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Guidelines for the Diagnosis and Treatment of Pediatric Familial Hypercholesterolemia 2022

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As atherosclerosis begins in childhood, early diagnosis and treatment of familial hypercholesterolemia (FH) is considered necessary. The basic diagnosis of pediatric FH (under 15 years of age) is based on hyper-low-density lipoprotein (LDL) cholesterolemia and a family history of FH; however, in this guideline, to reduce overlooked cases, "probable FH" was established. Once diagnosed with FH or probable FH, efforts should be made to promptly provide lifestyle guidance, including diet. It is also important to conduct an intrafamilial survey, to identify family members with the same condition. If the level of LDL-C remains above 180 mg/dL, drug therapy should be considered at the age of 10. The first-line drug should be statin. Evaluation of atherosclerosis should be started using non-invasive techniques, such as ultrasound. The management target level is an LDL-C level of less than 140 mg/dL. If a homozygous FH is suspected, consult a specialist and determine the response to pharmacotherapy with evaluating atherosclerosis. If the response is inadequate, initiate lipoprotein apheresis as soon as possible.

Key words: **Pediatric, Familial Hypercholesterolemia, Homozygote, Heterozygote, Diagnostic criteria, Treatment guidelines, Lifestyle, Pharmacological therapy, Low-density lipoprotein apheresis, Statins**

Introduction

Atherosclerotic pathological changes can already begin to develop in childhood; this is evidenced by the autopsy findings of the Bogalusa Heart Study[1)] and Pathological Determinants of Atherosclerosis in Youth (PDAY)[2)]. Familial hypercholesterolemia (FH) is an inherited disorder caused by mutations in the low-density lipoprotein (LDL) receptor (*LDLR*) and its related genes, resulting in hyper-LDL cholesterolemia. This condition where one is life-long exposed to elevated LDL-C puts him or her at high-risk for atherosclerosis, making early diagnosis and early intervention important. For patients with FH, there has long been no consensus in Japan on its screening in childhood (<15 years of age), the type and starting

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age of treatment, the assessment of atherosclerosis, and the goals of treatment. In 2017, the Japan Pediatric Society and the Japan Atherosclerosis Society jointly established the Guidance for Pediatric Familial Hypercholesterolemia 2017 (hereafter, Pediatric FH Guide 2017)[3] and proposed one guideline. This time, after 5 years, the entire guideline was reviewed and revised. Although there is little evidence in pediatric patients, we set up clinical questions, conducted an evidence evaluation, and used them in this new guideline for medical practice. As in the previous edition, the aim is to prevent possible future atherosclerosis by diagnosing the disease at an early stage and applying therapeutic intervention.

1. Background Question (BQ)/ Foreground Question (FQ)

BQ1. What is the Prevalence of FH in Japan?

In general, it is found in approximately 1 in 300 people in the general population, 1 in 30 people with coronary artery disease, and 1 in 15 people with premature coronary artery disease (CAD) or severe hyper-LDL cholesterolemia. (Level of evidence: E-2)

The prevalence of FH has been reported to be 1 in 500 people, but in recent years, a series of cross-sectional and cohort studies in the United States and Europe have shown a clearly higher prevalence than that. Moreover, in Japan, Mabuchi *et al.* examined the frequency of molecular epidemiology in the Hokuriku region and reported a prevalence rate of 1 in 208 people[4].

A systematic review/meta-analysis published in 2017 (not including Japanese) reported a frequency of 1 in 250 in the general population[5]. In addition, a subsequent systematic review/meta-analysis (including Japanese) reported a frequency of 1 in 313 [6] and 311 [7] people, respectively, in the general population. The meta-analysis, which reported 1 in 250 people had FH, included literature reporting extremely high frequencies due to the so-called founder effect, whereas the latter two reports excluded such studies. As the effect of increased frequency due to founder effect is assumed to exist in some regions, it is reasonable to assume that the number of cases is about 1 in 300 people, contrary to the report by Mabuchi *et al.* The number of Japanese in the above meta-analysis is small, and it is assumed that differences in frequency may be attributed to factors such as consanguineous marriages in some regions and demographic bottleneck effects, but there is no evidence of significant differences among races, so the results of the above meta-analysis may be applicable to Japanese as well.

BQ2. What are the Prognosis and Main Complications of Patients with FH ?

- **CAD: odds ratio 10–20 times higher than non-FH (Level of evidence: E-1a*)**
- **Peripheral arterial disease: odds ratio 5–10 times higher than non-FH (Level of evidence: E-1a)**
- **Stroke: no clear impact (Level of evidence: E-1a)**
- **Aortic valve stenosis: no epidemiological association has been shown, but there have been case reports of FH complicating the disease. (Level of evidence: E-3)**
- **Abdominal aortic aneurysm: no epidemiological association has been shown, but there have been case reports of FH complicating the disease. (Level of evidence: E-3)**

*Although there was no meta-analysis of cohort studies, we chose E-1a because of the existence of multiple cohort studies and identical results.

The major complication of systemic atherosclerosis in patients with FH is CAD[8]. A significantly higher prevalence of peripheral arterial disease and carotid atherosclerosis has been reported in addition to CAD compared to non-FH (systematic review/meta-analysis)[9, 10]. On the other hand, with regard to stroke, many reports state that its effects are not clear. Regarding aortic disease and valvular disease (aortic aneurysm, aortic stenosis, supravalvular stenosis, etc.), there are case reports showing an association with the disease, although no epidemiological reports have shown such an association.

Although there are no randomized controlled trials (RCTs) or systematic reviews on the prognosis of FH, Mabuchi *et al.* presented a study comparing the prognosis of FH heterozygotes (HeFH) and FH homozygotes (HoFH) in the pre- and post-statin era in Japan[11]. This report shows that before the advent of statins, 73% of men and 64% of women who suffered from HeFH died of cardiac death; the age of death for HeFH increased from an average of 63 years before statins to 76 years after statins; meanwhile, for HoFH, the average age of death increased from 28 years to 59 years after statins.

FQ1. Can Statins be Recommended as the First Choice in Drug Therapy for HeFH?

Strict lipid management with statins as first-line drug is recommended for the treatment of HeFH. (Level of evidence: 3; Recommendation level: A)

In total, there are 13 randomized, double-blind trials examining the LDL-C lowering effect of statin

in HeFH[12-24], including 9 placebo-controlled trials (2 in adult HeFH[12, 13], 6 in children to adolescent HeFH[15-20], and 1 in adult FH subjects without mention of whether they are HeFH or HoFH[14]). Its efficacy and safety have been established in both adult and pediatric cases. Furthermore, a randomized, double-blind, crossover study in HoFH has shown its efficacy[21]. In Japan, reports have been published showing that statin therapy reduces LDL-C in adults and pediatric patients[23, 24], which is consistent with the results of clinical trials in other countries.

A randomized, double-blind, comparative study has been published in adults[25] and pediatric patients[20], respectively, to investigate the efficacy of high-intensity statin therapy (80 mg atorvastatin, twice the Japanese approved dose in Japan) compared to standard-intensity statin therapy (40 mg simvastatin, twice the approved dose in Japan) in adults and standard-intensity statin therapy (20–40 mg pravastatin, the approved dose is 20 mg in Japan and no pediatric indication) compared to placebo in children. Both studies showed inhibition of the development of carotid artery intima Media Thickness (IMT). A sub-analysis of pediatric cases showed that statin initiation at an earlier age was associated with less IMT thickening[26]. In addition, a report of an observational study examining 2447 cases from the Netherlands has shown that statin use is associated with a lower incidence of CAD and lower all-cause mortality[27]. Although scientific evidence for prevention of atherosclerotic cardiovascular disease by direct comparison is deemed insufficient, statins appear to be the most recommended drug therapy at this time, given the abundant evidence in non-FH.

Four clinical studies that compare the LDL-C lowering effects of statins and other lipid-lowering drugs in FH have been published (all in adults, all with pravastatin, 2 in HeFH, and 2 in FH subjects). In a report comparing pravastatin 40 mg with cholestyramine 4 g (or cholestipol 5 g), both groups had significantly lower LDL-C from baseline, but the group of pravastatin had significantly lower LDL-C than the cholestyramine group[13]. On the other hand, reports comparing 40 mg of pravastatin with 16–24 g of cholestyramine (1.5–2 times the Japanese approved dose) did not show significant differences between the two groups, although both groups had significantly lower LDL-C from baseline[12, 14, 28]. These studies were conducted with pravastatin in the early 1990s, and since the newer generation of statins shows stronger lipid-lowering effects, statins are expected to be more effective than cholestyramine. Although there exist no direct comparative studies between statins and probucol, cholesterol transporter inhibitor at small intestine (ezetimibe), or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, there have been reports of trials of ezetimibe and PCSK9 inhibitors on top of statins[29-32].

FQ2. Is Lipoprotein Apheresis Therapy Recommended for HoFH and Severe HeFH with Drug Resistance ?

For HoFH and severe HeFH with drug resistance, strict control of LDL-C is recommended with lipoprotein apheresis therapy. (Level of evidence: 3; Recommendation level: A)

In the 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk[33], although there is no mention of evidence levels, etc., the lipoprotein apheresis is recommended as a treatment for HoFH.

A systematic review reported in 2016 analyzed a total of 38 articles (8 open-label clinical trials, 11 observational studies, 17 reviews/guidelines, and 2 medical technology evaluations)[34]. Although RCTs were not included, they have been shown to have clinical benefits in terms of lowering LDL-C, lowering lipoprotein (a) [Lp (a)], and preventing cardiovascular events. As each country has different rates of diagnosis of FH, availability and access to apheresis treatment, indications, methods, and costs, it will be necessary to evaluate the situation in Japan in the future. However, although there is a physical and social burden on the patient, we believe that lipoprotein apheresis is recommended for patients with FH who do not respond adequately to drug therapy in Japan, where access is relatively easy in terms of transportation and cost.

In 2019, a systematic review that examined 76 case reports (209 patients) of children with HoFH was reported[35]. Although it has not been shown whether lipoprotein apheresis is more or less beneficial than drug therapy alone for cardiovascular outcomes, it has been reported to lower LDL-C and reduce xanthomas with fewer adverse events, making it safe in general.

FQ3. Is it Recommended to Start Treatment Early in Pediatric Patients with FH?

FH is a high-risk condition for atherosclerotic diseases; thus, early initiation of treatment is recommended, depending on LDL-C levels*.

(Level of evidence: Consensus, Level of recommendation: A)

*See Flowchart of pediatric HeFH treatment (Fig. 3 in the text)

The US Food and Drug Administration guidelines “approve” pravastatin for pediatric FH

starting at age 8 and other statins starting at age 10 [36]. Our policy of "approving" pitavastatin for ages 10 and older, as we stated in Pediatric FH Guide 2017 [3], is in line with the global trend. The 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk[33] also has a level of evidence/recommendation of Class IIa, Level C, but it states that pediatric FH treatment should begin with statins at 8–10 years of age, with a goal of <135 mg/dL at ages 10 years and older. "Statins for children with familial hypercholesterolemia," which summarized nine studies using statins, found that statin therapy in children with FH successfully and safely reduced LDL-C without affecting liver function, muscle symptoms, muscle damage, and growth. They have also reported that carotid atherosclerosis can be reduced and some endothelial function improved, although the level of evidence is not high[37]. Furthermore, to date, RCTs and meta-analyses of RCTs and systematic reviews have shown that the use of statins, resins, and ezetimibe in pediatric patients of 10 years and older is safe and effective in lowering LDL-C levels.

Due to the limited number of RCTs that used statins in children due to the nature of their subjects and the short duration of statin treatment, no studies have been able to evaluate the incidence of atherosclerotic cardiovascular disease (ASCVD), cardiovascular death, and long-term safety. However, a 20-year follow-up study showed that starting statins at 13.0 ± 2.9 years (mean LDL-C 237.3 mg/dL) did not cause any mortality related to ASCVD by at least the age of 39 years, although the mean LDL-C level reached 160.7 mg/dL[38]. Since LDL-C accumulation levels, over time, are believed to be associated with the development of ASCVD, and since FH is a high-risk condition for atherosclerotic disease, early initiation of treatment in children is thus recommended.

2. Outline of FH

Key Points

- FH is an inherited disease associated with mutations in the LDL receptor (*LDLR*) and related genes and is inherited mainly in an autosomal dominant form.
- The frequency of FH in the general population is approximately 1 in 300 people and is even more frequent in patients with CAD, especially those with premature CAD.
- FH is classified into two categories, namely, heterozygotes and homozygotes, according to the number of pathogenic gene mutations.

What is FH: Its Etiology, Frequency, and Major Signs

FH is defined as an autosomal dominant hereditary disease in which mutations occur in the *LDLR* and its related genes. A recent meta-analysis of molecular epidemiological studies[6, 7] suggests that the frequency of HeFH in the general population is approximately 1 in 300 people worldwide. The meta-analysis of these molecular epidemiological studies includes data from Japan, with a total sample size of more than several million people, and is extremely important to determine the frequency of this disease. Furthermore, the frequency of FH in patients with CAD is thought to be approximately 1 in 30 people, while the frequency of FH in patients with premature CAD is approximately 1 in 15 people[6]. Currently, the diagnosis rate of FH, especially in children, is estimated to be extremely low, despite the fact that FH is considered the most common hereditary metabolic disease and is commonly encountered in daily medical practice.

The main clinical features of FH are hyper-LDL cholesterolemia, tendon and skin xanthomas, and premature CAD (onset of CAD before age 55 in men and 65 in women). However, it should be noted in pediatric HeFH that LDL-C levels decrease during puberty, as discussed below, and tendon xanthomas and premature CAD are rarely seen.

FH Causative Genes

Three genes are known to cause FH, namely, *LDLR*, which encode the LDL receptor; *APOB*, which encode the apolipoprotein B-100; and *PCSK9*, which encode the PCSK9 protein. If there is one pathogenic mutation, it corresponds to HeFH, and if there are two, it refers to HoFH (including compound heterozygotes and double heterozygotes). Most FH is caused by *LDLR* mutations; however, in Japan, about 5% of HeFH is determined to be caused by *PCSK9* gain-of-function mutations[11]. *APOB* mutations are relatively frequent in Europe due to the founder effect, but extremely rare in Japan[39].

On the other hand, autosomal recessive hypercholesterolemia (ARH) is an extremely rare disorder caused by the biallelic pathogenic mutations in low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*). ARH should be treated as HoFH. Carrier parents may present with mild hyper-LDL cholesterolemia, but usually do not develop the FH heterozygote phenotype[40]. ARH is very rare, with only a few cases reported in Japan[40].

Recently, in addition to FH associated with pathogenic genetic mutations of the *LDLR* and related genes as described above, it is suggested that there is

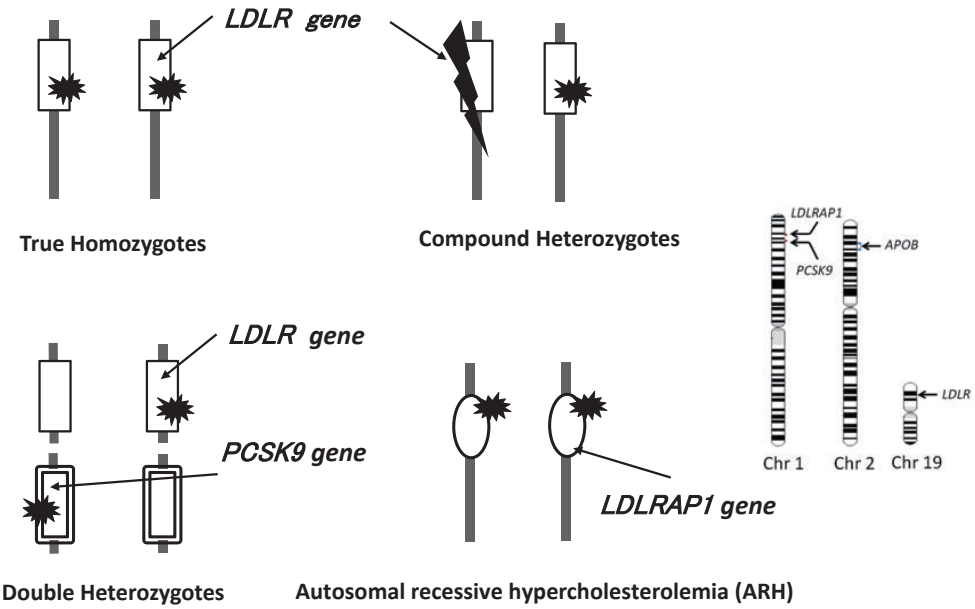


Fig. 1. Combination of genetic mutation showing HoFH clinically

so-called polygenic FH associated with the superposition of high-frequency genetic polymorphisms at loci involved in LDL metabolism[41]. However, there is no evidence that the superposition of high-frequency gene polymorphisms alone, in any combination known at this time, causes the so-called FH, which is believed to influence the phenotype of FH (and other hyper-LDL cholesterolemia) rather than being involved in the pathogenesis of FH.

Genotype Designations

Basically, HeFH has one pathogenic mutation and HoFH has two. HoFH may be further differentiated according to genotype as follows (Fig. 1): Autosomal mutated genes are inherited from both the paternal and maternal sides of the family. Two identical mutations of the same gene are identified as true homozygotes, a combination of the same gene but different mutations is a compound heterozygote, and a combination of different genes is a double heterozygote.

Signs of FH (Arteriosclerosis, Xanthomas, etc.)

Atherosclerotic disease is believed to progress in proportion to cumulative LDL-C levels[42]. In cases of FH, their cumulative LDL-C levels reach the threshold for developing CAD earlier due to prolonged exposure to marked hyper-LDL cholesterolemia since birth. Therefore, early intervention is necessary to prevent the development of atherosclerosis. Although premature CAD is one of the common phenotypes of FH in general, the degree of atherosclerotic lesions throughout the body can vary with age and the degree of concomitant risk factors. In particular, complications of aortic valve disease should be given the proper attention in FH practice, as it can be a cause of death at a young age. Xanthomas are the result of exposure to marked hyper-LDL cholesterolemia during childhood when the tissues are flexible. Tendon xanthomas are a highly specific physical finding in FH, except in rare conditions such as sitosterolemia and cerebral tendon xanthomatosis. However, it is difficult to use the presence of tendon xanthomas to diagnose a pediatric FH, because these often manifest in adulthood or later. On the other hand, if a child presents with xanthomas of the skin or tendons, homozygosity is strongly suspected, and consultation with a specialist is mandatory.

3. Diagnosis of Pediatric FH (Table 1)

Key Points

- Diagnose "FH" when there is hyper-LDL cholesterolemia (≥ 140 mg/dL) and a family history of FH (in parents and siblings).
- Diagnose "probable FH" when there is hyper-LDL cholesterolemia with a high parental LDL-C level (≥ 180 mg/dL) or with a family history of premature CAD in grandparents or parents (item 3).
- If the LDL-C is ≥ 180 mg/dL, diagnose "probable FH" on that basis alone. If item 3 is present in addition to that, diagnose "FH."
- Cases with LDL-C ≥ 250 mg/dL and those who are

Table 1. Diagnostic criteria for pediatric FH (under the age of 15)

1. Hyper-LDL cholesterolemia (untreated LDL-C level ≥ 140 mg/dL, confirmed multiple times) 2. Family history of FH (Parents or siblings) 3. Parental LDL-C ≥ 180 mg/dL or family history of premature coronary artery disease (Grand parent or parent)
After ruling out other primary and secondary Hyper-LDL cholesterolemia, ● Diagnose FH with items 1 and 2. ● Diagnose probable FH with items 1 and 3. If the individual's LDL-C is 180 mg/dL or higher, diagnose FH. ● Even if only item 1 is used, ≥ 250 mg/dL is diagnosed with FH and ≥ 180 mg/dL is diagnosed with probable FH.
• Differentiate HoFH when LDL-C is ≥ 250 mg/dL or xanthomas are present. • Diagnose FH if the individual has a pathogenic gene mutation for FH. If a parent, a brother, or a sister is found to have a pathogenic gene mutation for FH, that is considered to be the family history of FH (item 2). • Premature coronary artery disease is defined as coronary artery disease occurring at less than 55 years of age in men and less than 65 years of age in women. • Probable FH cases require further scrutiny and lipid-lowering therapy.

positive for pathogenic gene mutations of FH are diagnosed as "FH."

- Whenever a patient with "FH" or "probable FH" is diagnosed, a family survey should be conducted, in order to identify family members with FH.

Need for Proactive Diagnosis of FH from Childhood

In pediatric HeFH, hypercholesterolemia is present from birth, as described above, but few symptoms related to atherosclerosis have been observed. Therefore, in most cases, hyper-LDL cholesterolemia is detected by chance after a blood test at a pediatric checkup of lifestyle-related diseases or for other diseases, and a diagnosis rate of FH is low in Japan[42]. In Europe and the United States, pediatric FH diagnosis and treatment guidelines have been established, and active medical care is being provided[43]. In Japan, the Japan Pediatric Society and the Japan Arteriosclerosis Society jointly developed the first Pediatric FH Guide 2017 [3] 5 years ago. Based on subsequent clinical evidence, the diagnostic criteria have been revised in 2022.

The diagnosis of FH can be made clinically or genetically, but the former is the basis for the diagnosis of pediatric FH. However, since it cannot be ruled out that there may be some cases that fall outside the clinical diagnosis, additional genetic testing should be considered.

HeFH typically does not show cutaneous xanthomas or thickening of the Achilles tendon in childhood. Therefore, the diagnosis is based on hyper-LDL cholesterolemia and family history after excluding other dyslipidemias. In the Pediatric FH Guide 2017 [3], the diagnosis was based on two items: hyper-LDL cholesterolemia and family history of FH or premature CAD. In reality, however, it remains difficult to obtain a detailed family history, and there are many cases in which FH is not diagnosed, especially in lifestyle-related disease checkups[44]. Therefore, in the diagnostic criteria of the current guideline, a new category of "probable FH" was established. There are some differences from the simultaneously revised guidelines for adult FH (15 years and older), not only in terms of the value of high LDL-C but also items of family history. This is because we believe that it is important to increase sensitivity while maintaining specificity and to actively follow-up probable cases from the early stage to reduce the number of missed cases of FH in childhood.

Diagnostic Criteria for Pediatric FH

Table 1 shows the diagnostic criteria of this newly developed Guidelines for the Diagnosis and Treatment of Pediatric FH 2022.

The first step is to differentiate primary or secondary hyper-LDL cholesterolemia. It is possible that the patient originally has FH and is concurrently suffering from other diseases. Obese children do not always have elevated LDL-C. It is thus necessary to conduct a thorough family history interview and always keep FH in mind. When hyper-LDL cholesterolemia is found, FH and other diseases should actually be differentiated simultaneously.

Item 1 is the criterion for hyper-LDL cholesterolemia; a value of ≥ 140 mg/dL (95th percentile) is considered hyper-LDL cholesterolemia[45]. If total cholesterol (TC) is tested and is ≥ 220 mg/dL (95th percentile value), an LDL-C value should be obtained. This reference value can be used throughout childhood, but some infants can exhibit hyper-LDL cholesterolemia due to breastfeeding, in which case, the test should be repeated after weaning. Serum

LDL-C measurement is based on the Friedewald method, although a fasting blood sample is required. If fasting blood sampling is difficult, the direct method is then used, and non-HDL-C (≥ 150 mg/dL is considered high) is also used as a reference[46]. Furthermore, because LDL-C levels fluctuate (decrease) physiologically during puberty, LDL-C should be measured and evaluated multiple times[47].

Serum LDL-C levels in childhood decrease continuously from the age of puberty onset[48] and begin to increase after puberty is completed[47]. In other words, by considering the stage of puberty, it may be possible to predict the next variation in the LDL-C measurements[47]. The Tanner classification is a useful and convenient way to assess the stage of puberty[49]. The average decrease in LDL-C levels during puberty is approximately 10 mg/dL[48], but naturally there are individual differences in the age at which puberty begins and its duration. The range of variability in LDL-C is also likely to vary between individuals. Although multiple reference values for LDL-C appear in this guideline, multiple tests should be performed to ensure that the reference values are met.

If the LDL-C is ≥ 250 mg/dL, this alone is sufficient to diagnose "FH." It is difficult to imagine any other dyslipidemia in children with such high levels of LDL-C other than FH, and FH is strongly suspected even in adults[50]. Furthermore, in studies in which children were genetically tested, children with ≥ LDL-C 250 mg/dL were generally found positive for pathogenic gene mutations in the *LDLR* or *PCSK9*[44, 51]; negative cases are extremely rare. In such cases of markedly elevated LDL-C, the presence of xanthomas should also be investigated, and the possibility of HoFH should be considered.

Furthermore, since 180 mg/dL of LDL-C is approximately the 99.7th percentile value in children[44], LDL-C ≥ 180 mg/dL alone was considered "probable" FH. FH with pathogenic gene mutation-positive cases have significantly higher levels of LDL-C than mutation-negative cases. Many FH cases with the pathogenic gene mutation would be included if ≥ 180 mg/dL. The cutoff value of 180 mg/dL is considered to be fair for receiver operating characteristic analysis [44, 51].

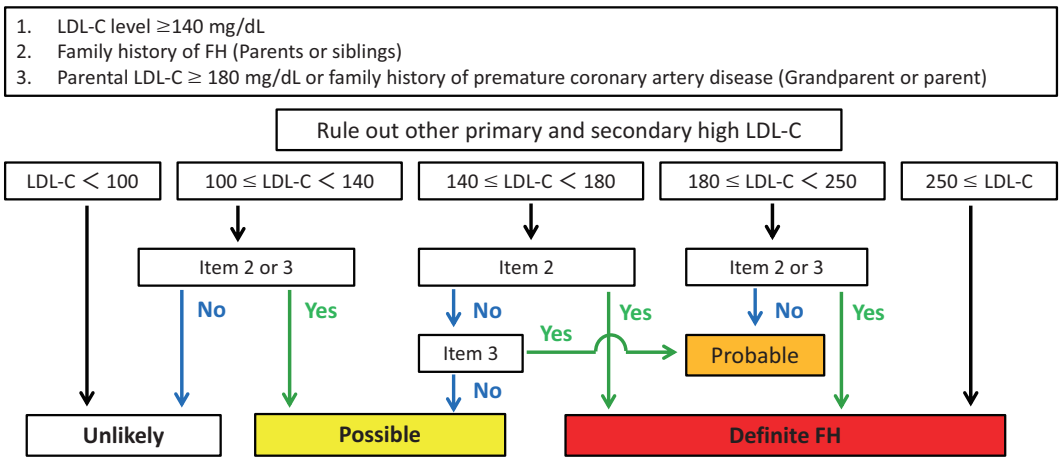
Item 2 is the family history of FH. In the previous Guidance for Pediatric FH 2017, the family history of FH and that of premature CAD were treated equally, but in this guideline, we separated the family history of FH from that of premature CAD. This is because premature CAD is sometimes due to causes other than FH. In addition, instead of using the term "parentage" as previously employed, FH's family history is to be examined by blood parents and siblings (first-degree relatives). Diagnose "FH" on items 1 and 2. If the grandfather or grandmother was diagnosed with FH, the father or mother is likely to have FH and thus requires close examination.

Item 3 is another family history set as an item followed by the item 2. When diagnosing pediatric FH, it is not always clear whether the parents have FH or not because information on grandparents is not often available. So, if the LDL-C of the father or mother is ≥ 180 mg/dL, it is highly likely associated with FH due to age in the absence of other diseases; in the 20s, the mean +2 SD is approximately 160 mg/dL, and in the 30s, it is approximately 180 mg/dL for men and 170 mg/dL for women[47, 52]. This content was noted within the previous diagnostic flowchart[3].

Premature CAD is defined as CAD that occurs at <55 years of age in men or <65 years of age in women. For premature CAD, it was decided to interview both parents and grandparents, since it is impossible to determine this in children without including grandparents. The combination of item 1 and item 3 results in "probable FH." However, if the child's LDL-C is very high (≥ 180 mg/dL) and item 3 is present, the diagnosis of "FH" is made. If there is a family history of premature CAD, a close examination of the family for FH is also recommended to improve the diagnostic yield.

"Probable FH" cases are those that are considered to require further scrutiny and follow-up. Continue detailed family research, including blood tests. Since LDL-C is elevated, lifestyle guidance, including diet, should be provided even in "probable FH" cases. If necessary, refer to a specialist, and consider genetic testing of the child and family members. Consider pharmacotherapy in cases of persistently high LDL-C (≥ 180 mg/dL, see Treatment section). The reason for setting "probable FH" cases in this guideline is that although they do not currently meet the diagnostic criteria for FH, they are suspected to have FH and are meant to provide guidance to prevent complications such as obesity, type 2 diabetes, and hypertension to prevent future atherosclerotic diseases.

Genetic testing is not essential for diagnosis, but cases with FH pathogenic gene mutations are diagnosed as "FH" (see section on FH Causative Genes). Approximately half of the children clinically diagnosed with FH in Japan have a pathogenic gene mutation that causes FH[51]. In difficult to diagnose cases or in severe cases, such as homozygotes, genetic testing should be performed with consent, if necessary. If a parent or sibling is found to have a pathogenic gene mutation for FH, this constitutes a family history of FH and is considered as item 2 (see About Genetic Testing and Genetic Counseling in FH).



	The child's LDL-C (mg/dL)				
	<100	100-139	140-179	180-249	≥250
Family history of FH	Unlikely	Possible	FH	FH	FH
Parental LDL-C ≥ 180 mg/dL or family history of premature CAD	Unlikely	Possible	Probable	FH	FH
No family history of FH	Unlikely	Unlikely	Possible	Probable	FH

Fig. 2. Flowchart of pediatric FH diagnosis

Although diagnostic criteria differ from country to country even in Europe[53], where FH research is active, the European Atherosclerosis Society (EAS) has recommended to screen at 5 years old and established the following criteria for pediatric FH: (1) LDL-C ≥ 190 mg/dL, (2) LDL-C ≥ 160 mg/dL and family history of premature CAD or hyper-LDL cholesterolemia in one parent, or (3) LDL-C ≥ 130 mg/dL and a pathogenic gene mutation in the parent (or a pathogenic gene mutation in the patient), while LDL-C 110 mg/dL or higher should be followed[43].

Flowchart of Diagnosis (Fig. 2)

FH is diagnosed when (1) both item 1 (≥ LDL-C 140 mg/dL) and item 2 are met, (2) both the individual's LDL-C is ≥ 180 mg/dL and item 3 is present, or (3) the LDL-C is ≥ 250 mg/dL. Once the diagnosis of FH is made, differentiate between heterozygotes and homozygotes as needed. In addition, the diagnosis of "FH" is made if the genetic test shows pathogenic mutations. (1) If items 1 and 3 are present, or (2) if the individual's LDL-C is only ≥ 180 mg/dL, the patient is "probable FH." If item 2 or item 3 is present but LDL-C is 100–139 mg/dL, or if LDL-C is 140–179 mg/dL but family history is not clear, FH cannot be ruled out, and annual follow-up should be done (yellow on chart). Otherwise, i.e., if there is a family history of FH, including item 3, but LDL-C is <100 mg/dL, or if there is no family history at all and LDL-C is <140 mg/dL, it is considered "unlikely" (not inherited). In this case, no follow-up is required (white on the chart).

In cases that are difficult to diagnose, consult with a specialist and consider genetic testing. If LDL-C increases during the course of the disease or if a family history becomes apparent, the diagnosis should be re-assessed.

Screening for Pediatric FH

With the enactment of the Basic Law for Child and Maternal Health and Child Development in 2019, it is required to provide the seamless provision of necessary child-rearing medical care, etc., to children in the process of growing up and their guardians and others. It is important to establish a screening system that enables early diagnosis, early treatment, and follow-up of pediatric FH.

In the 1990s, universal screening was conducted in Kumamoto City with the cooperation of the local government using 1 year and 6-month health

Table 2. Differential Diagnosis of Secondary Hyper-LDL cholesterolemia

disease name	Points of differentiation
Nephrotic syndrome	Increased cholesterol and apoprotein synthesis in the liver. Edema is observed. It is important to check proteinuria and serum albumin levels.
Obesity	Measure height, weight, percentage of body fat, waist circumference, etc. and correctly evaluate the degree of obesity. High TG and low HDL-C occurs mainly by visceral fat accumulation. LDL-C also tend to be high.
Hypothyroidism	Systemic metabolic function decreases. Hyper-LDL cholesterolemia is caused by decreased expression and activity of the LDL receptor. Because Hashimoto's disease is common, autoantibodies should be measured.
Anorexia nervosa	The patient presents with a high degree of emaciation. Low T3 syndrome leading to hyper-LDL cholesterolemia. Sex hormones and other factors are also suppressed.
Diabetes mellitus	Diagnosis is based on blood glucose and HbA1c levels. Hyper-LDL cholesterolemia, hypertriglyceridemia, and hypo-HDL cholesterolemia are often seen. Diabetes is a major risk for atherosclerotic disease, and glycemic control alone has little preventive effect.
Cushing's syndrome	Excessive cortisol secretion promotes VLDL synthesis in the liver, resulting in hyper-LDL cholesterolemia. In children, the disease is characterized by weight gain without height growth and early onset of puberty due to androgen excess.
Pheochromocytoma	Excessive secretion of catecholamines promotes VLDL synthesis in the liver, resulting in hyper-LDL cholesterolemia. Suspected when symptoms such as headache, palpitations, sweating, and hypertension (paroxysmal or persistent) are present.
Diet related (excessive intake of cholesterol)	Excessive cholesterol intake may cause hyper-LDL cholesterolemia. In particular, if breastfeeding results in marked hyper-LDL cholesterolemia, the child should be retested after weaning to differentiate from sitosterolemia. Examine for the presence of xanthomas.
Cholestatic liver disease	FH-like hyper-LDL cholesterolemia may occur with biliary atresia and cholestatic liver disease.
Drug-induced (steroids, cyclosporin, etc.)	The diagnosis and treatment can be made by with drawal or reduction of the suspected drug.

checkups, wherein many pediatric HeFH were identified[54]. Currently, several municipalities and medical associations are taking the lead in implementing pediatric lifestyle-related disease checkups, including LDL-C testing. However, the follow-up system is not sufficient in many areas. In Kagawa Prefecture, universal screening for FH has been conducted since 2018 using the Kagawa Lifestyle-related Disease Prevention Health Examination for 4th graders in elementary schools throughout the prefecture. Many pediatric HeFHs have been identified and followed through the combined efforts of the government, medical associations, and core hospitals[44]. With children as the probands, CAD has become evident in their parents, and the establishment of a pediatric FH screening system (reverse cascade screening), in addition to traditional cascade screening, is expected to dramatically improve the diagnosis rate of FH in both children and adults.

When conducting cascade screening, it is important to remember that FH is primarily an autosomal dominant inherited disease. If one parent is HeFH, there is a 50% chance that the child will also be HeFH, and if both parents are HeFH, the child has a 25% chance of being HoFH and a 50% chance of being HeFH. Additionally, one of the parents of an FH-affected child found by reverse cascade screening is FH.

Since early diagnosis of FH can prevent atherosclerotic heart disease, it is recommended that at least TC be tested once there is an opportunity to draw blood. High-risk cases should be diagnosed by testing for LDL-C at 10 years at the latest (earlier for HoFH). Pediatric HeFHs are eligible for chronic pediatric diseases and are subsidized for medical expenses.

Differential Diseases

Secondary hyper-LDL cholesterolemia, as shown in **Table 2**, should be excluded. Many of these are conditions that can be diagnosed and treated. Other diseases that are particularly important to differentiate from HoFH are listed in **Table 3**. All these present an

Table 3. Differential Diagnosis of Primary hyper LDL cholesterolemia

Disease name	Cause	Identifying points
Sitosterolemia	ATP-binding cassette sub- family G member 5/8 (*ABCG5*, *ABCG8*) abnormality	Autosomal recessive inheritance Raised serum sitosterol Hyper-LDL cholesterolemia may not be significant even in the presence of xanthomas. Transiently in infancy, patients may present with hyper-LDL cholesterolemia at levels suspicious for HoFH.
Cerebrotendinous xanthomatosis (27-hydroxylase deficiency)	Sterol 27-hydroxylase (*CYP27A1*) abnormality	Autosomal recessive inheritance Progressive neurological disorders Raised serum cholestanol Serum cholesterol levels may not be high, but xanthomas are prominent. It also accumulates in the brain.
Wolman disease Cholesteryl ester storage disease (lysosomal acid lipase deficiency)	Lysosomal acid lipase (*LIPA*) abnormality	Autosomal recessive inheritance Hepatomegaly Typical cases present with marked hepatosplenomegaly and liver damage leading to fatty liver and cirrhosis, but the severity of the disease varies and some cases are not diagnosed until adulthood. Adults often present with hyper-LDL cholesterolemia .

autosomal recessive form of inheritance.

About Genetic Testing

Ethical considerations must be made regarding genetic testing (germline human genetic testing) for FH, whether in adults or children. The Japanese Association of Medical Science's "Guidelines for Genetic Testing and Diagnosis in Medical Care" is a guideline for conducting genetic testing[55]. According to this, when testing a child, it is necessary to obtain the consent of a person who is in a position to consent to the test on behalf of the child, and the best interests of the examinee should be fully considered in doing so. In addition, it is desirable to provide explanations that are appropriate to the level of understanding of the examinee and to obtain his/her consent (informed assent). Also provide genetic counseling as needed. For a definitive diagnosis in cases where the disease is already present (e.g., high LDL-C levels), genetic testing can be considered in children as needed, since there are treatment options for FH. On the other hand, for diagnosis of asymptomatic disease (no symptoms at all, including cholesterol), genetic diagnosis should be postponed until the patient is an adult and able to make autonomous decisions. The handling of incidental/secondary findings in genetic testing as part of the research framework is the policy of each principal investigator and should be well explained and understood when obtaining informed consent from the participant[56].

Genetic testing for HoFH has been covered by insurance from April 2022 in Japan and is expected to be used for the definitive diagnosis and selection of treatment options.

Genetic Counseling in FH[57]

Genetic counseling should be provided at the appropriate time, if necessary, at the time of genetic testing and diagnosis. Genetic counseling should provide not only information but also psychological and social support to allow the patient/subject to make autonomous choices. Therefore, genetic counseling should be performed as a team medicine, with cooperation between physicians with extensive experience treating FH and persons skilled in genetic counseling (such as clinical genetic specialists and certified genetic counselors). As the basic form of FH is an autosomal dominant inherited disease, the case of autosomal dominant inheritance due to abnormalities in three etiologic genes (*LDLR*, *APOB*, *PCSK9*) is described here. If the child is HeFH, either parent is HeFH. If one parent is HeFH, there is a 50% chance that the child will also be HeFH, and if both parents are HeFH, the child has a 75% chance of developing this disease (25%: HoFH, 50%: HeFH). When both parents of an HeFH child are clinically unremarkable, it is necessary to consider the possibility of a *de novo* mutation in the affected child, or both parents have mild symptoms, or the child is not truly related to the parents by adoption. Prenatal diagnosis and preimplantation diagnosis are attempted in some cases; however, these procedures should be considered

very carefully, given that there is no intellectual abnormality and treatments exist even if the child is homozygous for FH.

Notes on Genetic Test Results for FH

Like other genetic diseases, not just FH, current genetic testing also has its limitations. The detection rate of pathogenic mutations in clinically diagnosed cases of FH is reported to be approximately 60%–80% in adults[58]. Furthermore, approximately 10% of the causative genetic mutations in FH are structural mutations in the *LDLR*[58]. Therefore, care should be taken because some analytical methods do not identify such structural variations.

4. Diagnosis of Pediatric HoFH

Key Points

- The child meets the diagnostic criteria for pediatric FH; in many cases, the parents are heterozygous for FH.
- Skin or tendon xanthomas are present, and LDL-C levels are approximately twice those of the parent.
- Two pathogenic mutations are identified in the FH causative gene.

Clinical Presentation of Pediatric HoFH

As a rule, pediatric HoFH inherit the FH-causing gene mutation from both parents and are clinically diagnosed when serum LDL-C levels are approximately twice those of parents and other family members who are HeFH. Untreated LDL-C is usually ≥ 500 mg/dL; if ≥ 400 mg/dL, suspect HoFH. It is important to confirm serum levels of LDL-C in family members (parents and siblings), clinical characteristics such as tendon xanthomas, premature CAD, and the presence of consanguineous marriages as much as possible. HoFH are exposed to very high LDL-C from fetal life, and the appearance of cutaneous xanthomas at skin flexures such as wrists and ankles during infancy is often a trigger for consultation. Nodular xanthomas, interdigital xanthomas, and buttock xanthomas are also findings suggestive of HoFH. These manifestations improve with early LDL-C lowering therapy. Tendon xanthomas are usually unremarkable in infancy, but appear earlier than HeFH and are highly thickened.

Genetic Testing for HoFH

As mentioned above, the diagnosis of HoFH, in the broad sense, is confirmed when two pathogenic mutations in the FH causative gene (*LDLR*, *PCSK9*, *APOB*) are identified at two loci. When two pathogenic mutations in *LDLRAP1* are identified across two loci, it leads to the diagnosis of ARH.

In Japan, double heterozygotes with *LDLR* and *PCSK9* gain-of-function mutations have been reported. Their phenotypes were milder than that of true homozygotes or compound heterozygotes with *LDLR*, and the response to pharmacotherapy such as statins was preserved[59, 60]. Even when two *LDLR* mutations are present, the receptor-defective type is considered less severe than the receptor-negative type. As HoFH patients with different mutations respond differently to treatment, it is advisable to confirm the genetic mutation as much as possible when FH homozygosity is suspected. Note that in the case of double heterozygotes, phenotypic inheritance may not follow a simple Mendelian inheritance form, as the HoFH phenotype may be inherited from one parent, or, conversely, the child may have the normal form. This kind of definitive diagnosis, including comprehensive genetic tests, such as panel analysis, may lead to a differential diagnosis of sitosterolemia and other disorders[61].

Notes on Diagnosis

The clinical presentation of HoFH can vary to some extent, and even patients whose LDL-C below 500 mg/dL may be diagnosed as HoFH based on genetic testing.

HoFH are known to have a very poor prognosis, as atherosclerotic diseases such as coronary atherosclerosis and aortic valve disease (Appendix Fig.1) rapidly progress from childhood, and they may die at their childhood. In addition, cutaneous xanthomas are often seen in HoFH (Appendix Fig. 2).

If HoFH is suspected, such as the presence of cutaneous xanthomas, marked tendon xanthomas, or higher levels of LDL-C levels compared with HeFH, a diagnosis and treatment plan must be determined by a specialist such as a Japan Atherosclerosis Society Board Certified Specialist. For a list of facilities where FH patients can be referred and the physicians in charge, please refer to the website of the Japan Arteriosclerosis Society (https://www.j-athero.org/jp/wp-content/uploads/specialist/pdf/fh_institution.pdf).

HoFH are also designated as intractable diseases in addition to chronic childhood diseases and are eligible for subsidies for medical expenses.

Differential Diagnosis

If there is no clinical evidence of HeFH in both parents, ARH or other conditions are suspected. Other diseases in which xanthomas are prominent include sitosterolemia, in which serum plant sterols are elevated, and cerebrotendinous xanthomatosis, in which serum cholestanol is elevated **(Table 3)**.

Sitosterolemia, in particular, can present with highly variable cholesterol levels and skin and tendon xanthomas with LDL-C levels similar to those of HoFH in infancy[62].

5. Evaluation of Atherosclerotic Disease in Pediatric FH

Key Points

- If Achilles tendon thickening and carotid atherosclerosis are observed in patients with HeFH, regular examination considering the possibility of CAD is advisable.
- Due to the early development of atherosclerotic lesions in patients with HoFH, regular evaluation of systemic atherosclerotic disease by a specialist is necessary. In particular, evaluation for the presence of CAD, aortic valve and supravalvular stenosis, and thoracic and abdominal aortic aneurysms is recommended.
- In children, the examination should start with ultrasound methods (carotid ultrasound, transthoracic echocardiography, and abdominal ultrasound) to avoid the effects of radiation exposure as much as possible.
- If deemed necessary, CAD is screened by coronary computed tomography (CT), and if stenosis is suspected, coronary angiography is performed after hospitalization.

FH Heterozygote

HeFH develop CAD less frequently in childhood, but atherosclerotic lesions develop earlier than in healthy children, so non-invasive testing should be performed primarily when necessary. The presence of thickening or plaque on carotid ultrasound, or thickening of the Achilles tendon, should prompt suspicion of atherosclerotic disease and periodic examination.

HoFH

1) Interview

Ischemic symptoms of CAD can occur even in childhood, including chest pain and anterior chest tightness during exertion and radiating pain to the neck and left hand, which should be assessed for improvement with rest. For peripheral artery disease (PAD), the patient is asked if he or she has muscle pain (intermittent claudication) when walking and if it disappears with rest. In aortic valve and supravalvular stenosis, the patient should be asked about shortness of breath during exertion.

2) Physical Findings

Although the physical findings of CAD remain scarce, confirm the presence or absence of arterial pulsatility and attenuation, especially in the lower extremities by palpation of the femoral, popliteal and dorsal ankle arteries, and measurement of the ankle-brachial index when PAD is suspected. A systolic murmur of the aortic valve in auscultation suggests aortic valve/supravalvular stenosis, and a vascular murmur in the limb arteries suggests arterial stenosis.

3) Biochemical Examination

CK-MB and cardiac troponin are elevated during acute myocardial infarction.

4) Morphological Examination

Non-invasive examination

Exercise stress EKG: Exercise stress EKG using a treadmill is useful, but it should be performed after evaluating the presence of aortic and supravalvular stenosis by transthoracic echocardiography. Be aware of the risk of ventricular fibrillation, etc., due to induced myocardial ischemia.

Ultrasound: It is useful for assessing the degree of peripheral arteries, especially the carotid arteries, and is evaluated by the presence or absence of plaque and changes in IMT, and the rate of change over time is also considered. Transthoracic echocardiography is used to diagnose aortic valve and supravalvular stenosis and to evaluate cardiac function.

CT: Cerebrovascular lesions are rare in pediatric HoFH, and the evaluation of the coronary artery is the main focus. Due to the high radiation dose, coronary CT should be performed only when necessary in children.

Magnetic resonance imaging (MRI), MRA (MR angiography): It is now possible to delineate stenotic lesions of the aorta, peripheral arteries, and coronary arteries. CT and MRI scans require sedation depending on the age of the patient, and care must be taken to avoid accidents.

Invasive Examination

If progression of atherosclerosis is suspected, angiography is used to evaluate the narrowing of the luminal diameter of the vessel, but radiation exposure should be reduced as much as possible. In particular, if CAD is suspected, the patient should be admitted to the hospital for coronary angiography and left ventricular and aortic angiography as well.

6. Treatment of Pediatric FH

Once FH is diagnosed, lifestyle advice should be provided as early as possible in order to reduce the risk of atherosclerosis, including lowering LDL-C levels. If

lifestyle modification is insufficient, consider starting drug therapy at around 10 years of age. Pediatric HoFH should consult with a specialist to determine response to pharmacotherapy, and if the response is inadequate, initiate lipoprotein apheresis immediately.

1) Lifestyle Improvement/Guidance

Key Points

- Provide guidance on lifestyle, including diet, as early as possible. The guidance should continue after the initiation of drug therapy.
- Diet: Total energy intake should be calorie requirements by age and height. The energy ratio should be 20%–25% fat and 50%–60% carbohydrates. Saturated fatty acids should be less than 7% of the energy ratio and cholesterol less than 200 mg/day. Reduce trans-fatty acid intake. Focus on traditional Japanese food and eat enough vegetables.
- Obesity control: Maintain an appropriate weight. Severe obesity also requires limiting energy intake. Develop a proper rhythm of life, eating habits, and exercise routines.
- Exercise therapy: Attempt to develop and maintain an exercise routine. Encourage patients to lead active lifestyles, which include avoiding long periods of sedentary time.
- Prevention of smoking and passive smoking: Emphasize the point that the patient should never smoke during their lifetime. In addition, the cooperation of family and those around the patient should be obtained in preventing passive smoking.

Lifestyle Guidance

Once FH is diagnosed, lifestyle guidance should begin as early as possible for HoFH and heterozygotes alike[45]. Investigate lifestyle habits, including diet, exercise habits and rhythm of life, and guide improvements[45]. However, it is often difficult to reduce and manage LDL-C levels by lifestyle modification alone. In such cases, pharmacotherapy should be added, and lipoprotein apheresis should be considered for patients homozygous for FH[63]. After the start of these treatments, the guidance regarding lifestyle habits should continue **(Figs. 3 and 4)**.

Dietary Therapy

Even in the absence of obesity, total daily energy intake should be the required calorie intake by age and height to maintain an appropriate body weight[64]. Evaluate the progress of height and weight over time, and adjust diet and exercise accordingly.

For energy distribution, the 2017 edition of the Guidelines for the Prevention of Atherosclerotic Disease recommends a fat energy ratio of 20%–25% and a carbohydrate energy ratio of 50–60% for dyslipidemia in adults[45]. The Dietary Reference Intakes for Japanese (2020) recommend a fat energy ratio of 20%–30% and a carbohydrate energy ratio of 50%–65%[64], which is the same from age 1 to 75 years and older, so children should also follow the same standards as adults.

The Dietary Reference Intakes for Japanese (2020) do not set an upper limit for cholesterol intake because of the large individual differences in cholesterol absorption from the diet and the inconsistent effects of diet therapy[64]. However, in hypercholesterolemic patients, cholesterol intake restriction has also been suggested to be effective in lowering LDL-C[65]. In the 2017 edition of the Guidelines for the Prevention of Atherosclerotic Diseases, the Japan Atherosclerosis Society recommends less than 7% saturated fatty acids, reduced trans-fatty acids, and less than 200 mg/day of cholesterol for hypercholesterolemia[45, 63, 66].

In recent years, due to westernization of diets, fat intake has tended to be high even in children. As in adults, a slight moderation in fat and carbohydrates is needed. In other words, children should be instructed to eat a diet based on traditional Japanese food patterns, with low intake of animal fat and a good balance of fish, vegetables, soybeans (products), mushrooms, and fruits. Also, beware of excessive salt intake[45, 63].

Anti-Obesity Therapy

1) Prevention of Obesity

Use the percentage of overweight (POW) to determine obesity in children[67, 68]. POW is a physique index obtained by [(actual weight/standard weight)/standard weight] × 100(%). Use the standard weight by sex, age, and height according to school health statistics as the standard weight. The appropriate POW is within ± 20% for schoolchildren and ± 15% for young children (< 6 years old)[67].

Visceral fat evaluation is also important in children, as excessive accumulation of visceral fat can lead to abnormal secretion of various adipocytokines[68, 69]. Waist circumference is a useful alternative to CT for a simple marker of visceral fat accumulation. The standard for school-age children is 80 cm, above which visceral fat over-accumulation is suspected[68].

In dietary guidance, reference should be made to the guidelines for intake by four food groups based on the Dietary Reference Intakes for Japanese (2020)[64]. Use the "Dietary Balance Guide[70]" for meal distribution.

The 2017 Guidelines for the Management of

Obesity Disease in Children and Adolescents recommend at least a total of 60 minutes per day of moderate- to high-intensity exercise as physical activity to prevent obesity[67]. It is also important to regulate the rhythm in life. For young children, it is recommended that they sleep at least 10.5 hours and watch no more than 2 hours of TV; for school-age children, it is recommended that they avoid sleeping less than 8 hours and long periods of screen time[67].

2) In Case of Obesity

If there is an excess of dietary intake, it should be restored to an appropriate level. However, due to the growth period, energy intake should not be extremely restricted, but rather nutritional balance should be maintained, and energy expenditure through exercise should be increased[67]. Energy intake should be set according to the level of physical activity for each sex and age group[64]. In the case of severe obesity, energy intake can be limited to 90%.

Exercise Therapy

In HoFH and severe cases of HeFH, exercise instruction should be given after a cardiac ultrasound and a close examination for CAD (see the Examination section). Exercise therapy is as important as dietary guidance because it improves glucose and lipid metabolism and optimizes adipocytokines in children[70]. In particular, obese children and children who do not have an exercise routine should be thoroughly instructed.

In adults, it is recommended that aerobic exercise, mainly at moderate intensity or higher, be performed regularly (at least 30 minutes total daily, with a goal of at least 3 days per week)[45, 63], and the same should be done in children. In the early elementary grades, the main focus will be on increasing the amount of physical activity, such as encouraging outdoor play.

Prevention of Smoking and Passive Smoking

Smoking is not only a risk factor for atherosclerotic disease, but it also increases the risk of developing diabetes, dyslipidemia, and metabolic syndrome and is associated with a general increased risk of atherosclerotic disease[45, 63]. Teach children from childhood to avoid smoking throughout their lives. Moreover, passive smoking is a risk factor for CAD and stroke. It has also been reported to increase the risk of diabetes[45, 63]. Promptly encourage all those around children, including family members, to quit smoking.

2) Pharmacotherapy of Pediatric HeFH

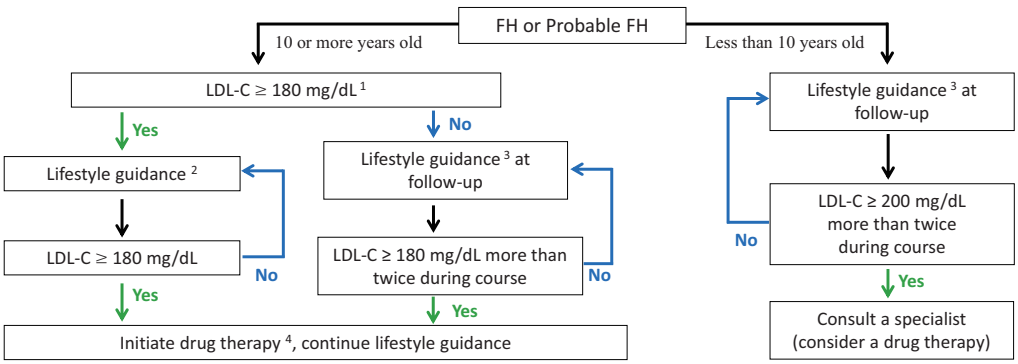
Key Points

- If LDL-C 180 mg/dL or higher persists after adequate lifestyle guidance, drug therapy should be considered at age 10, regardless of sex.
- The target of management is an LDL-C level of less than 140 mg/dL.
- First-line drug therapy is statins, starting with the lowest dose. In addition to lipid levels, blood tests such as liver function and CK, and other parameters, as well as symptoms such as muscle pain should be followed every month at first and then every 3–4 months once the dosage has stabilized, to monitor for the onset of side effects. Simultaneously monitor growth and also secondary sexual characteristics.
- The cases of "probable FH" are considered in the same way as FH. Adequate lifestyle guidance should be provided, and drug therapy should be considered, taking into account LDL-C levels and background factors.

Criteria for Consideration of Drug Treatment Initiation

Hyper-LDL cholesterolemia from childhood is an independent risk of atherosclerosis, and IMT thickening is already known to develop in many pediatric HeFH from late school-age[71]. In recent years, many overseas guidelines have highlighted the importance of treatment from childhood for the prevention of future cardiovascular events[43, 72, 73]. In administering drug therapy to pediatric HeFH, it is thus important to fully explain the need for treatment to parents and, whenever possible, to the affected child, to gain their understanding, given the long-term nature of the medication.

Fig. 3 shows the treatment flowchart for pediatric HeFH. If LDL-C 180 mg/dL or higher persists despite lifestyle modifications such as diet and exercise, consider starting drug therapy at 10 years of age or older, regardless of gender[43, 72, 73]. In cases of markedly elevated LDL-C, drug therapy should be administered as early as possible, as improved diet and lifestyle alone are not sufficient to lower LDL-C. Cases around 180 mg/dL should be monitored, taking into account pubertal fluctuations, and if they continue to exceed 180 mg/dL (multiple times), drug therapy should be administered. The "probable FH" cases are also likely to be FH, and persistent LDL-C 180 mg/dL or higher is an indication for pharmacotherapy. Cases requiring pharmacotherapy should be referred or consulted with a specialist to determine a treatment plan. Even in patients younger than 10 years, consult a specialist in cases of persistently markedly high levels of 200 mg/dL or



1. Check multiple times.
2. In the case of very high LDL-C, LDL-C level should be reevaluated after about one month of guidance and the patient should be initiated to drug therapy. Cases that are slightly above 180 mg/dL should be followed up periodically to ensure that they have exceeded 180 mg/dL, and then initiated to drug therapy.
3. Continue lifestyle guidance and evaluate LDL-C levels several times a year.
4. The first-line drug should be a statin. The control target value should be less than 140 mg/dL. Ensure <140 mg/dL if there is a family history of premature CAD, diabetes, hypertension, high-Lp(a), or obesity.

	The child's LDL-C (mg/dL)				
	<100	100-139	140-179	180-249	≥250
Family history of FH	Unlikely	Possible	FH	FH	FH
Parental LDL-C ≥ 180 mg/dL or family history of premature CAD	Unlikely	Possible	Probable	FH	FH
No family history of FH	Unlikely	Unlikely	Possible	Probable	FH

＜10 or more years old＞

Orange: Indications for drug therapy
Blue: Follow-up several times a year
Light blue: Follow-up once a year

Fig. 3. Flowchart of treatment for pediatric FH heterozygotes

higher even after dietary guidance. Early initiation of drug therapy should also be considered, taking into account LDL-C, age, risk factors, and family history.

Drug Selection

The first-line drug is statin, starting at the lowest dose. In Japan, pitavastatin has been indicated for children 10 years of age and older since 2015. Looking at the status of pediatric indications for statins in each country, simvastatin, atorvastatin, pravastatin, fluvastatin, and rosuvastatin have been approved for pediatric use in the United States and Europe. Most are approved for use in children as young as 10 years, but pravastatin has been approved for use at ages 8 and up in the United States, rosuvastatin at ages 6 and up in Europe, and atorvastatin at ages 6 and up in Australia. If statin alone is found to be not effective enough, consider (1) increasing the dose, (2) changing to a more intensive one and increasing the dose, or (3) combining a lipid-lowering drug with another mechanism in addition to the statin.

Adjunctive agents that have been reported to be effective in childhood are small intestinal cholesterol transporter inhibitors (ezetimibe) and resins (anion exchange resins: cholestyramine and cholestimide). Ezetimibe is indicated in the United States and Europe for children 10 years of age and older. Resin had also been the first-line drug for children in Japan due to its history as the first-line drug for hypercholesterolemia in the United States in the past. However, it has many side effects such as abdominal pain, bloating, and constipation and thus is not indicated for pediatric use in Europe, and there is little evidence of its effectiveness in preventing atherosclerosis. It inhibits the absorption of folic acid and fat-soluble vitamins, so regular monitoring and occasional supplementation are required. In a recent survey of eight European countries, about half of the statin-treated children were on combination therapy, although there were differences from country to country, and ezetimibe was used very commonly as a concomitant drug (96% of all concomitant cases)[53]. Even in children, the combination of high-intensity statins and ezetimibe can reduce LDL-C by approximately 50% of the pretreatment values. Combined agents of statin and ezetimibe are currently available in Japan.

LDL-C Control Target Values

The target value for the management of pediatric FH is the same as in Pediatric FH Guide 2017 [3], with an LDL-C level of 140 mg/dL. Ensure to maintain

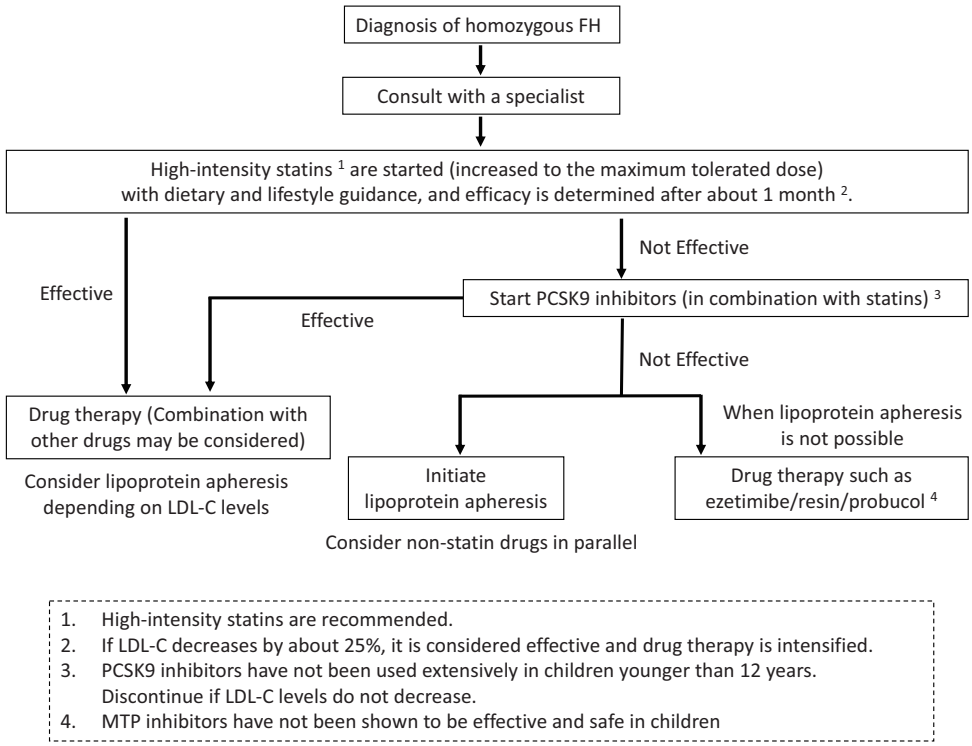


Fig. 4. Flowchart of treatment for pediatric FH homozygotes

below 140 mg/dL in cases with a family history of premature CAD or risk factors such as diabetes (described later). Although it is difficult to achieve the goal in severe cases, try to get as close to the goal with the use of drug combination therapy. Even after the start of drug therapy, lifestyle guidance, including diet, should be provided. The LDL-C control goal for adults is less than 100 mg/dL. For reference, the ESC/EAS guideline is <135 mg/dL for children[43].

Risk Factors

In addition to common risk factors such as smoking (passive smoking), hypertension, diabetes, other dyslipidemias, and obesity, Lp(a) has been emphasized abroad.

Lp(a) is a lipoprotein consisting of apoprotein(a) S-S bound to B-100, the apoprotein of LDL, and its molecular weight is noted to vary from individual to individual. Apoprotein (a) is highly homologous to plasminogen and is considered highly atherosclerosis-promoting in terms of both lipid deposition and thrombus formation[74]. Hyper-Lp(a)emia is associated with a 1.5-fold increased risk of premature CAD[43]. There are also reports of Lp(a) deposition in the aorta (mainly near the internal elastic plate) from the age of 10 [75]. Serum Lp(a) concentrations can vary widely among individuals, are independent of LDL-C, and are strongly influenced by genetic factors. In Japan, a level above 30 mg/dL is generally considered high for adults[63], and the same is true for children. Sometimes, there are cases of very high Lp(a) even in pediatric FH. In patients with hyper-Lp(a)emia, it is recommended that LDL-C should be maintained at <140 mg/dL after starting therapy, considering the same risk factors.

Follow-Up

The safety and tolerability of statins in children are similar to those in adults. Statin use in children should be started at the lowest dose, and symptoms such as liver function, including AST and ALT, CK, serum lipid levels, and muscle pain should be evaluated 1 month after initiation. Compared to values prior to drug initiation, the development of side effects such as hepatic dysfunction, myopathy, and, although extremely rare, rhabdomyolysis, should be noted. The patient continues to be examined and tested in the following month, if necessary, depending on the state of LDL-C decline and side effects. If there are no side effects and the LDL-C level and other parameters are stable, follow-up visits should be conducted three to four times a year.

In children, growth and pubertal state (secondary sexual characteristics) should also be routinely

assessed. In children, CK elevation is often seen with strenuous exercise, so it is important to distinguish CK elevation from drug-induced elevation. It is advisable to follow-up on blood glucose levels and HbA1c, as statins have been reported to increase new onset of diabetes in adults[76]. Special attention should be paid to side effects when taking high doses of statins.

For Cases where Statins are Difficult to Continue

There are rare cases in which statins are difficult to continue due to strong side effects. Currently, six statins are available in Japan, with slightly different strengths of LDL-C lowering and metabolic pathways. If side effects occur with one statin, it is advisable to start with a lower dose of a statin with a different metabolic pathway. For the cases of so-called statin intolerance, in which multiple statins cannot be used, the Japan Atherosclerosis Society has published the "Statin Intolerance Clinical Guide 2018 [77]". The "Muscle Flowchart" and "Liver Flowchart" are defined for two major categories of reasons for the difficulty in continuing statins: muscle damage and liver dysfunction.

For Patients under 10 Years of Age

As mentioned above, in cases of persistently high LDL-C (≥ 200 mg/dL) in children younger than 10 years, drug therapy should also be considered, taking into account the background of the affected child. Although there is no evidence, the theory of cumulative LDL-C (Chol-year) suggests that the earlier it is lowered, the better the prognosis. It needs to be lowered immediately, especially if it is markedly high, as in the case of HoFH.

The problem is that younger children cannot take the tablets. Crushed statin tablets are not suitable for administration. Pitavastatin and rosuvastatin are available in tablets that disintegrate orally, making them relatively easy to take for those under 10 years of age, but only pravastatin is available in a powder formulation. Ezetimibe is a tablet, but it is the size of a grain of rice (8.1 mm × 4.1 mm), making it relatively easy to take internally. Currently in Japan, the indication for pitavastatin is strictly for ages 10 and older, and ezetimibe also does not have a pediatric indication. In general, many drugs in the pediatric field have "no established safety profile for children," but in reality, they are used empirically for many diseases. For younger children, there is also an option of waiting until the age of 10 years to intensify the treatment, since it is not necessary to lower the level to the control target (140 mg/dL), as it can be considered a popular HeFH level if it is lowered to 200 mg/dL or less.

Pregnancy

Since there have been reports of malformations in newborns of pregnant women who accidentally took statins in early pregnancy[78], statins are contraindicated in women who wish to become pregnant, pregnant women, and nursing mothers[45]. When starting statins in girls, explain the risks of teratogenicity and the importance of a planned pregnancy to the patient and her parents prior to starting.

(3) Pharmacotherapy of Pediatric HoFH

Key points

- Once HoFH is diagnosed, they should consult with a medically experienced specialist. Determine the effect of statins as early as possible, and if the reduction in LDL-C levels is not sufficient, PCSK9 inhibitors and further lipoprotein apheresis therapy should be initiated. In parallel, additional administration of other drugs should be considered.
- Probucol is effective in promoting the reduction and disappearance of skin and tendon xanthomas, but the side effect of QT prolongation should be noted.

Genetic Mutations and the Effects of Drug Therapy

The efficacy of lipid-lowering drugs such as statins, ezetimibe, and resins is primarily attributed to increased LDLR activity, and HoFH are often less responsive to drugs than HeFH. For HoFH of receptor-negative type that have no LDLR activity, the above drugs are not effective in lowering LDL-C levels, but improved prognosis has been reported with statin administration[79]. On the other hand, for the receptor-defective type, which has a small amount of LDLR activity, there are reports of significant efficacy of combination therapy with resins, statins, nicotinic acid, etc.[80]. In cases called double heterozygotes, in which the patient has an *LDLR* loss-of-function mutation and a *PCSK9* gain-of-function mutation, a certain level of efficacy can be expected.

Pharmacotherapy Practice

The treatment of HoFH should be performed by a specialist with medical experience. Treatment and drug use should only be started after the effects and possible side effects have been fully explained to parents or guardians and their consent obtained. If diagnosed as HoFH, any of the above types should first be started on high-intensity statins and increased to the maximum tolerated dose. After approximately 1 month, the effect of statins will be determined, and if the effect is insufficient, a PCSK9 inhibitor will be

started to check the response of LDL-C levels. If the target values are not reached after three doses, lipoprotein apheresis is then initiated. Parallelly, examine the effects of drugs other than statins (e.g., ezetimibe, resin, probucol) **(Fig. 4)**. A report examining the effect of atorvastatin on HoFH under treatment with lipoprotein apheresis showed an average decrease in LDL-C levels of approximately 20%, with little response in the receptor-negative type[81]. Probucol has been reported to have a certain lowering effect on TC levels (lowering of LDL-C and HDL-C) and reduction or disappearance of skin and tendon xanthomas in HoFH[82]. In a retrospective study examining adult HeFH in Japan, significantly fewer recurrent cardiovascular events were reported in patients treated with probucol[83]. However, probucol has the side effect of QT prolongation[84] and thus requires periodic ECG testing[85]. Ezetimibe has been reported to be effective in delaying post-treatment re-elevation of LDL-C levels in HoFH undergoing lipoprotein apheresis treatment[86].

PCSK9 inhibitors, which inhibit LDLR degradation, have been shown to be effective in lowering LDL-C even in adult HoFH[31], but there is not much experience with their use in younger than 12 years of age, even overseas. Although there are benefits in lowering LDL-C early in children, it should be noted that safety has not yet been fully tested. If LDL-C levels do not decrease with receptor-negative type, discontinue early. In addition, PCSK9 inhibitors are supposed to be used in combination with the maximum tolerated dose of statins in Japan. Microsomal triglyceride transfer protein inhibitor (lomitapide) is an oral drug indicated only for HoFH, but has been reported to have side effects of gastrointestinal symptoms, liver dysfunction, and fatty liver; thus, caution should be exercised, especially in pediatric patients. Currently, pediatric indications are not approved in any country.

Liver transplantation is an option for patients who are resistant or intolerant to all of the above treatments, but there are currently very few cases of liver transplantation in Japan[87, 88].

7. Lipoprotein Apheresis

Key Points

- If drug therapy is not adequate, initiate lipoprotein apheresis therapy promptly.
- Lipoprotein apheresis therapy should be performed once every 1–2 weeks while monitoring LDL-C levels before and after treatment.
- Three different methods are used: simple plasma exchange therapy, double membrane filtration, and selective LDL adsorption.

Start of Lipoprotein Apheresis Therapy

HoFH generally respond poorly to drugs, and lipoprotein apheresis therapy is indicated in many cases. Realistically, treatment should begin at 4–6 years of age, when the patient is bedridden and extracorporeal circulation can be performed, although there have been reports of treatment beginning at 3.5 years of age[89]. As there are cases of coronary artery stenosis, complete occlusion, aortic stenosis, and supravalvular stenosis noted in childhood, and the later the time of initiation, the worse the prognosis, one should not hesitate to start lipoprotein apheresis therapy if the response to the drug remains poor[90]. Patients who are too young to be treated with lipoprotein apheresis should have regular checkups and examinations. If possible, pharmacotherapy should be used until a time when apheresis is possible.

Methods of Lipoprotein Apheresis

Lipoprotein apheresis is performed once every 1–2 weeks while monitoring LDL-C levels before and after treatment. Blood access is usually to the elbow veins of both upper extremities. In cases of poor access, shunt surgery may be performed, but care should be taken due to the high-risk of obstruction due to high levels of LDL-C and other factors. Currently, there are three major types of lipoprotein apheresis therapy in Japan, namely, simple plasma exchange, double membrane filtration, and LDL adsorption therapy. Double membrane filtration and LDL adsorption therapy are widely used because they can selectively remove LDL. Plasma exchange therapy may be used for these treatments due to the large extracorporeal circulating volume when the patient weighs less than 30 kg.

Long-Term Therapeutic Effect of Lipoprotein Apheresis for HoFH

There are many reports of favorable long-term effects of lipoprotein apheresis treatment for HoFH, including regression of skin and tendon xanthomas, lessening of symptoms of angina pectoris, and inhibition of the development of atherosclerotic lesions in the coronary arteries, as well as the effect of regression[90-93]. A systematic review from reports of 209 pediatric FH homozygotes also stated that lipoprotein apheresis has few adverse events and is generally safe in lowering LDL-C levels and further reduce xanthomas[35]. On the other hand, if lipoprotein apheresis is delayed in HoFH, there have been reports of deaths from myocardial infarction[93]; thus, lipoprotein apheresis should be introduced in

cases where it is necessary.

8. Supplementary Provisions

Public Subsidies

Pediatric HeFH are eligible for the chronic childhood diseases[94]. HoFH, in addition to being designated as the chronic childhood diseases, are also designated as an intractable disease based on the "Law Concerning Medical Care for Patients with Intractable Diseases[95]" and are eligible for public subsidies for medical expenses.

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Classification of Level of Evidence for Treatment and Diagnosis

1+	High-quality RCTs* and their MA/SR
1	Other RCTs and their MA/SR
2	Prospective cohort studies, their MA/SR, (predefined) RCT sub-analysis
3	Non-randomized controlled trials, before and after studies, retrospective cohort studies, case-control studies, and their MA/SR and RCT post hoc sub-analysis
4	Cross-sectional studies, case series
Consensus	By consensus of the supervisory committee members and the members who prepared the report

RCT: randomized controlled trial, MA: meta-analysis, SR: systematic review

*A high-quality RCT is defined as (1) large number of subjects; (2) double-blind, independent assessment; (3) high follow-up rate (low dropout rate); (3) low protocol deviation, (4) clear random allocation method, etc.

Classification of Level of Evidence for Epidemiological Studies

E-1a	Meta-analysis of cohort studies
E-1b	Cohort studies
E-2	Case-control studies, cross-sectional studies
E-3	Descriptive studies (case series)

Recommended level

A	Strongly Recommended
B	Weakly Recommended

Conflicts of Interest

The following discloses the conflicts of interest of the members of the Joint Working Group of the Japan Pediatric Society and the Japan Atherosclerosis Society for the Development of Guidelines for the Treatment of Pediatric Familial Hypercholesterolemia for the years 2017 - 2021.

Names	Disclosure Item 1	Disclosure Item 2	Disclosure Item 3	Disclosure Item 4	Disclosure Item 5	Disclosure Item 6
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Ohtake A.	None	None	None	Sanofi K.K.	None	SBI Pharmaceuticals Co., Ltd.
	None	None	None	None	None	None
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	None	None	None	None	None	None
Yamamoto M.	None	None	None	None	None	None
	None	None	None	None	None	None

【Disclosure Item】
1. Assuming a position of a board member or advisor in a profit-making business,/ Advisory role (1,000,000 yen or more annual compensation from a single business entity, or group)
2. Stock holdings or options (Annual profit of 1,000,000 yen or more/ownership of 5% or more of total shares)
3. Patent royalties/licensing fees (1,000,000 yen or more annual income per patent)
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5. Fees for promotional materials (e.g. manuscript fee) (500,000 yen or more total annual income from a single company or organization)
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9. Others (e.g. trips, travel, or gifts, which are not related to research) (50,000 yen or more annually from a single company or organization)

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10. Assuming a position of a board member or advisor in a profit-making business,/ Advisory role (1,000,000 yen or more annual compensation from a single business entity, or group)
11. Stock holdings or options (Annual profit of 1,000,000 yen or more/ownership of 5% or more of total shares)
12. Patent royalties/licensing fees (1,000,000 yen or more annual income per patent)
*The company name is the name of the company as it was at the time of filing.

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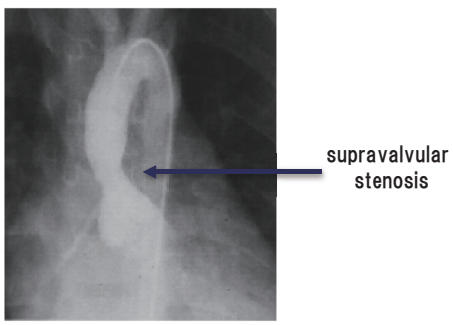
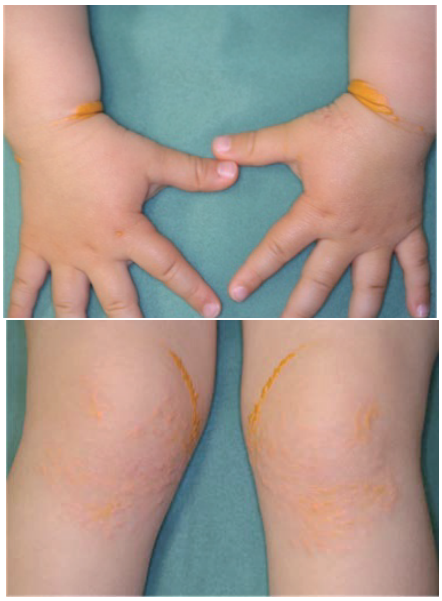


Appendix Fig. 1. Supravalvular aortic stenosis



Appendix Fig. 2. 3-year-old boy, HoFH, xanthoma cutis