Genetics and preventive health care

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BACKGROUND
Advances in our understanding of the genetics of common chronic disease is beginning to impact on clinical practice and preventive health care.

OBJECTIVE
This article discusses the potential for genetic medicine to inform disease prevention strategies. It describes two examples already affecting clinical general practice: familial hypercholesterolaemia and hereditary haemochromatosis. These represent important inherited conditions that, if diagnosed early, can be simply treated and their complications avoided.

DISCUSSION
General practitioners can play an important role in the early diagnosis of these conditions and subsequent screening of at risk relatives. These conditions highlight the potential for genetic medicine to be applied to support tailored disease prevention in general practice.

With the mapping and sequencing of the human genome, knowledge about the genetics of common chronic diseases is growing rapidly. While the 'genetics revolution' still has some time before it has widespread impact on clinical practice, there are several examples of how the application of new genetic knowledge may play a significant role in preventive health care. Perhaps the earliest examples have come from the discovery of genes that predispose to certain cancers.[1,2] In this article we discuss two specific conditions that demonstrate the role of genetic medicine in chronic disease prevention: familial hypercholesterolaemia (FH) and hereditary haemochromatosis (HH).[3] The article is based on sections from *Genetics in family medicine: the Australian handbook for general practitioners*.[3]

Familial hypercholesterolaemia

Familial hypercholesterolaemia is due to an inherited susceptibility to high levels of low density lipoprotein (LDL) cholesterol. Other environmental factors such as lifestyle and diet associated with coronary heart disease (CHD) must also be present for the condition to develop.[4,5]

High LDL generally follows a pattern of autosomal dominant inheritance with an ~50% risk for offspring and siblings of affected family members. Familial hypercholesterolaemia is caused by mutations in one of a number of genes that code for the LDL receptor (LDLR), the LDL ligand or a protease known as NARC-1. To date, about 1000 mutations have been identified in the LDLR gene. However, most are family specific, which makes the search for an unknown mutation challenging and expensive. Homozygotes typically have higher levels of LDL and a more severe phenotype than heterozygotes. A mutation in the apolipoprotein B gene (APOB) may result in a clinical and biochemical picture that is indistinguishable from classic FH, although cholesterol levels are generally not as elevated and tendon xanthomas are less common.

Familial hypercholesterolaemia is thought to account for 5–10% of CHD in patients less than 55 years of age.[4] It is estimated that, of the roughly 40 000 cases of FH in Australia, about 20% are diagnosed and less than 10% are adequately treated. In the general population, frequency of FH heterozygosity for a mutation in one of the genes involved is about one in 500, while the homozygous state is exceedingly rare (~1/1 million). Familial hypercholesterolaemia is more common in those with Christian Lebanese (1/170), Afrikaaner (1/70–100) and French Canadian (1/200) ancestries.[5,6]

Clinical features

Affected individuals suffer metabolic and clinical features including:

- lifelong marked hypercholesterolaemia (LDL cholesterol >5 mmol/L)
- cholesterol deposition in tissues causing: corneal arcus, palpebral xanthomas and xanthelasma, and tendinous xanthomata (particularly involving the Achilles) (*Figure 1a–c*), and
- atherosclerosis beginning in early childhood at a rate proportional to plasma LDL cholesterol levels.

Diagnosis

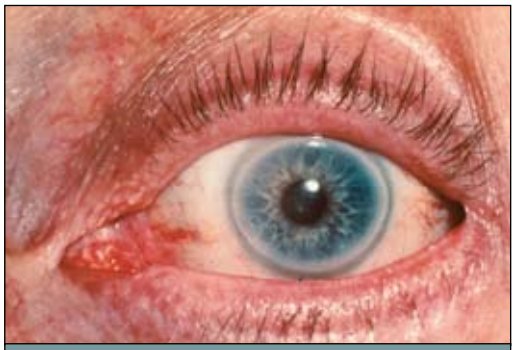
Clinical diagnosis of FH is made by applying diagnostic criteria based on:

- personal and family history of early onset CHD
- abnormal lipids
- tendon xanthomas, and in specific cases
- the existence of a known mutation (*Table 1*).

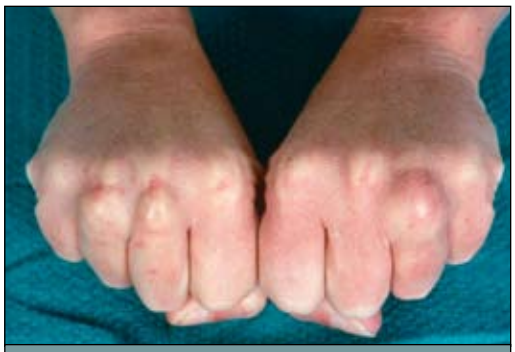
In general practice, this highlights the importance of identifying patients with a family history of premature CHD, determining their lipid profile and examining for clinical features. Those meeting diagnostic criteria, including 'possible FH' should be offered referral to a specialist lipid clinic, cardiologist or combined cardiology/genetics clinic.

Without treatment, 50% of heterozygous males will develop CHD before the age of 50 years and 100% by the age of 70 years.[7] Approximately 12% of heterozygous females will have CHD by the age of 50 years, increasing to 74% by age 70 years.[7] Rigorous management of all cardiovascular risk factors with statins, lifestyle management and other pharmacological interventions where indicated (eg. for hypertension or diabetes), significantly reduces cardiovascular morbidity and mortality in FH.[7] In the rare homozygous form of FH, drugs are less effective and FH is typically lethal at an early age without special intervention such as LDL aphaeresis and liver transplantation.[4]

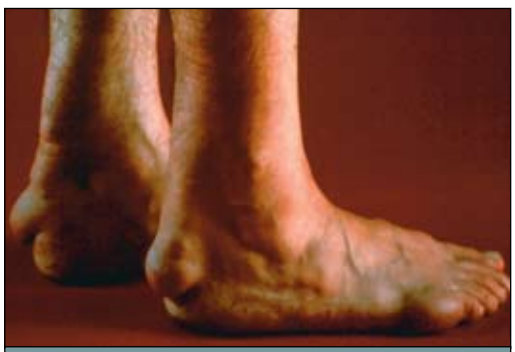
Molecular genetic testing has a role in confirming diagnosis, particularly in those with high prevalence ancestry such as Afrikaaner in whom specific 'founder mutations' in the LDLR gene can be more easily identified. Regardless of whether the diagnosis of FH is based on phenotypic features or the result of molecular genetic testing, it is important to discuss with the patient the need for cascade testing of all first degree relatives. All first degree relatives of an individual with definite FH are at 50% risk of inheriting FH and should be offered clinical examination and lipid screening to determine FH status, applying the same diagnostic criteria as previously discussed. Children of an affected parent should be screened and, where appropriate, genetic testing discussed, as a normal lipid profile does not necessarily rule out carrier status for an FH causing gene mutation. Children with FH should be placed on a cholesterol lowering diet and advised strongly against smoking. Statin therapy is only used in children from severely affected families.[5] Cascade screening of all first degree relatives has been shown to be a cost effective strategy for reducing cardiovascular disease due to FH and is currently being established in some Australian states.[7] General practitioners should consider FH in those with a personal or family history of premature CHD, and those with very high LDL or total cholesterol.[8]



1a. Corneal arcus



1b. Extensor tendon xanthomata



1c. Achilles tendon xanthomata

Figure 1a-c. Clinical signs of familial hypercholesterolaemia

Table 1. Diagnostic criteria for familial hypercholesterolaemia

a. DNA mutation
b. Tendon xanthomas in patient or first/second degree relative
c. Family history CHD <50 years of age in second degree relative or <60 years of age in first degree relative
d. Family history of cholesterol >7.5 in first or second degree relative
e. Cholesterol >7.5 (adult) or >6.7 (age <16 years)
f. LDL-C >4.9 (adult) or >4.0 (age <16 years)

Diagnosis	Combinations of criteria as described above
Definite FH	(e or f) + a
Probable FH	(e or f) + b
Possible FH	(e or f) + (c or d)

Table 2. Frequency of HFE genotypes in the Australian population

HFE genotype	Frequency
No gene mutation found	2/3
Homozygous C282Y	1/200
Compound heterozygote (C282Y/H63D)	1/50
Heterozygous C282Y	1/10
Heterozygous H63D	1/6
Homozygous H63D	1/100

Table 3. Clinical features and complications of HH

Common clinical features	Complications
• Lethargy and weakness	• Hepatic fibrosis or cirrhosis
• Arthralgia	• Arthritis/osteophytosis at the metacarpal heads (particularly second and third MCP joints)
• Loss of libido	• Impotence
• Upper abdominal discomfort	• Diabetes mellitus
• Hepatomegaly	• Cardiomyopathy and arrhythmias
• Grey/bronze skin pigmentation	• Hepatocellular carcinoma (~30% of patients with cirrhosis)
• Testicular atrophy	
• Joint swelling/tenderness	

Table 4. Response of different features of HH to venesection

Symptom	Good	Variable	Poor
Fatigue	*		
Skin pigmentation	*		
Abdominal pain	*		
Cardiomyopathy		*	
Diabetes		*	
Hypogonadism		*	
Hepatic fibrosis			*
Arthropathy			*
Cirrhosis			*

Hereditary haemochromatosis

Hereditary haemochromatosis is a common condition in which excessive iron absorption leads to greatly increased body iron stores. The deposition of iron occurs in parenchymal cells of the liver, heart, pancreas and other organs.[9]

The most common form of HH is due to mutations in the HFE gene. Frequency of HFE genotypes in the Australian population are shown in *Table 2*.[10] Hereditary haemochromatosis is most prevalent in those of northern European ancestry: 90% of those with HH are homozygous for the C282Y mutation in the HFE gene; and ~2% have a C282Y gene mutation in one copy of the HFE gene and an H63D gene mutation in the other copy (compound heterozygotes).[10] Hereditary haemochromatosis follows an autosomal recessive pattern of inheritance so there is often no family history of the condition.

Clinical features

In the majority of patients with overt HH, the first symptoms develop at around 30–60 years of age. Menstruation and pregnancy account for delayed presentation in women. Common clinical features and the complications of HH are listed in *Table 3*.

Diagnosis

Some early symptoms are common and relatively nonspecific, therefore HH should be considered, particularly in those with clusters of these symptoms and/or signs. Liver function tests are frequently normal in asymptomatic patients, but may be abnormal in symptomatic patients. If there is no relevant family history but HH is suspected, the most useful initial laboratory tests are fasting transferrin saturation and serum ferritin. A fasting transferrin saturation >45% is the most sensitive test for detecting early iron overload, but a raised fasting transferrin saturation or ferritin is not diagnostic of HH. Hereditary haemochromatosis is unlikely if the ferritin is very high and the transferrin saturation is normal. If the fasting transferrin saturation or serum ferritin is increased on more than one occasion, HH should be suspected, even if there are no clinical symptoms or abnormal liver function tests.[9] In this situation, the HFE gene test should be ordered.

If the HFE gene test shows a patient to be a C282Y homozygote and iron overload is present or the patient has other complications of HH, lifelong venesection will be required. An initial course of 1–2 venesections per week is performed until iron levels return to normal; venesection is then necessary every 3–4 months. Patients should be advised to limit their red meat intake, avoid vitamin C

supplements, and abstain from alcohol until iron levels are normalised. The response to venesection treatment depends on the presenting symptoms and the stage of the condition at the time of diagnosis (*Table 4*). Noncirrhotic patients diagnosed and treated early have a normal life expectancy provided they continue venesection.[11] Patients with cirrhosis at diagnosis are at increased risk of hepatocellular cancer even when complete iron depletion is achieved. These patients should be screened every 6 months with hepatic ultrasound and serum α-fetoprotein levels.[9]

Hereditary haemochromatosis is a treatable condition if diagnosed early. First degree relatives, in particular siblings and children of affected individuals, should be offered HFE testing, available through the Medicare Benefits Schedule.[12] Although still the subject of some uncertainty, it is estimated that 60–70% of C282Y homozygotes will develop iron overload during their lifetime.[12] In contrast, compound heterozygotes have a ~1% lifetime risk of developing HH. Both C282Y homozygotes and compound heterozygotes require regular follow up of iron status to identify early signs of iron overload.[12]

The role of general population screening for HH is still a matter of debate, principally due to uncertainty about the natural history of genotypes associated with HH.[13] For example, it is unclear what proportion of the general population who are C282Y homozygotes will develop significant clinical disease if left untreated. A large Australian study of population screening in a workplace setting demonstrated that screening for HH using HFE testing was acceptable and feasible.[14] Ninety-six percent of those offered screening agreed to the test and, of the 47 C282Y homozygotes identified (0.42% of population screened), 30 had raised serum transferrin levels and were subsequently managed through further assessment and venesection.

Conclusion

Familial hypercholesterolaemia and HH represent two relatively common inherited conditions that cause significant morbidity and mortality. General practitioners can play an important role in the diagnosis of these conditions and subsequent screening of at risk relatives. These conditions highlight the potential for genetic medicine to be applied to support tailored disease prevention in general practice.

Conflict of interest: none declared.

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