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REVIEW

*Clinical update*

# Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society

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**Aims** Homozygous familial hypercholesterolaemia (HoFH) is a rare life-threatening condition characterized by markedly elevated circulating levels of low-density lipoprotein cholesterol (LDL-C) and accelerated, premature atherosclerotic cardiovascular disease (ACVD). Given recent insights into the heterogeneity of genetic defects and clinical phenotype of HoFH, and the availability of new therapeutic options, this Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society (EAS) critically reviewed available data with the aim of providing clinical guidance for the recognition and management of HoFH.

**Methods and results** Early diagnosis of HoFH and prompt initiation of diet and lipid-lowering therapy are critical. Genetic testing may provide a definitive diagnosis, but if unavailable, markedly elevated LDL-C levels together with cutaneous or tendon xanthomas before 10 years, or untreated elevated LDL-C levels consistent with heterozygous FH in both parents, are suggestive of HoFH. We recommend that patients with suspected HoFH are promptly referred to specialist centres for a comprehensive ACVD evaluation and clinical management. Lifestyle intervention and maximal statin therapy are the mainstays of treatment, ideally started in the first year of life or at an initial diagnosis, often with ezetimibe and other lipid-modifying

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therapy. As patients rarely achieve LDL-C targets, adjunctive lipoprotein apheresis is recommended where available, preferably started by age 5 and no later than 8 years. The number of therapeutic approaches has increased following approval of lomitapide and mipomersen for HoFH. Given the severity of ACVD, we recommend regular follow-up, including Doppler echocardiographic evaluation of the heart and aorta annually, stress testing and, if available, computed tomography coronary angiography every 5 years, or less if deemed necessary.

**Conclusion** This EAS Consensus Panel highlights the need for early identification of HoFH patients, prompt referral to specialized centres, and early initiation of appropriate treatment. These recommendations offer guidance for a wide spectrum of clinicians who are often the first to identify patients with suspected HoFH.

**Keywords** Homozygous familial hypercholesterolaemia • Diagnosis • Genetics • Phenotypic heterogeneity • Statins • Ezetimibe • Lipoprotein apheresis • Lomitapide • Mipomersen

## Introduction

Homozygous familial hypercholesterolaemia (HoFH) is a rare and life-threatening disease originally characterized clinically by plasma cholesterol levels >13 mmol/L (>500 mg/dL), extensive xanthomas, and marked premature and progressive atherosclerotic cardiovascular disease (ACVD). Studies in cultured fibroblasts from these patients showed a severe defect in the ability to bind and internalize LDL particles, subsequently shown to be caused by mutations in both alleles of the gene encoding the LDL receptor (*LDLR*).[1] Recent genetic insights, however, indicate that mutations in alleles of other genes, including *APOB*, *PCSK9*, and *LDLRAP1*, may be present in some individuals with HoFH.

Untreated, most patients with markedly elevated LDL-C levels develop overt atherosclerosis before the age of 20 years, and generally do not survive past 30 years.[1] Thus, the primary goals of management are prevention of ACVD by early and comprehensive control of hypercholesterolaemia, and early detection of complications, with specific focus on ostial occlusion and aortic stenosis.[2] Unfortunately, HoFH is typically diagnosed when considerable coronary atherosclerosis has already developed, emphasizing the need for optimization of treatment in childhood.

Recent advances have highlighted the (i) prevalence and (ii) heterogeneity of the genetic defects underlying HoFH and its clinical phenotype, which are both more pronounced than originally believed. Therefore, this Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society (EAS) critically reviewed current and emerging data with the aim of providing clinical guidance for the recognition and management of HoFH patients. These recommendations are directed not only to cardiologists and lipid specialists, but also to a wide spectrum of clinicians, including primary care physicians, paediatricians, dermatologists, and endocrinologists, who are often the first to see and hopefully refer these patients. These recommendations will also be a useful reference when decisions are made about provision of healthcare for HoFH.

## Prevalence of clinical and genetically confirmed homozygous familial hypercholesterolaemia

Historically, the frequency of clinical HoFH has been estimated at 1 in 1 000 000 and for heterozygous FH (HeFH) 1 in 500,[1] although higher frequencies in specific populations, such as French Canadians, Afrikaners in South Africa, or Christian Lebanese, have been reported due to founder effects.[3] However, recent studies in unselected general populations suggest that the prevalence of HeFH based on the Dutch Lipid Clinic Network criteria may be as high as 1 in ~200[4] or, for molecularly defined HeFH, 1 in 244.[5] Consequently, HoFH may affect as many as 1 in 160 000–300 000 people (*Figure 1*).

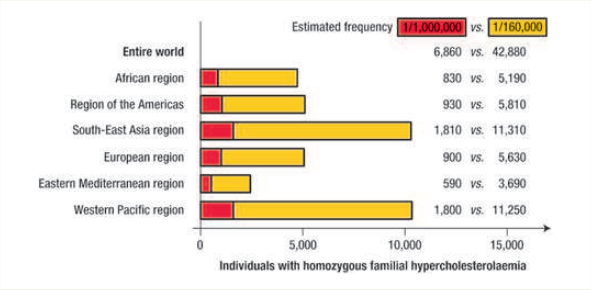


**Figure 1** Estimated number of individuals worldwide with homozygous familial hypercholesterolaemia by the World Health Organization region. Estimates are based on historical prevalence data (1 in a million with homozygous familial hypercholesterolaemia), as well as directly detected estimates of familial hypercholesterolaemia in the Danish general population (~1/160 000). Data from Nordestgaard *et al.*[4]

## Genetics of homozygous familial hypercholesterolaemia

The proteins known to affect LDL receptor function and their role are summarized in *Figure 2*. Most patients with genetically confirmed HoFH have two mutant alleles of the *LDLR* gene (*MIM 606945*) and their parents each have HeFH. Recently, mutations in alleles of three other genes were identified as causal in some cases with a severe phenotype resembling HoFH. These secondary genes are *APOB (MIM 107730)* encoding apolipoprotein (apo) B, *PCSK9 (MIM 607786)* encoding proprotein convertase subtilisin/kexin type 9 (PCSK9), and *LDLRAP1 (MIM 695747)* encoding LDL receptor adapter protein 1, which uniquely causes a recessive phenotype, since carrier parents have normal lipid profiles.[6] Patients are homozygotes with the same

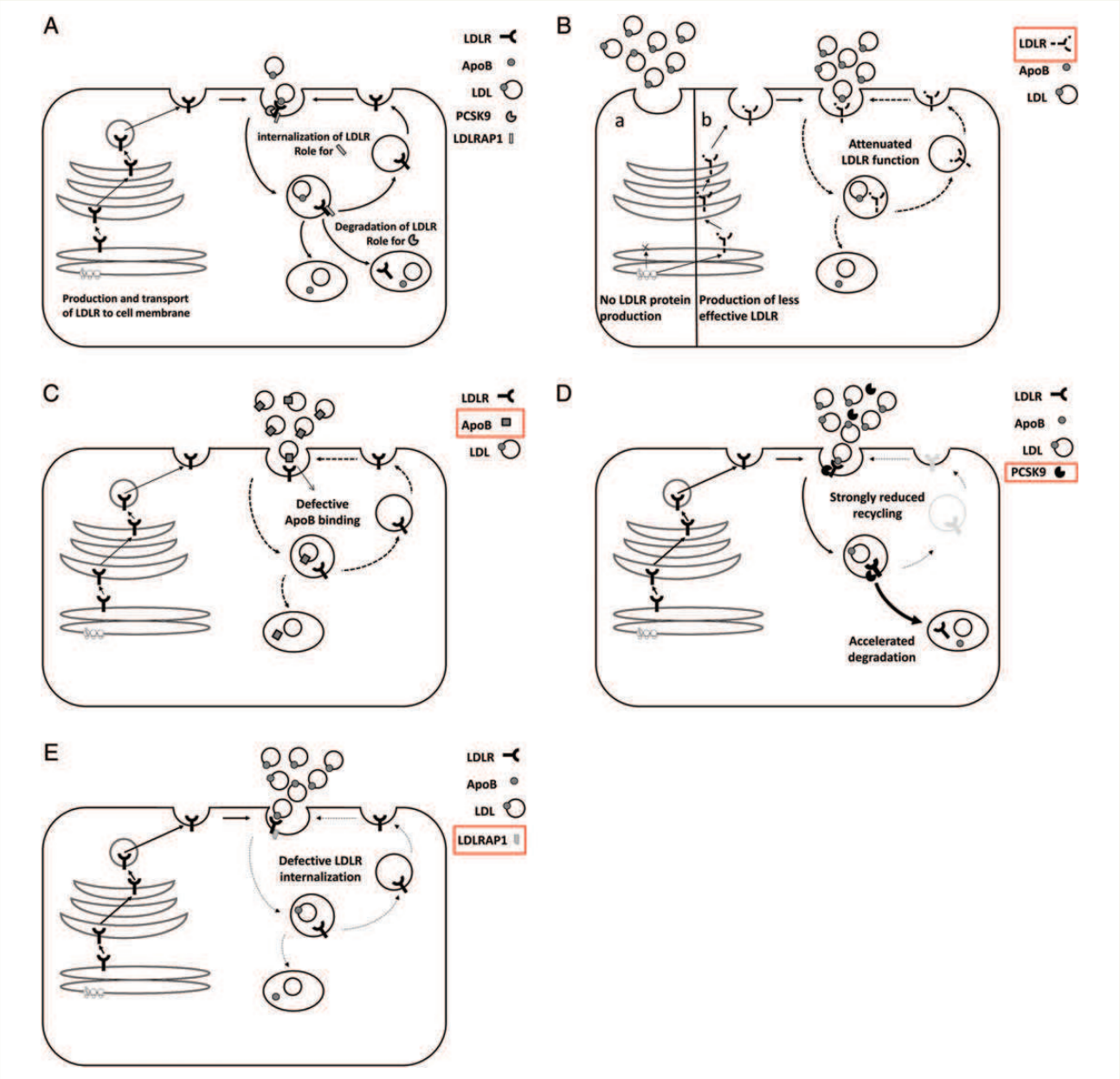


**Figure 2** Proteins affecting low-density lipoprotein receptor function. (*A*) (1) Newly synthesized low-density lipoprotein receptor (LDLR) is transported to the cell membrane. After reaching the cell surface, the low-density lipoprotein receptor binds apolipoprotein B-100 (apoB-100), the main protein on LDL, forming a complex. (2) The low-density lipoprotein receptor–low-density lipoprotein complex, located in a clarithin-coated pit, is endocytosed via interactions that involve the low-density lipoprotein receptor Adaptor Protein 1 (LDLRAP1). (3) Inside the endosome, the complex dissociates: apoB-100 and lipids are targeted to the lysosome and degraded, the low-density lipoprotein receptor recycles to the cell membrane. (4) Pro-protein convertase subtilisin/kexin type 9 (PCSK9) acts as a post-transcriptional low-density lipoprotein receptor inhibitor and through an interaction with it, targets the low-density lipoprotein receptor for degradation, instead of recycling. (*B*) In the presence of loss-of-function mutations in the gene encoding for the low-density lipoprotein receptor, the low-density lipoprotein receptor is either not synthesized, not transported to the surface, or is present on the surface, but its function is altered. (*C*) In the presence of mutations in the low-density lipoprotein receptor-binding region of apoB, its ability to bind to low-density lipoprotein receptor is reduced, with consequent reduction in low-density lipoprotein particle uptake. (*D*) In the presence of gain-of-function mutations in the gene encoding PCSK9, more low-density lipoprotein receptors are targeted for degradation, with consequent reduction in the number of low-density lipoprotein receptors which recycle to the cell surface. (*E*). In the presence of loss-of-function mutations in the gene encoding for LDLRAP1, which facilitates the interaction between the low-density lipoprotein receptor and the cell machinery regulating the endocytic process, low-density lipoprotein receptor–low-density lipoprotein complex internalization is impaired.

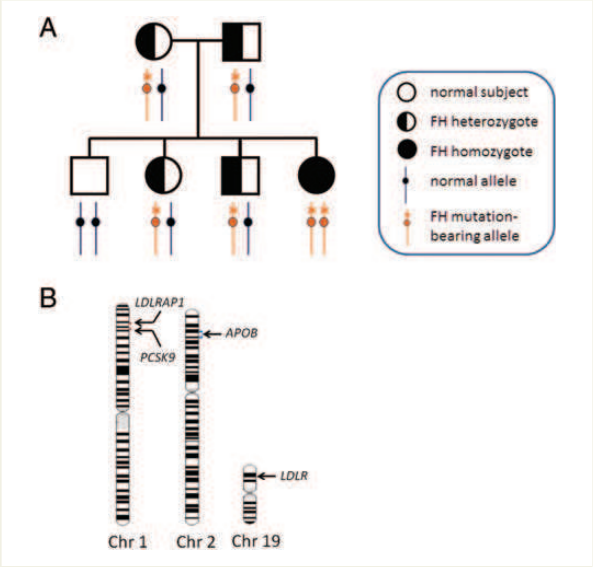


**Figure 3** Genetics and genetic heterogeneity of homozygous familial hypercholesterolaemia. (*A*) Inheritance of homozygous familial hypercholesterolaemia in a pedigree. In a mating between heterozygous parents who each carry one copy of a familial hypercholesterolaemia-mutation-bearing allele, 25% of children will carry two copies of wild-type alleles (homozygous normal); 50% will be heterozygotes; and 25% will carry two copies of familial hypercholesterolaemia-mutation-bearing alleles (homozygous familial hypercholesterolaemia). The particular genes and mutation types inherited determine whether the affected individual is a simple homozygote, or compound or double heterozygote. (*B*) Genetic heterogeneity of familial hypercholesterolaemia. Ideograms for chromosomes 1, 2, and 19 indicate the positions of the four main familial hypercholesterolaemia-causing genes, which in the descending order of frequency are *LDLR* (>95%), *APOB* (2–5%), *PCSK9* (<1%), and *LDLRAP1* (<1%). For the vast majority of homozygous familial hypercholesterolaemia patients represented in (*A*), mutation-causing alleles are within the same gene (usually *LDLR*) and patients are referred to as 'true homozygotes'. Homozygous familial hypercholesterolaemia patients who carry the same mutation on each allele are called 'simple homozygotes', while those who inherit different mutations from within the same gene are called 'compound heterozygotes'. Finally, very rare homozygous familial hypercholesterolaemia patients have familial hypercholesterolaemia mutation-bearing alleles from two different familial hypercholesterolaemia loci: the first is almost always within the *LDLR*, while the second is from one of the other three loci. Such patients are called 'double heterozygotes'.

mutation in both alleles of the same gene, or more commonly, compound heterozygotes with different mutations in each allele of the same gene, or double heterozygotes with mutations in two different genes affecting LDL receptor function (*Figure 3*).

## Genetic heterogeneity translates to phenotypic variability

Irrespective of the underlying genetic defect, the severity of the HoFH phenotype depends on residual LDL receptor activity. Based on *in vitro* assays in their cultured fibroblasts, patients with clinically defined HoFH have been conventionally classified as either receptor-negative (<2% residual activity) or receptor-defective (2–25% residual activity).[1] Homozygous familial hypercholesterolaemia patients who are *LDLR*-negative have higher LDL-C levels and poorer clinical prognosis than *LDLR*-defective patients.[2,7,8]

Residual LDL receptor activity has not been systematically evaluated in patients carrying mutations in *APOB* and *PCSK9* genes. In patients carrying *LDLRAP1* mutations, LDL receptor activity in fibroblast culture is normal, although the cause remains unclear.[6] Nevertheless, emerging data suggest that carriers of mutations in these genes may present a milder phenotype compared with that of receptor-negative subjects.[6] Overall, mean LDL-C levels by genotype generally increase as follows: HeFH<double heterozygote (e.g. *LDLR*+*PCSK9* gain-of-function or *APOB* mutation) <homozygous *APOB* or *PCSK9* gain-of-function mutation <homozygous *LDLRAP1* or *LDLR*-defective mutations <compound heterozygote *LDLR*-defective+*LDLR*-negative mutations <homozygous *LDLR*-negative mutations (see Supplementary material online and *Figure 4*).

Other sources of variability in the HoFH phenotype may arise from small effect genetic variants (common single nucleotide polymorphisms), gene–gene and gene–environment interactions, and non-Mendelian and epigenetic influences.[6,9,10] Greater access and wider clinical application of next generation sequencing are critical to defining such variability, as well as additional causative genes, all of which have important prognostic and therapeutic implications.

## Metabolic characteristics of homozygous familial hypercholesterolaemia

Impaired functionality of the LDL receptor underlies the hypercholesterolaemia of HoFH. While defective hepatic LDL uptake is the main and most direct consequence, other metabolic perturbations may contribute to the metabolic characteristics and accelerated atherosclerotic disease associated with HoFH. ApoB metabolism in HoFH remains incompletely defined, although *in vitro* and *in vivo* studies suggest that *LDLR*-negative mutations are associated with hepatic oversecretion of apoB. In addition, while levels of triglycerides are frequently within the normal range, hypertriglyceridaemia has been observed, and may be more common with an increasing prevalence of the metabolic syndrome. Decreased catabolism of triglyceride-rich lipoproteins may result from deficient LDL receptor function and account for postprandial dyslipidaemia. Familial hypercholesterolaemia is also associated with increased plasma levels of lipoprotein(a) [Lp(a)] by an undefined mechanism that may not directly involve the LDL receptor pathway. Lipoprotein(a) levels tend to be higher in HoFH than HeFH, and are independent of genetic variation in apolipoprotein(a).[4] Finally, HoFH patients frequently have low levels of high-density lipoprotein cholesterol (HDL-C), probably due to accelerated turnover of HDL apoA-I, and defective HDL-driven cholesterol efflux. These metabolic perturbations have been extensively reviewed.[11]

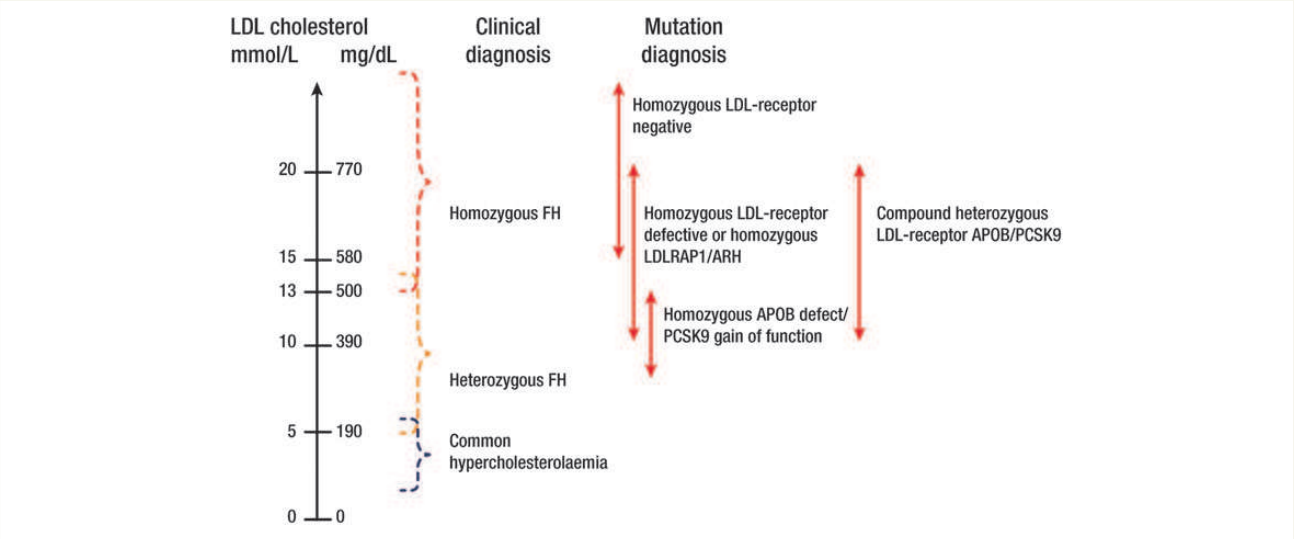


**Figure 4** Phenotypic variability in homozygous familial hypercholesterolaemia. For full explanation and relevant literature refer to Supplementary material online. LDL, low-density lipoprotein; APOB, apolipoprotein B; PCSK9, pro-protein convertase subtilisin/kexin type 9; LDLRAP1, LDL receptor adaptor protein 1 (i.e. ARH, autosomal recessive hypercholesterolaemia).

## Diagnosis of homozygous familial hypercholesterolaemia

Diagnosis of HoFH can be made on the basis of genetic or clinical criteria (Box 1). While genetic testing may provide a definitive diagnosis of HoFH, it is recognized that in some patients genetic confirmation remains elusive, despite exhaustive investigation; indeed, the existence of additional FH genes cannot be excluded.[4] Historically, HoFH has been most commonly diagnosed on the basis of an untreated LDL-C plasma concentration >13 mmol/L (>500 mg/dL), or a treated LDL-C concentration of ≥8 mmol/L (≥300 mg/dL), and the presence of cutaneous or tendon xanthomas before the age of 10 years, or the presence of untreated elevated LDL-C levels consistent with HeFH in both parents.

**Box 1 Criteria for the diagnosis of homozygous familial hypercholesterolaemia**

- Genetic confirmation of two mutant alleles at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* gene locus

OR

- An untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C ≥8 mmol/L (300 mg/dL)* together with either:
  - Cutaneous or tendon xanthoma before age 10 years

or

  - Untreated elevated LDL-C levels consistent with heterozygous FH in both parents

* These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH

### Plasma low-density lipoprotein cholesterol levels

Within a family, the plasma LDL-C level is the critical discriminator, being about four times and about two times higher in family members with HoFH or HeFH, respectively, compared with unaffected members.[6] At the population level, however, the range of LDL-C levels may overlap significantly between HeFH and HoFH (*Figure 4*), and untreated LDL-C levels <13 mmol/L (<500 mg/dL) can be found in genetically confirmed HoFH.[5,8] This is especially relevant for children, who tend to have lower LDL-C levels than adults. More than 50% of HoFH children identified in the Netherlands have LDL-C levels between 5.6 and 9.8 mmol/L (*A Wiegman personal communication*). Such phenotypic heterogeneity can be at least partly explained by the previously described genotypic heterogeneity. Thus, the LDL-C cut-offs given here should not be the sole guide for diagnosis. Indeed, the treated LDL-C cut-off of >8 mmol/L (>300 mg/dL) is now considered obsolete, given the multiplicity of lipid-lowering treatments that these patients typically receive. This point is clearly illustrated in a recent trial, in which HoFH patients with a confirmed genetic diagnosis had baseline LDL-C levels as low as 3.9 mmol/L (~150 mg/dL) while on multiple LDL-C lowering agents,[12] as well as in a recent report.[5]

### Xanthomas and arcus corneae

Although not exclusively associated with HoFH, the presence of cutaneous or tuberous xanthomas in children is highly suggestive of diagnosis (*Figure 5*). Evidence of arcus corneae reinforces the clinical diagnosis. As seen for LDL-C levels, variability in the age at appearance and extension of xanthomas can be partly explained by the underlying mutations, with earlier appearance of xanthomas associated with receptor-negative vs. receptor-defective status.[2,8] Cholesterol deposits in the tendons and joints may lead to tendinitis and joint pain, which impairs the quality of life of patients, and these may

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