Family history of premature coronary artery disease or myocardial infarction is often sought during the initial clinical encounter, but a definitive genetic diagnosis is rarely made. We review potential monogenic causes of coronary artery disease and explore the clinical genetics that might initiate molecular testing or specialist referral.

Coronary artery disease (CAD) and myocardial infarction (MI) are often viewed as prototypical complex genetic disorders. However, when the presentation occurs early in life or when the disease appears to segregate in families, it may be related to one of several Mendelian disorders with CAD or MI as part of the phenotypic expression. The most useful evaluation tool at present is a definitive, carefully curated family history focused on the identification of the limited number of testable genetic causes while avoiding additional testing for conditions with low pretest probability. Here we review the potential genetic causes to consider when assessing a patient with premature MI or CAD and outline recommendations for genetic testing or consideration of referral to a center specializing in cardiovascular genetics.

Typical Case

A 35-year-old man presents with crescendo angina culminating in rest pain with ECG changes in the precordial leads and associated biomarker abnormalities. He has no past medical history and has no risk factors for vascular or metabolic disease. His most recent fasting lipid panel was completely normal. An initial family history is notable for “heart” problems in his mother’s side of the family. At coronary angiography he is found to have a 95% stenosis of his proximal left anterior descending artery which is successfully treated by percutaneous coronary intervention including a drug-eluting stent. A subsequent detailed family history with objective confirmation reveals that his mother presented with an acute left anterior descending syndrome at the age of 42 and two of her male siblings underwent coronary revascularization before the age of 40. The patient’s maternal grandfather died suddenly of myocardial infarction at the age of 40. The patient’s maternal grandmother (individual I-2) who suffered an MI later in life, probably unrelated to the inherited cause in the family, had no history of premature CAD (many individuals in the population sharing these risk factors will not develop MI or CAD), the presentation here is likely multifactorial (ie, the culmination of genetic and nongenetic factors), reflecting the presence of shared genetic and environmental factors among family members. In addition, the clustering in such families does not typically fit a Mendelian pattern, but rather suggests a complex inheritance (ie, the phenotype may be under the influence of multiple causal genes), a substantial dependence on an environmental factor or factors (eg, tobacco), or even misdiagnosis of some of the pedigree members.

A discrete pattern of familial clustering is observed in the pedigree described in the introduction (Figure 1), with several notable features. Multiple family members are affected at a precocious age without the influence of traditional environmental risk factors, increasing the likelihood that a genetic factor of strong effect is influencing the inheritance of the trait. The specific pattern—both genders are affected from multiple generations and male-to-male transmission is observed—suggests autosomal dominant inheritance. We also see several common confounders typical of pedigrees with a strong history of MI/CAD. Phenocopies (the presence of the trait in an individual who has not inherited the causal allele) can be common given the high population prevalence of MI/CAD and the restricted biological resolution of the techniques used to diagnose MI/CAD. This is likely the case for the proband’s maternal grandmother (individual I-2) who suffered an MI later in life, probably unrelated to the inherited cause in the remainder of the family. Incomplete penetrance (an individual...
who has inherited the causal allele but does not manifest the trait) is also common because of the long subclinical course of atherosclerosis. For example, individual II-7 seems to be a nonpenetrant obligate carrier of the presumed inherited predisposition to MI/CAD given his affected son (individual III-4) but may have subclinical coronary atherosclerotic disease without manifest CAD symptoms. Incomplete history may also give the impression of incomplete penetrance (the proband’s maternal grandfather, individual I-1, is probably affected; however, a complete history is not accessible).

The overall degree to which heritable factors influence MI in the population has been estimated using epidemiological

Figure 1. Representative pedigree of a family demonstrating presumed Mendelian inheritance of myocardial infarction (MI). Squares indicate males, and circles indicate females. Shaded individuals are known to be affected with MI/coronary artery disease (CAD). The arrow indicates the proband in the family. Roman numerals on the left indicate generations. Identifiers, relevant medical history, and ages are listed below individuals. CVD indicates cardiovascular disease.

Figure 2. Representative pedigree of a family demonstrating presumed complex genetic inheritance of myocardial infarction (MI). Squares indicate males, and circles indicate females. Shaded individuals are known to be affected with MI/coronary artery disease; a question mark indicates unclear disease status. The arrow indicates the proband in the family. Roman numerals on the left indicate generations. Identifiers, relevant medical history, and ages are listed below individuals. ACS indicates acute coronary syndrome; DM, diabetes mellitus; HL, hyperlipidemia; and HTN, hypertension.
studies. The most conceptually straightforward of these types of studies is a twin study in which the concordance of disease is compared between monozygotic twins (siblings sharing 100% of their genetic material) and dizygotic twins (siblings sharing 50% of their genetic material on average). Because of a substantial environmental influence on the MI phenotype, dizygotic twins are used as a reference rather than nontwin full siblings to minimize the impact of environment on the phenotypic variance. Through various studies the heritability of MI has been estimated to be ≈50%, meaning that additive genetic variance explains roughly half of the phenotypic variability in the population. However, this may be an underestimate however, because of intrinsic study biases and incomplete ascertainment of cases. An early age at presentation is associated with higher heritability (≤63%), while certain patterns of disease are associated with lower heritability (distal coronary disease, in particular).

While informative from a population perspective, these heritability estimates say little about specific biology of individual cases or about the range of potential genes and genetic effect sizes that might act to generate the heritability observed in the disease. To gain insight into an individual’s risk (eg, family members of individuals with premature MI), we can turn to lessons learned through studying Mendelian disorders with MI or CAD as major or minor manifestations of the disease.

### Inherited Forms of Premature Atherosclerosis

Of the monogenic disorders with definitive evidence of MI or CAD as part of the phenotypic expression (see Table 1), many primarily affect plasma lipid levels reflecting the strong etiologic role of lipoprotein biology in the pathogenesis of MI and CAD. The most notable of these involve mutations in the gene encoding the low-density lipoprotein receptor (LDLR), first identified by Brown and Goldstein as they sought to discover the mechanism of familial hypercholesterolemia (FH). FH, a

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Associated Genes</th>
<th>Pattern of Inheritance</th>
<th>Association With CAD/MI</th>
<th>OMIM Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>LDLR, APOB, PCSK9</td>
<td>Autosomal dominant</td>
<td>Carriers at increased risk, typically related to magnitude of LDL-C level elevation</td>
<td>143890, 144010, 603776</td>
</tr>
<tr>
<td>Autosomal recessive hypercholesterolemia</td>
<td>LDLRAP1</td>
<td>Autosomal recessive</td>
<td>Similar to ADH</td>
<td>603813</td>
</tr>
<tr>
<td>Type III hyperlipoproteinemia (dysbetaIipoproteinemia)</td>
<td>APOE</td>
<td>Autosomal dominant, autosomal recessive</td>
<td>Elevated plasma cholesterol and triglyceride levels associated with xanthomas and premature CAD/MI</td>
<td>107741</td>
</tr>
<tr>
<td>Siosterolemia</td>
<td>ABCG5, ABCG8</td>
<td>Autosomal recessive</td>
<td>Similar to ADH however clinical manifestations unrelated to LDL-C levels</td>
<td>210250</td>
</tr>
<tr>
<td>Autosomal dominant coronary artery disease 2</td>
<td>LRP6</td>
<td>Autosomal dominant</td>
<td>Metabolic syndrome and premature coronary atherosclerosis reported</td>
<td>603507</td>
</tr>
<tr>
<td>Familial thoracic aortic aneurysm and dissection</td>
<td>ACTA2</td>
<td>Autosomal dominant</td>
<td>Premature vascular disease including CAD/MI, stroke, and Moyamoya disease</td>
<td>611788</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>CBS, MTHFR</td>
<td>Autosomal recessive</td>
<td>Premature coronary atherosclerosis</td>
<td>236200, 236250</td>
</tr>
<tr>
<td>Familial antiphospholipid antibody syndrome</td>
<td>Unknown</td>
<td>Multifactorial</td>
<td>Accelerated atherosclerosis and coronary thrombosis</td>
<td>107320</td>
</tr>
<tr>
<td>Pseudoxanthoma elasticum</td>
<td>ABCG6</td>
<td>Autosomal dominant, autosomal recessive</td>
<td>Coronary calcification and accelerated atherosclerosis</td>
<td>264800</td>
</tr>
<tr>
<td>Hutchison–Gifford progeria</td>
<td>LMNA</td>
<td>Dominant (typically caused by de novo mutations)</td>
<td>This premature aging syndrome includes accelerated atherosclerosis</td>
<td>176670</td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>RECQL2</td>
<td>Autosomal recessive</td>
<td>Similar phenotypic presentation to Hutchison–Gifford progeria</td>
<td>277700</td>
</tr>
<tr>
<td>Williams–Beuren syndrome</td>
<td>7q11 deletion</td>
<td>Autosomal recessive</td>
<td>Arterial stenosis</td>
<td>194050</td>
</tr>
<tr>
<td>Familial partial lipodystrophy 1</td>
<td>Unknown</td>
<td>Autosomal dominant</td>
<td>Lipodystrophy, insulin resistance, and vascular disease</td>
<td>608600</td>
</tr>
<tr>
<td>Familial partial lipodystrophy 2</td>
<td>1q21</td>
<td>Autosomal dominant</td>
<td>Lipodystrophy, insulin resistance, and vascular disease</td>
<td>151660</td>
</tr>
</tbody>
</table>

ADH indicates autosomal dominant hypercholesterolemia; CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and OMIM, Online Mendelian Inheritance in Man.
disorder characterized by high levels of low-density lipoprotein cholesterol (LDL-C), tendon xanthomas, corneal arcus at a young age, and premature CAD, is caused by mutations in LDLR leading to defective cellular uptake of low-density lipoprotein cholesterol. When homozygous FH is present (an individual who inherits 2 defective copies of the LDLR gene), CAD can even develop in early childhood or adolescence. As opposed to LDLR mutations, which typically exhibit incomplete dominance or codominance (the phenotype of the heterozygote individual is often intermediate between the 2 homozygote phenotypes), there are additional forms of hypercholesterolemia that exhibit true autosomal dominant or autosomal recessive patterns. Two defective copies of LDLRAP1 are needed to acquire autosomal recessive hypercholesterolemia, a disorder with similar characteristics to individuals carrying LDLR mutations. In contrast, only one gain-of-function mutation is needed in PCSK9 to cause FH (named as such because it was the third gene discovered to cause FH after LDLR and APOB). Sitosterolemia, a rare autosomal recessive disorder of plant sterol metabolism, presents with clinical features similar to FH including premature CAD and has been linked to mutations in both ABCG5 and ABCG8. There have been mixed results in definitively associating MI or CAD with Mendelian dyslipidemias primarily affecting lipoproteins that are not processed via the LDLR.

There have been several attempts to find a molecular basis for apparent Mendelian forms of pure CAD or MI. As one might imagine, such studies are difficult and likely to be confounded by both false-negative diagnoses (eg, family members with significant subclinical CAD labeled as unaffected) and phenocopies (eg, family members with MI because of other causes—such as heavy cigarette smokers—labeled as affected). The first of these studies identified MEF2A as the putative gene responsible for CAD or MI in a large family of 21 individuals (13 of whom were affected with CAD or MI). Linkage analysis assuming an autosomal dominant mode of transmission suggested that the causal gene was located in a region containing 93 genes at chromosome 15q26. Further analysis identified a 21-base pair in-frame deletion in MEF2A that appeared to segregate with disease in this family. When additional sequencing was performed in an independent cohort, however, the same 21-bp deletion (in addition to other mutations) in MEF2A failed to segregate with disease, suggesting that this gene does not play a causal role in CAD/MI. Linkage analysis was successful in another family with apparent autosomal dominant inheritance of premature CAD/MI and metabolic syndrome. The investigators subsequently identified LRP6 (LDLR-related protein 6) as the putative causal gene. This gene seems to be a rare cause of CAD and metabolic syndrome.

**Inherited Vasculopathies**

There are several inherited disorders without a primary defect in lipid metabolism but with CAD/MI as part of the clinical presentation. Williams–Beuren syndrome (also called Williams syndrome) is a rare disorder caused by a hemizygous deletion in a region of chromosome 7q11.23. Initially characterized as the combination of supravalvular aortic stenosis, mental retardation, and characteristic facies, the phenotypic manifestations can involve multiple organ systems. The vascular complications of Williams–Beuren syndrome typically present as stenoses in large- or medium-sized arteries, however, there have been reports of coronary involvement leading to premature CAD/MI. Fibromuscular dysplasia is another vascular disorder that can affect the coronary arteries as well as other mid-sized arteries. More common in women than in men, the disorder is often readily recognized on angiography and can occasionally segregate as an autosomal dominant trait. Mutations in ACTA2, known to cause familial thoracic aortic aneurysms and dissections, have also been associated with a variety of vascular disorders including premature CAD, stroke, and Moyamoya disease. Families with ACTA2 mutations display incomplete penetrance (only half of ACTA2 mutation carriers will develop aortic disease, and other vascular complications are also incompletely penetrant) and striking phenotypic heterogeneity (one family member may exhibit aortic dissection, while another develops CAD, and a third develops stroke). CAD was previously reported to be associated with other vascular dysplastic syndromes including disorders on the aortic coarctation spectrum. However, more recent data do not clearly support such an association. Heterogeneity of the underlying disorders is a significant confounder for such studies, and ultimately a molecular taxonomy of vasculopathies will help to resolve these discrepancies.

In classic homocystinuria, homozygous or compound heterozygous (an individual inheriting 2 independent loss-of-function mutations in the same gene) mutations in cystathionine β-synthase lead to defects in sulfur metabolism. These mutations, inherited in an autosomal recessive fashion, lead to mental retardation, ectopic lentis (and other Marfanoid characteristics), as well as thrombosis, including MI. In addition to cystathionine β-synthase, homocystinuria is also caused by recessive inheritance of mutations in the MTHFR gene. Pseudoxanthoma elasticum is a multisystem disorder characterized by connective tissue calcification, affecting elastic tissue in the arterial media, dermis, and Bruch’s membrane in the eye. Patients often present with pseudoxanthomas, the classic cutaneous finding of multiple small yellow–orange papules in the axilla, neck, flank, or abdomen, often described as looking like chicken skin. Arterial complications can precede epidermal changes, however, and include accelerated atherosclerosis because of calcific deposition in the internal elastic lamina. Any arterial bed, including the coronary circulation, can be involved. Pseudoxanthoma elasticum is caused by mutations in the ABCC6 gene and has been described with both recessive and dominant patterns of inheritance.

**Inherited Aneurysmal Disorders**

Kawasaki disease (KD), a childhood febrile mucocutaneous syndrome, can involve the coronary arteries, characteristically leading to coronary aneurysms. Although the majority of these will spontaneously resolve, some will persist as aneurysms, while others will progress to develop coronary stenosis with or without MI. A genetic contribution to KD is just beginning to be uncovered with the reports of several common DNA variants associated with modestly increased risk of KD. There are rare reports of familial forms of KD although the genetic basis of these has been difficult to decipher in the context of a possible unidentified infectious agent. In addition, many KD cases are...
Inherited Coagulopathies

Several hypercoagulable states are heritable, and the spectrum of arterial thrombosis is often raised to explain unusual presentations of MI. However, most of these conditions are not associated with CAD or MI. The most common heritable hypercoagulable syndromes involve mutations in the genes encoding factor V (the most prevalent form of heritable thrombophilia is the factor V Leiden mutation, carried by 3% to 5% of the population), antithrombin, prothrombin (including G20210A, carried by 2% to 3% of the population), and proteins C and S. While carriers of these mutations have varied risk of venous thromboembolism, these are not clearly linked to arterial thrombosis or MI. Antiphospholipid syndrome, in contrast, is associated with both venous and arterial thrombosis and can present with acute MI because of in situ coronary thrombosis. In addition, there is evidence that antiphospholipid syndrome itself can accelerate the development of coronary atherosclerosis. There is a familial form of antiphospholipid syndrome (Online Mendelian Inheritance in Man 107320) although the genetic basis of this form is unknown. Inherited dysfibrinogenemia along with other congenital bleeding disorders are reported to be rare causes of arterial thrombosis and MI.

Complex Inheritance of CAD and MI

Starting with the identification of an association between a common variant on chromosome 9p21 and MI/CAD, genome-wide association studies have successfully identified over 45 loci associated with the risk of MI/CAD. In both case–control and prospective population-based cohort studies, increasing numbers of risk alleles are associated with increasing odds of developing disease, consistent with a polygenic model where disease is a consequence of inheritance at many loci, each contributing a modest effect on phenotype. It is possible that families with an unusually strong clustering of MI/CAD have a large proportion of these common risk alleles, but this has not been formally studied. Other complex disorders also influence the risk of CAD and MI. There have been ≥157 genetic loci associated with lipid traits, and several of these are associated with increased risk of CAD or MI.

Approach to the Patient With Premature MI/CAD

As with any medical evaluation, the approach to the patient with premature MI or CAD begins with a careful history and physical examination (Table 2). Unlike most evaluations, however, in which questions regarding family history are often grouped

<table>
<thead>
<tr>
<th>Category</th>
<th>Test</th>
<th>Indication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evaluation</td>
<td>History</td>
<td>Define history, risk factors, and associated</td>
<td>Define age at onset, associated signs, and symptoms that may suggest a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phenotypes</td>
<td>genetic or an environmental cause</td>
</tr>
<tr>
<td></td>
<td>Family history</td>
<td>Define affected individuals to determine likely</td>
<td>A detailed 4-generation pedigree should be obtained when possible. Given</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mode of inheritance. Define vital status (living</td>
<td>a wide variety of events labeled heart attack by families, primary data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or deceased), age (or age at death), age at MI/</td>
<td>review when possible is essential for accurate phenotyping in the kindred</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAD, objective testing results (both affected and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>unaffected), and presence of risk factors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical examination</td>
<td>Evaluate for stigmata of Mendelian disorders</td>
<td>When evaluating unaffected family members, evaluation for stigmata of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>such as those listed in Table 1</td>
<td>peripheral vascular disease can be useful as CAD may be subclinical</td>
</tr>
<tr>
<td>Laboratory evaluation</td>
<td>Cholesterol panel</td>
<td>Evaluate for hypercholesterolemia, a leading</td>
<td>Although a strong risk factor, almost half of the premature MI cases may</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cause of premature MI/CAD</td>
<td>have normal cholesterol levels</td>
</tr>
<tr>
<td></td>
<td>Metabolic profile,</td>
<td>Evaluate for secondary causes of dyslipidemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>urinalysis, thyroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>function</td>
<td>Consider with history of recurrent thrombosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Homocysteine level</td>
<td>Consider with history of recurrent thrombosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antiphospholipid antibodies</td>
<td>(can be both venous and arterial)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plant sterols</td>
<td>Clinical suspicion of familial hypercholesterolemia with normal plasma cholesterol levels</td>
<td>Individuals with sitosterolemia will have elevated campesterol levels</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>Single-gene testing</td>
<td>High clinical suspicion for a Mendelian disorder</td>
<td>Referral to cardiovascular genetics specialist recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td>listed in Table 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genomic sequencing in</td>
<td>Strong family history, minimal risk factors, and</td>
<td>Consider referral for research-based genomic sequencing</td>
</tr>
<tr>
<td></td>
<td>experienced center</td>
<td>lack of definitive diagnosis based on above</td>
<td></td>
</tr>
</tbody>
</table>
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