycystic kidney disease, which is characterized by marked variation in the severity and progression of renal and extrarenal phenotypes. The results suggested that inherited modifiers in the genetic background were important contributors to the diversity in traits, including serum creatinine, urinary protein excretion, renal volume, number of liver cysts, and age at diagnosis of hypertension and end-stage renal disease.43 The approach was subsequently applied to a number of quantitative traits associated with arrhythmogenic cardiomyopathy, also known for its broad phenotypic spectrum. Heritability estimates ranged from 20% to 77%, being highest for left ventricular ejection fraction and lowest for the ventricular arrhythmia grade, suggesting differing genetic and environmental contributions to these traits. ANOVA models indicated a predominant mutation effect for left ventricular fibrosis, as indicated by late gadolinium enhancement on cardiac magnetic resonance. Conversely, the modifier genetic effect appeared significant for right ventricular end-diastolic volume and ejection fraction, left ventricular ejection fraction, and importantly, for arrhythmic events.44

Implications of Inheritance

Acquiring a reliable and comprehensive family history is the first step to determining whether an observed trait might have a hereditary basis. If familial clustering is observed, then pedigree analysis of a kindred or heritability estimation of a cohort facilitates confirmation of inheritance. Establishing a trait as heritable has important implications for both clinical practice and public health promotion.

Clinical Practice

An inherited trait influences every component of the clinical pathway, from history taking to physical examination, investigations, diagnosis, and therapy. The forthcoming review series in Circulation: Cardiovascular Genetics focuses on the impact of heredity in specific cardiovascular disorders. The general principles are introduced here with a few key examples.

History and Physical Examination

Revisiting the clinical history is often necessary after compiling a detailed pedigree. Multiple instances of SCD in the family of an index case with apparent dilated cardiomyopathy may instigate reinterrogation for palpitation and symptoms of impaired consciousness, which, if predominant, suggest an alternative diagnosis. The time course also is relevant: presentation with symptoms suggestive of arrhythmia, with eventual progression to left ventricular failure, is more typical of left-dominant or biventricular arrhythmogenic cardiomyopathy; in dilated cardiomyopathy heart failure is typically the first manifestation of the disease.45 The propensity to arrhythmia and SCD is also prominent in familial dilated cardiomyopathy with conduction system disease; any history of accompanying skeletal muscle weakness raises suspicion of Emery-Dreifuss muscular dystrophy, which may be transmitted as an autosomal dominant, recessive, or X-linked trait.46

Recurrent extracardiac abnormalities in relatives may point to an inherited multisystems disorder in spite of apparently isolated cardiovascular disease in the index case; confirmation warrants a careful review of systems in all family members to ensure early recognition of complications. The example shown in Figure 2 is that of Anderson-Fabry disease; the family history was the first clue to the diagnosis in an index case who presented with apparently uncomplicated left ventricular hypertrophy.

Suspicion of an inherited trait also merits vigilance for specific features on physical examination. Recurrent hyperlipidemia within the family may prompt the clinician to seek abdominal tenderness from pancreatitis, lipaemia retinalis, various types of xanthomata, xanthelasma, and arcus cornealis;
the presence of stigmata may give clues to the Fredrickson type before lipid subtraction analysis or genotyping can be conducted on all family members. Returning to the example of Anderson-Fabry disease, angiokeratoma may be the most visible early clinical feature, taking the form of a reddish purple maculopapular rash on abdomen, thighs, and hips; corneal opacities may also be detected by slit lamp examination.

Investigations and Diagnosis

Subsequent investigations will also need tailoring. Prospective assessment for dilated cardiomyopathy usually is confined to a 12-lead ECG and 2D-echocardiogram; ambulatory ECG monitoring is performed for risk prediction on diagnostic confirmation. If the family history is suggestive of left-dominant arrhythmogenic cardiomyopathy or dilated cardiomyopathy with conduction system disease, however, ambulatory ECG monitoring and exercise testing should be integral components of the screening work-up. Any hint of Anderson-Fabry disease in a pedigree from a family with apparent hypertrophic cardiomyopathy warrants assay of \( \alpha \)-galactosidase A activity in leukocytes, which (if low) is diagnostic in men. Although the disease is inherited as an X-linked recessive trait, women may be affected owing to random X-chromosome inactivation; their \( \alpha \)-galactosidase A activity may be normal, however, necessitating mutation screening of the \( GLA \) gene for confirmation.

A critical aspect of the diagnosis of Anderson-Fabry disease is the recognition that a single family member (particularly a woman) may not express the phenotype to an extent sufficient to arouse clinical suspicion. Diagnosis often requires recognition of a pattern within the extended family: the coexistence of apparently disparate abnormalities, such as nephropathy, ischemic cerebrovascular disease, progressive hearing loss and vestibular impairment, and even less well-known complications, such as osteoporosis and chronic cough and wheeze from respiratory involvement. This need to build up a composite familial phenotype is also inherent to the evaluation of the surviving relatives of sudden unexplained death victims. Postmortem examination of the index case has proved noncontributory, and family members often demonstrate ostensibly nonspecific abnormalities. The experienced clinician may, however, be able to discern a pattern from the findings in the extended family; for example, right precordial T-wave inversion in a parent, combined with arrhythmia of right ventricular origin in 1 or more siblings, raises suspicion of arrhythmogenic right ventricular cardiomyopathy, a disease commonly missed on autopsy.

Perhaps the most important impact of proven heredity is in lowering the threshold necessary for diagnosis of the trait in relatives. In the index case, a key challenge in establishing the diagnosis is the exclusion of phenocopies: nonhereditary states that mimic the genetically determined disease. The likelihood of disease in a relative is, however, manifold higher than the baseline prevalence in the general population, reducing, albeit not obviating, the need to exclude phenocopies. Furthermore, as previously discussed, the affected relatives of index cases with Mendelian disorders commonly show incomplete phenotypic expression; less stringent diagnostic criteria may be requisite for recognition of familial disease. The increased pretest probability, coupled with variable expressivity, is reflected by the provision of modified diagnostic guidelines for relatives in hypertrophic cardiomyopathy and a number of other inherited diseases.

Prognostication and Therapy

The role of heredity in prognostication and therapy is currently less well-defined. In hypertrophic cardiomyopathy, follow-up studies repeatedly have confirmed a family history...
of SCD as risk factor for events in the individual.\textsuperscript{52} Experience indicates that the predictive capacity of family history holds true for disease due to mutations in 3 out of 4 of the major genes: \textit{MYH7}, \textit{MYBPC3}, and \textit{TNNT2}. The exception is \textit{TNNT3} disease, which is characterized by markedly variable penetrance and expressivity in affected families.\textsuperscript{53} Knowledge of the mutation itself does not enhance the prognostic power above that of family history. In contrast, there is no evidence to support the use of family history as a prognostic indicator in arrhythmogenic cardiomyopathy.\textsuperscript{7} In dilated cardiomyopathy, its primary importance may be to identify the subset of families with associated conduction system disease and high arrhythmic risk, which can be verified by mutation screening of \textit{LMNA}, or emerin (\textit{EMD}) in families with \textit{X}-linked recessive Emery-Dreifuss muscular dystrophy.\textsuperscript{46} A similar scenario arises in long QT syndrome: the family history is useful chiefly as lead-in to genotyping. The trigger for events may provide a clue to the disease subtype (and hence the causal gene). The most well-known precipitants include swimming and diving for LQT1 (\textit{KCNQ1}), auditory stimuli for LQT2 (\textit{KCNH2}), and sleep for LQT3 (\textit{SCN5A}), underscoring the importance of determining the circumstances of any sudden deaths in the family.\textsuperscript{47,48} Regardless of whether the family history suggests a particular subtype, however, a definitive clinical diagnosis of long QT syndrome merits mutation screening of the main causal genes to enable predictive testing and guide treatment. Beta-blocker therapy, for example, is particularly efficacious in LQT1 patients, but perhaps less so in LQT2 and LQT3.\textsuperscript{47,54}

Although seldom factored into clinical decision making, heredity also influences risk and therapeutic response in common, complex diseases. The Paris Prospective Study included over 7000 men aged 43 to 52 years without a known history of ischemic heart disease, who were followed for an average of 23 years. Parental sudden death was associated with a relative risk of 1.8 for sudden death in the individual, after adjusting for confounders, including family history of myocardial infarction.\textsuperscript{55} The case-control AGNES study included individuals with and without ventricular fibrillation during the early phase of a first ST-elevation myocardial infarction; familial sudden death occurred significantly more frequently among cases than controls (43.1\% and 25.1\%, odds ratio 2.72).\textsuperscript{56} A replicated association was subsequently found between a common variant at 21q21 and ventricular fibrillation during acute myocardial infarction.\textsuperscript{57} Family history of SCD is, therefore, relevant not only in the identification of inherited arrhythmogenic disease, but also in the risk stratification of ischemic heart disease. In the therapeutic arena, hereditary factors in the form of common genetic variants have also been implicated in the risk of overanticoagulation and bleeding events from warfarin, and in the development of myopathy from statins.\textsuperscript{58,59}

**Public Health Promotion**

For inheritance to become a tool for preventive medicine at a population level, at least 3 conditions would have to be met. First, heredity would have to be a simple, inexpensive, and reliable risk factor for a substantial proportion of diseases of public health significance. The most obvious solution would be to employ family history as a surrogate for more definitive proofs of heredity, such as inheritance patterns or genotype. Accumulating evidence confirms that family history indicates susceptibility to a majority of common, chronic, or life-threatening diseases, including diabetes, asthma, osteoporosis, breast, prostate, or colorectal cancer, and melanoma.\textsuperscript{60} Second, the selected marker of heredity, in this case, family history, should not just identify a minority of high risk subjects, but stratify subjects into high, moderate, and average (general population level) risk categories. The predictive capacity of family history, in isolation, increases with the number of family members affected, with the proximity of the kinship to affected relatives, and by the prematurity of onset of the disease. Various scoring systems and risk classifications have been proposed that take these factors into account; the ideal tool would also be robust to family size and inflation by a single individual, and incorporate covariates such as age and sex.\textsuperscript{61}

Using a standardized quantitative family risk score, the degree of familial aggregation of ischemic heart disease, stroke, hypertension, and diabetes was obtained from \textgreater\ 120 000 families, chiefly from Utah. A positive family history of ischemic heart disease was present in only 14\% of the general population, but accounted for 72\% of premature cases and 48\% of cases at all ages. For cerebrovascular disease, 11\% of families with a positive risk score accounted for 86\% of early (<75 years) and 68\% of all strokes. The instrument used to collect family history showed 77\% sensitivity and 85\% specificity.\textsuperscript{60,62} Family history tools appear, therefore, to satisfy the criteria of feasibility, validity, and use.

The third requirement for an effective public health (or clinical) tool is tangible benefit to the subjects. Neither early prediction nor diagnosis is arguably of value unless effective strategies exist for prevention or intervention. Pervasive non-compliance with lifestyle advice, such as smoking cessation, suggests that knowledge of risk is frequently insufficient to modify behavior. The motivation to do so may, however, may be enhanced by the belief that change is both possible and salutary. Participation in screening programs for colorectal and breast cancer, for example, appears to be higher among individuals with a family history of the disease.\textsuperscript{60} Public health campaigns have been successful in areas ranging from cot death to skin cancer prevention; with increasing media attention and research focus on genetic discoveries, there has arguably never been a better time to highlight the importance of familial disease and its implications to both healthcare providers and consumers.\textsuperscript{53} Until comprehensive genomic profiling becomes scientifically achievable, commercially viable, and universally accessible, such time-honored surrogates for inheritance will retain their value in both clinical management and public health promotion.

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