= Familial hypercholesterolemia =

Familial hypercholesterolemia (abbreviated FH , also spelled familial hypercholesterolaemia) is a genetic disorder characterized by high cholesterol levels , specifically very high levels of low @-@ density lipoprotein (LDL , " bad cholesterol ") , in the blood and early cardiovascular disease . Since individuals with FH underlying body biochemistry is slightly different , their high cholesterol levels are less responsive to the kinds of cholesterol control methods which are usually more effective in people without FH (such as dietary modification and statin tablets) . Nevertheless , treatment (including higher statin doses) is usually effective .

Many people have mutations in the LDLR gene that encodes the LDL receptor protein , which normally removes LDL from the circulation , or apolipoprotein B (ApoB) , which is the part of LDL that binds with the receptor ; mutations in other genes are rare . People who have one abnormal copy (are heterozygous) of the LDLR gene may develop cardiovascular disease prematurely at the age of 30 to 40 . Having two abnormal copies (being homozygous) may cause severe cardiovascular disease in childhood . Heterozygous FH is a common genetic disorder , inherited in an autosomal dominant pattern , occurring in 1 : 500 people in most countries ; homozygous FH is much rarer , occurring in 1 in a million births .

Heterozygous FH is normally treated with statins , bile acid sequestrants , or other lipid lowering agents that lower cholesterol levels . New cases are generally offered genetic counseling . Homozygous FH often does not respond to medical therapy and may require other treatments , including LDL apheresis (removal of LDL in a method similar to dialysis) and occasionally liver transplantation .

= = Signs and symptoms = =

= = = Physical signs = = =

High cholesterol levels normally do not cause any symptoms . Yellow deposits of cholesterol @-@ rich fat may be seen in various places on the body such as around the eyelids (known as xanthelasma palpebrarum) , the outer margin of the iris (known as arcus senilis corneae) , and in the tendons of the hands , elbows , knees and feet , particularly the Achilles tendon (known as a tendon xanthoma) .

= = = Cardiovascular disease = = =

Accelerated deposition of cholesterol in the walls of arteries leads to atherosclerosis , the underlying cause of cardiovascular disease . The most common problem in FH is the development of coronary artery disease (atherosclerosis of the coronary arteries that supply the heart) at a much younger age than would be expected in the general population . This may lead to angina pectoris (chest pain or tightness on exertion) or heart attacks . Less commonly , arteries of the brain are affected ; this may lead to transient ischemic attacks (brief episodes of weakness on one side of the body or inability to talk) or occasionally stroke . Peripheral artery occlusive disease (obstruction of the arteries of the legs) occurs mainly in people with FH who smoke ; this can cause pain in the calf muscles during walking that resolves with rest (intermittent claudication) and problems due to a decreased blood supply to the feet (such as gangrene) . Atherosclerosis risk is increased further with age and in those who smoke , have diabetes , high blood pressure and a family history of cardiovascular disease .

= = Diagnosis = =

Approximately 85 % of individuals with this disorder have not been diagnosed and consequently are not receiving lipid @-@ lowering treatments . Physical examination findings can help a physician

make the diagnosis of FH . Tendon xanthomas are seen in 20 @-@ 40 % of individuals with FH and are pathognomonic for the condition . A xanthelasma or corneal arcus may also be seen . These common signs are supportive of the diagnosis , but are non @-@ specific findings .

= = = Lipid measurements = = =

Cholesterol levels may be determined as part of health screening for health insurance or occupational health , when the external physical signs such as xanthelasma , xanthoma , arcus are noticed , symptoms of cardiovascular disease develop , or a family member has been found to have FH . A pattern compatible with hyperlipoproteinemia type IIa on the Fredrickson classification is typically found : raised level of total cholesterol , markedly raised level of low @-@ density lipoprotein (LDL) , normal level of high @-@ density lipoprotein (HDL) , and normal level of triglycerides . Total cholesterol levels of 350 ? 550 mg / dL are typical of heterozygous FH while total cholesterol levels of 650 ? 1000 mg / dL are typical of homozygous FH . The LDL is typically above the 75th percentile , that is , 75 % of the healthy population would have a lower LDL level . Cholesterol levels can be drastically higher in people with FH who are also obese .

= = = Mutation analysis = = =

On the basis of the isolated high LDL and clinical criteria (which differ by country) , genetic testing for LDL receptor mutations and ApoB mutations can be performed . Mutations are detected in between 50 and 80 % of cases ; those without a mutation often have higher triglyceride levels and may in fact have other causes for their high cholesterol , such as combined hyperlipidemia due to metabolic syndrome .

= = = Differential diagnosis = = =

FH needs to be distinguished from familial combined hyperlipidemia and polygenic hypercholesterolemia . Lipid levels and the presence of xanthomata can confirm the diagnosis . Sitosterolemia and cerebrotendineous xanthomatosis are two rare conditions that can also present with premature atherosclerosis and xanthomas . The latter condition can also involve neurological or psychiatric manifestations , cataracts , diarrhea and skeletal abnormalities .

= = Genetics = =

The most common genetic defects in FH are LDLR mutations (prevalence 1 in 500 , depending on the population) , ApoB mutations (prevalence 1 in 1000) , PCSK9 mutations (less than 1 in 2500) and LDLRAP1 . The related disease sitosterolemia , which has many similarities with FH and also features cholesterol accumulation in tissues , is due to ABCG5 and ABCG8 mutations .

= = = LDL receptor = = =

The LDL receptor gene is located on the short arm of chromosome 19 (19p13.1 @-@ 13 @.@ 3) . It comprises 18 exons and spans 45 kb , and the protein gene product contains 839 amino acids in mature form . A single abnormal copy (heterozygote) of FH causes cardiovascular disease by the age of 50 in about 40 % of cases . Having two abnormal copies (homozygote) causes accelerated atherosclerosis in childhood , including its complications . The plasma LDL levels are inversely related to the activity of LDL receptor (LDLR) . Homozygotes have LDLR activity of less than 2 % , while heterozygotes have defective LDL processing with receptor activity being 2 ? 25 % , depending on the nature of the mutation . Over 1000 different mutations are known .

There are five major classes of FH due to LDLR mutations :

Class I : LDLR is not synthesized at all .

Class II : LDLR is not properly transported from the endoplasmic reticulum to the Golgi apparatus

for expression on the cell surface .
Class III : LDLR does not properly bind LDL on the cell surface because of a defect in either apolipoprotein B100 (R3500Q) or in LDL @-@ R.
Class IV : LDLR bound to LDL does not properly cluster in clathrin @-@ coated pits for receptor @-@ mediated endocytosis (pathway step 2) .
Class V : LDLR is not recycled back to the cell surface (pathway step 5) .

= = = Apolipoprotein B = = =

Apolipoprotein B , in its ApoB100 form , is the main apolipoprotein , or protein part of the lipoprotein particle . Its gene is located on the second chromosome (2p24 @-@ p23) and is between 21 @.@ 08 and 21 @.@ 12 Mb long . FH is often associated with the mutation of R3500Q , which causes replacement of arginine by glutamine at position 3500 . The mutation is located on a part of the protein that normally binds with the LDL receptor , and binding is reduced as a result of the mutation . Like LDLR , the number of abnormal copies determines the severity of the hypercholesterolemia .

= = = PCSK9 = = =

Mutations in the proprotein convertase subtilisin / kexin type 9 (PCSK9) gene were linked to autosomal dominant (i.e. requiring only one abnormal copy) FH in a 2003 report . The gene is located on the first chromosome (1p34.1 @-@ p32) and encodes a 666 amino acid protein that is expressed in the liver . It has been suggested that PCSK9 causes FH mainly by reducing the number of LDL receptors on liver cells .

= = = LDLRAP1 = = =

Abnormalities in the ARH gene , also known as LDLRAP1 , were first reported in a family in 1973 . In contrast to the other causes , two abnormal copies of the gene are required for FH to develop (autosomal recessive) . The mutations in the protein tend to cause the production of a shortened protein . Its real function is unclear , but it seems to play a role in the relation between the LDL receptor and clathrin @-@ coated pits . People with autosomal recessive hypercholesterolemia tend to have more severe disease than LDLR @-@ heterozygotes but less severe than LDLR @-@ homozygotes .

= = Pathophysiology = =

LDL cholesterol normally circulates in the body for 2 @.@ 5 days , and subsequently the apolipoprotein B portion of LDL cholesterol binds to the LDL receptor on the liver cells , triggering its uptake and digestion . This process results in the removal of LDL from the circulatory system . Synthesis of cholesterol by the liver is suppressed in the HMG @-@ CoA reductase pathway . In FH , LDL receptor function is reduced or absent , and LDL circulates for an average duration of 4 @.@ 5 days , resulting in significantly increased level of LDL cholesterol in the blood with normal levels of other lipoproteins . In mutations of ApoB , reduced binding of LDL particles to the receptor causes the increased level of LDL cholesterol . It is not known how the mutation causes LDL receptor dysfunction in mutations of PCSK9 and ARH .
Although atherosclerosis occurs to a certain degree in all people , people with FH may develop accelerated atherosclerosis due to the excess level of LDL . The degree of atherosclerosis approximately depends on the number of LDL receptors still expressed and the functionality of these receptors . In many heterozygous forms of FH , the receptor function is only mildly impaired , and LDL levels will remain relatively low . In the more serious homozygous forms , the receptor is not expressed at all .
Some studies of FH cohorts suggest that additional risk factors are generally at play when a person develops atherosclerosis . In addition to the classic risk factors such as smoking , high blood

pressure , and diabetes , genetic studies have shown that a common abnormality in the prothrombin gene (G20210A) increases the risk of cardiovascular events in people with FH . Several studies found that a high level of lipoprotein (a) was an additional risk factor for ischemic heart disease . The risk was also found to be higher in people with a specific genotype of the angiotensin @-@ converting enzyme (ACE) .

= = Screening = =

Screening among family members of people with known FH is cost @-@ effective . Other strategies such as universal screening at the age of 16 have also been suggested . The latter approach may however be less cost @-@ effective in the short term . Screening at an age lower than 16 would lead to an unacceptably high rate of false positives .

A 2007 meta analysis found that , " The proposed strategy of screening children and parents for familial hypercholesterolaemia could have considerable impact in preventing the medical consequences of this disorder in two generations simultaneously . " " The use of total cholesterol alone may best discriminate between people with and without FH between the ages of 1 to 9 years . "

= = Treatment = =

= = = Heterozygous FH = = =

FH is usually treated with statins . Statins act by inhibiting the enzyme hydroxymethylglutaryl CoA reductase (HMG @-@ CoA @-@ reductase) in the liver . In response , the liver produces more LDL receptors , which remove circulating LDL from the blood . Statins effectively lower cholesterol and LDL levels , although sometimes add @-@ on therapy with other drugs is required , such as bile acid sequestrants (cholestyramine or colestipol) , nicotinic acid preparations or fibrates . Control of other risk factors for cardiovascular disease is required , as risk remains somewhat elevated even when cholesterol levels are controlled . Professional guidelines recommend that the decision to treat a person with FH with statins should not be based on the usual risk prediction tools (such as those derived from the Framingham Heart Study) , as they are likely to underestimate the risk of cardiovascular disease ; unlike the rest of the population , FH have had high levels of cholesterol since birth , probably increasing their relative risk . Prior to the introduction of the statins , clofibrate (an older fibrate that often caused gallstones) , probucol (especially in large xanthomas) and thyroxine were used to reduce LDL cholesterol levels .

More controversial is the addition of ezetimibe , which inhibits cholesterol absorption in the gut . While it reduces LDL cholesterol , it does not appear to improve a marker of atherosclerosis called the intima @-@ media thickness . Whether this means that ezetimibe is of no overall benefit in FH is unknown .

There are no interventional studies that directly show mortality benefit of cholesterol lowering in FH . Rather , evidence of benefit is derived from a number of trials conducted in people who have polygenic hypercholesterolemia (in which heredity plays a smaller role) . Still , a 1999 observational study of a large British registry showed that mortality in people with FH had started to improve in the early 1990s when statins were introduced .

A cohort study suggested that treatment of FH with statins leads to a 48 % reduction in death from coronary heart disease to a point where people are no more likely to die of coronary heart disease than the general population . However , if the person already had coronary heart disease the reduction was 25 % . The results emphasize the importance of early identification of FH and treatment with statins .

Alirocumab and evolocumab , both monoclonal antibodies against PCSK9 , are specifically indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia , who require additional lowering of LDL cholesterol .

= = = Homozygous FH = = =

Homozygous FH is harder to treat . The LDL receptors are minimally functional , if at all . Only high doses of statins , often in combination with other medications , are modestly effective in improving lipid levels . If medical therapy is not successful at reducing cholesterol levels , LDL apheresis may be used ; this filters LDL from the bloodstream in a process reminiscent of dialysis . Very severe cases may be considered for a liver transplant ; this provides a liver with normally functional LDL receptors , and leads to rapid improvement of the cholesterol levels , but at the risk of complications from any solid organ transplant (such as rejection , infections , or side @-@ effects of the medication required to suppress rejection) . Other surgical techniques include partial ileal bypass surgery , in which part of the small bowel is bypassed to decrease the absorption of nutrients and hence cholesterol , and portacaval shunt surgery , in which the portal vein is connected to the vena cava to allow blood with nutrients from the intestine to bypass the liver .

Lomitapide , an inhibitor of the microsomal triglyceride transfer protein , was approved by the US FDA in December 2012 as an orphan drug for the treatment of homozygous familial hypercholesterolemia . In January 2013 , The US FDA also approved mipomersen , which inhibits the action of the gene apolipoprotein B , for the treatment of homozygous familial hypercholesterolemia . Gene therapy is a possible future alternative .

= = = Children = = =

Given that FH is present from birth and atherosclerotic changes may begin early in life , it is sometimes necessary to treat adolescents or even teenagers with agents that were originally developed for adults . Due to safety concerns , many physicians prefer to use bile acid sequestrants and fenofibrate as these are licensed in children . Nevertheless , statins seem safe and effective , and in older children may be used as in adults .

An expert panel in 2006 advised on early combination therapy with LDL apheresis , statins and cholesterol absorption inhibitors in children with homozygous FH at the highest risk .

= = Epidemiology = =

The global prevalence of FH is approximately 10 million people . In most populations studied , heterozygous FH occurs in about 1 : 500 people , but not all develop symptoms . Homozygous FH occurs in about 1 : 1 @,@ 000 @,@ 000 .

LDLR mutations are more common in certain populations , presumably because of a genetic phenomenon known as the founder effect ? they were founded by a small group of individuals , one or several of whom was a carrier of the mutation . The Afrikaner , French Canadians , Lebanese Christians , and Finns have high rates of specific mutations that make FH particularly common in these groups . APOB mutations are more common in Central Europe .

= = History = =

The Norwegian physician Dr C. Müller first associated the physical signs , high cholesterol levels and autosomal dominant inheritance in 1938 . In the early 1970s and 1980s , the genetic cause for FH was described by Dr Joseph L. Goldstein and Dr Michael S. Brown of Dallas , Texas . Initially , they found increased activity of HMG @-@ CoA reductase , but studies showed that this did not explain the very abnormal cholesterol levels in people with FH . The focus shifted to the binding of LDL to its receptor , and effects of impaired binding on metabolism ; this proved to be the underlying mechanism for FH . Subsequently numerous mutations in the protein were directly identified by sequencing . They later won the 1985 Nobel Prize in Medicine for their discovery of the LDL receptor and its impact on lipoprotein metabolism .