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Study Profile

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Prospective Registry Study of Primary Dyslipidemia (PROLIPID): Rationale and Study Design

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Introduction: **Primary dyslipidemias are inherited disorders in plasma lipoprotein metabolism that lead to serious cardiovascular and other complications. The Japanese Ministry of Health, Labor and Welfare (MHLW) covers medical expenses, under the Research Program on Rare and Intractable Diseases, for homozygous familial hypercholesterolemia (FH), familial chylomicronemia, sitosterolemia, cerebrotendinous xanthomatosis, lecithin:cholesterol acyltransferase deficiency, Tangier disease, and abetalipoproteinemia. Apolipoprotein A1 deficiency, heterozygous FH, and type III hyperlipoproteinemia are covered by the MHLW Pediatric Chronic Disease Program. Heterozygous FH and type III hyperlipoproteinemia are also important for their relatively common prevalence and, accordingly, high impact on Japanese public health by significant contribution to the overall prevalence of cardiovascular diseases. Therefore, a systemic survey of these diseases is mandatory to estimate their actual situation, such as prevalence, clinical manifestations, and prognoses among the Japanese population. The impact of these rare and intractable diseases on cardiovascular and other complications will likely be higher among Japanese people than other ethnicities because the general Japanese population has many cardioprotective aspects. The current study intends to conduct a multicenter registry of these diseases to assess their demographics and clinical features comprehensively.**

Methods and Analysis: **The Prospective Registry Study of Primary Dyslipidemia is a registry-based prospective, observational, multicenter cohort study in Japan, enrolling patients who fulfill the Japanese clinical criteria of the primary dyslipidemias listed above, from 26 participating institutes from August 2015 to March 2023. A total of 1,000 patients will be enrolled in the study and followed for 10 years. Clinical parameters are collected, including physical and laboratory findings, genetic analysis, drugs, lifestyle management, and clinical events, especially cardiovascular events. The primary endpoint of this study is the new onset of cardiovascular disease and acute pancreatitis, and the secondary endpoint is death from any causes.**

Ethics and Dissemination: **This study complies with the Declaration of Helsinki, the Ethical Guidelines for Medical and Health Research Involving Human Subjects, and all other applicable laws and guidelines in Japan. The institutional review boards have approved this study protocol at all participating institutes. The final results are to be published at appropriate international conferences and in peer-reviewed journals.**

Trial registration: This study was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN ID: UMIN000042782).

Key words: **Intractable disease, Dyslipidemia, Genetics, Registry**

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Introduction

Molecular and genetic bases have been clarified for many primary dyslipidemias and monogenic inherited disorders of lipid and lipoprotein metabolism during the past decades. There have also been extensive efforts to improve their morbidity and mortality, including attempted gene therapies. However, many of them remain intractable, leaving patients to suffer from poor prognoses by their complications. Under these circumstances, the Japanese Ministry of Health, Labor and Welfare (MHLW) specified seven primary dyslipidemias were "rare and intractable diseases" to cover the cost of their medical care and alleviate patients' economic burden, including homozygous familial hypercholesterolemia (HoFH), sitosterolemia, cerebrotendinous xanthomatosis (CTX), lecithin cholesterol acyltransferase (LCAT) deficiency, Tangier disease, primary chylomicronemia, and abetalipoproteinemia. In addition, APOA1 deficiency, heterozygous FH (HeFH), and type III hyperlipoproteinemia are covered under the MHLW program for Pediatric Chronic Diseases. Heterozygous FH and type III hyperlipoproteinemia are also important because of their relatively high prevalence among the general population and their substantial impact on public health in Japan due to their risk for cardiovascular complications. Both of the disorders are treatable to reduce cardiovascular risk and therefore should be paid more attention to from the public health viewpoint.

Since saving patients with rare and intractable diseases by clarifying the disease causes will surely lead to saving the general dyslipidemias caused by common genetic variations, it is important to investigate the real situation of these diseases across general populations. Some cross-sectional studies estimated the prevalence, clinical manifestations, and complications in Japanese patients with FH or CTX[1, 2]. However, these studies were underpowered because of their relatively small sample size, and cross-sectional nature of study design limits the power of assessments for their clinical events. In that sense, few longitudinal cohort studies have been performed in a large scale to find the current status, clinical features, and prognosis of the primary dyslipidemias in particular. A Prospective Registry Study of Primary Dyslipidemia (PROLIPID) was launched in 2015 to circumvent these issues, aiming to recruit at least 1,000 patients with the primary dyslipidemias specified above.

Familial hypercholesterolemia (FH) is an autosomal dominant inherited disorder caused by mutations in the genes related to the LDL receptor pathway to clear plasma LDL. The prevalence of heterozygous FH (HeFH) has been estimated as 1 in 300 among general populations worldwide[3, 4]. Hyper-LDL-cholesterolemia, systemic xanthomas characterize heFH, and premature coronary artery disease, accounting for one of the major causes of premature CVD[5]. HyperLDLemia in HeFH is mostly treatable by lifestyle management and/or drug therapy to reduce the CVD risk to a similar level to the general population if initiated early[6, 7]. The other common primary dyslipidemia is type III hyperlipoproteinemia. This disease is mainly caused by E2/E2 genotype in apolipoprotein E (*APOE*) as 1 for 1,600 in the general Japanese population under certain nutritional conditions[8]. It is known to be associated with elevated CVD risk mainly due to the elevation in remnant lipoprotein cholesterol[9]. The risk of this type of dyslipidemia is also manageable by lifestyle control and drug regimens.

Pathogenic mutations in two alleles cause homozygous FH (HoFH), either in LDL receptor (*LDLR*), apolipoprotein B (*APOB*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*), or *LDLR* adaptor protein 1 (*LDLRAP1*) or by the mutations combined in those genes and exhibits much severer clinical manifestation than HeFH. The prevalence is estimated as 1 in 300,000[10, 11]. Timely diagnosis and commencement of LDL-lowering therapies would significantly reduce cardiovascular complication risk in FH patients[12, 13]. Similar to HoFH, sitosterolemia is caused by double pathogenic mutations in ATP-binding cassette sub-family G member 5 (*ABCG5*) or ATP-binding cassette sub-family G member 8 (*ABCG8*) to exhibit systemic xanthomas and premature cardiovascular disease (CVD) associated with elevated LDL cholesterol and sitosterol[14, 15]. Double pathogenic mutations cause CTX in *CYP27A* to show very similar clinical manifestations that can be difficult to differentiate from HoFH and sitosterolemia. CTX is characterized by progressive cerebellar ataxia after puberty along with juvenile cataracts, chronic diarrhea of juvenile or infantile-onset, childhood neurological deficit, and tendinous or tuberous xanthomas[16]. In contrast, abetalipoproteinemia is characterized by extremely low LDL cholesterol and triglycerides, caused by double deleterious mutations in microsomal triglyceride transfer protein. Patients with this disorder typically suffer from complications such as spinocerebellar degeneration and pigmentary degeneration of the retina due to fat-soluble vitamin deficiencies[17].

Pathogenic mutations cause familial chylomicronemia in lipoprotein lipase (*LPL*), or its regulators, apolipoprotein CII (*APOC2*), apolipoprotein A5

(*APOA5*), glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (*GPIHBP1*), and lipase maturation factor 1 (*LMF1*). The patients have severe hypertriglyceridemia and fasting chylomicronemia, and this phenotype predisposes the affected individuals to acute pancreatitis[18].

The other group of intractable dyslipidemia is a disorder of HDL metabolism; Tangier disease, lecithin cholesterol acyltransferase (LCAT) deficiency, and apolipoprotein A1 (APOA1) deficiency. Tangier disease is caused by double pathogenic mutations in ATP-binding cassette transporter A1 (*ABCA1*) and appears with an extremely low level of plasma HDL cholesterol. Patients with this disease develop massive cholesterol ester depositions in various organs, including tonsils, liver, and spleen. In addition, these patients often develop premature atherosclerosis caused by fatty deposits in the arteries[19]. LCAT deficiency is caused by double pathogenic mutations in the *LCAT* gene and appears in two different forms. Familial LCAT deficiency is caused by complete loss of the LCAT activity, while in fish-eye disease, LCAT activity is partially deficient. LCAT is the enzyme that transfers acyl chain from the 2-position of lecithin to cholesterol on HDL to generate cholesterol acylester and leads HDL to "maturation." Clinical manifestations of this disease include diffuse corneal opacity, "target cell" hemolytic anemia, renal failure, atherosclerosis, hepatosplenomegaly, and enlarged lymph nodes, due to accumulated unesterified cholesterol[20]. APOA1 deficiency also exhibits extremely low levels of HDL cholesterol, caused by double pathogenic mutations in *APOA1* gene. The manifestations of this disease include xanthomas, corneal opacity, and CVD[21, 22].

Due to their rarity, the accumulation of the data of these intractable diseases is not adequate for their natural history, current clinical situations, and factors associated with prognosis. However, several large scale registry studies have clarified some useful clinical information and genetic backgrounds[23-29]. Therefore, it is essential to understand the unique profiles of these diseases in Japan for frequency, phenotype, and genotype and their clinical prognosis, hopefully, based on the registration of all the patients, to help useful feedback to the current guidelines for their diagnosis and management. In addition, it is also important to investigate the real fact in Japan on heterozygous FH and type III hyperlipoproteinemia from the viewpoint of public health for their phenotype and genotype and clinical prognosis, in order to shape up the current guidelines and criteria to evaluate the socioeconomic value of treatment of these disorders.

Under these conditions, a nationwide, multicenter registry was organized by the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labor and Welfare of Japan to comprehensively assess their phenotypes and genotypes. This should lead to a better understanding of these genetic disorders, not only for Japanese patients but also for patients elsewhere in the world.

Methods

Study Design

This nationwide, registry-based prospective, observational, multicenter cohort study starts from August 2015 to March 2023. Enrolled patients have primary dyslipidemias, including FH (homozygous or heterozygous), type III hyperlipoproteinemia, familial chylomicronemia, sitosterolemia, CTX, LCAT deficiency, Tangier disease, APOA1 deficiency, and abetalipoproteinemia who fulfill the clinical criteria of each disorder[9-11, 15-21] from 26 participating institutes across Japan **(Fig. 1)**. The patients are to be followed for 10 years. A total of 1,000 patients will be enrolled. This is based on the numbers of registered patients of intractable diseases in 2019 open to the public by MHLW of Japan[30], and those with other diseases who can register in this study. **Fig. 1** shows the participating institutes. Participating institutes where the members and supporters of the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the MHLW of Japan are working have been selected. **Table 1** shows a schedule of the assessments and evaluations of this study. The primary outcome is the new onset of CVD events or acute pancreatitis. The secondary outcome is all causes of death.

The protocol of this study (version 9.0, dated 7 Feb 2020) has been approved by the Institutional Review Board at National Cerebral and Cardiovascular Center and all institutes participating in this study. In addition, this study complies with the Declaration of Helsinki, the Ethical Guidelines for Medical and Health Research Involving Human Subjects, and all other applicable laws and guidelines in Japan. It was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000042782).

Study Participants

Patients clinically diagnosed with each intractable disease are recruited from August 2015 to March 2023 and followed up over 10 years. The participants fulfilling both inclusion criteria participate in this study **(Table 2)**. The participants with any of the

Fig. 1. Participating study centers, including 26 institutes across Japan
Blue circles indicate the institutes participating in this study.

Table 1. Assessments of this study

Units	Baseline	1 yr	2-4 yr	5 yr	6-9 yr	10 yr
Entry	X					
Demographics	X					
Untreated lipids	X					
Blood tests	X					
Physical and imaging	X					
Family history	X					
Medical history	X					
Medicine	X			X		X
Lifestyle habits	X					
DNA	X					
Events (CVD)		X	X	X	X	X
Events (Stroke)		X	X	X	X	X
Events (valvular and aortic disease)		X	X	X	X	X
Events (acute pancreatitis)		X	X	X	X	X
Events (adverse events)		X	X	X	X	X

exclusion criteria are excluded **(Table 3)**. Written informed consents are obtained from all the participants in a form approved by the IRB.

Collection of Data

The doctors in charge of each patient assess clinical data. Each doctor will input data into the Research Electronic Data Capture (REDcap), and then we will refer to those data, which is the browser-based electronic data capture (EDC) system. **Table 1** shows the timing of data collection following patient enrollment. We will collect many phenotypes, including clinical, demographic, laboratory data, and events. Details are described in Supplemental Material. Events include new onset of general events, CVD, stroke, valvular/aortic, acute pancreatitis, and adverse events. In addition, we monitor clinical events specific to each intractable disease.

In this study, an independent staff member conducts data monitoring. The trial institution is monitored after patients' initial enrollment and every 6 months until each participant has a case report on file. The independent staff member monitors and reviews the trial database, and data queries and

Table 2. Inclusion criteria

1) Diagnosed either as HeFH, HoFH, type III hyperlipoproteinemia, familial chylomicronemia, sitosterolemia, CTX, LCAT deficiency, Tangier disease, APOA1 deficiency, and abetalipoproteinemia, according to the criteria set by Japan Atherosclerosis Society or the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labor and Welfare of Japan.
2) Provide written informed consent.

Table 3. Exclusion criteria

1) Patients who refuse to consent to this study.
2) Considered inappropriate to participate by the doctors in charge.

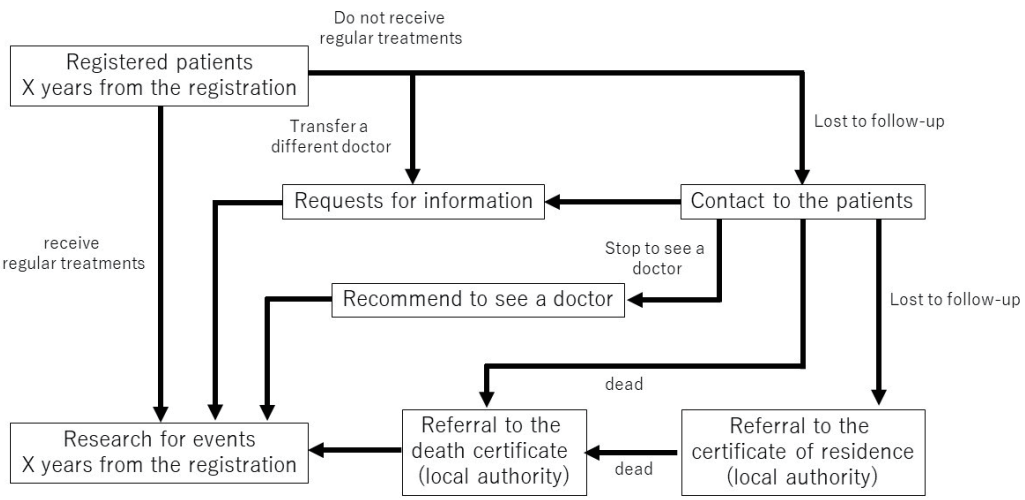

Fig. 2. Tracking of patients

cleaning will be raised if necessary.

Outcomes

The primary endpoint of this study is new CVD events, including myocardial infarction or angina pectoris, or acute pancreatitis. The secondary endpoint is death from any causes. Details are described in the Supplemental Material. The information of death and its cause are colleced to local authorities.

Schedule of the Study

Table 1 shows the schedule of this study. Follow-up visits are anticipated at each participated institute based on the conditions of the patients. Drop-out patients are to be traced by direct approach to the patients first and the maximum effort for further tracking **(Fig. 2)**. Nevertheless, we will collect those clinical variables at least once a year through the EDC system. Independent staff members monitor data at a certain interval (almost once a year). Whenever necessary, data queries will be sent to the investigators to check the data collection status and ensure the accuracy of the dataset.

Statistical Analysis

Mean values of continuous variables will be compared using Student's *t*-test for independent data variables, and median values will be compared using nonparametric Wilcoxon Mann–Whitney rank-sum test. Chi-square or Fisher's post-hoc tests will be used for categorical variables. A multivariable logistic regression model will be used to assess events and variables. Cox proportional hazard model will be used to assess relationships between all variables and events. Cumulative Kaplan–Meier survival curves starting at baseline will be constructed to compare times to the first events to find the meaningful variable. The statistical analysis was conducted using R statistics (https://www.r-project.org). *P*-values <0.05 were considered statistically significant.

Data Availability Statement

Dataset will not be available to public.

Discussion

The PROLIPID registry, organized by the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the MHLW of Japan, is a nationwide, registry-based prospective, observational, multicenter cohort intended to understand clinical characteristics, genetic backgrounds, treatments, and prognosis of patients with primary dyslipidemias, including intractable diseases in Japan. This is a unique attempt, especially the registry, which will include rare lipid-related intractable diseases. This registry accepts all the patients with these intractable diseases treated in participating centers, trying to avoid selection bias, leading to illuminate a more detailed information of those disorders. We set the primary endpoint as new CVD events, and the secondary endpoint is all causes of death. Patients with HeFH, HoFH, type III hyperlipoproteinemia, sitosterolemia, LCAT deficiency, Tangier disease, and APOA1 deficiency are at increased risk for CVD because of their lifelong elevation of LDL cholesterol and/or extremely low HDL cholesterol. On the other hand, the patients with abetalipoproteinemia is quite cardioprotective while they suffer from various complications associated with deficiency of soluble vitamin. FH-associated mutation status is associated with an increased risk for CVD[31]. Moreover, classical risk factors for CVD, including hypertension, smoking, or diabetes, have been associated with worsening the phenotype of HeFH although it is known as primary dyslipidemia[32]. Given these facts, we try to assess those factors as well as genetic factors as well in order to understand the factors contributing to affect their phenotype fully. In addition, we set no exclusion criteria to include as many patients as possible, including those at younger ages, enabling us to know the age of onset of the clinical manifestations and complications in each disorder.

We emphasize that the inclusion of genetic information for all patients is one of our major strengths. Genetic testing can provide us an accurate diagnosis of these intractable diseases and risk stratifications for future CVD risk/other complications and help us support decision-making and facilitate cascade screening of those patients. Furthermore, this study provides us a useful insight into improving the current clinical diagnostic criteria of those diseases. Results of the genetic testing will be informed to the patients when necessary.

We hypothesize that patients with pathogenic mutations and/or other classical risk factors for CVD/other complications are associated with an increased risk of CVD/other complications. We also expect that interventions manipulate their increased risk via genetic factors and/or classical risk factors according to treatment initiation and/or the intensiveness of the treatments. We hope to see more and more patients with these diseases are diagnosed accurately through this registry of these lipid-associated intractable diseases.

This study has several limitations. First, the final number of cases registered should vary by each disease, and that it is very difficult to assume the number of patients who will be enrolled. However, we set 1,000 as a target of the total number. Meanwhile, we will try to recruit consecutive patients with these disorders and enroll as many patients as possible. Second, blood testing will not be collected at follow-up, while medications will be followed for 5 years and 10 years. However, analyses will be performed based on baseline characteristics as well as medications as variables. Third, genotyping for all of the rare and intractable diseases included in this study is not covered by the public health insurance of Japan as of September 2021. In that sense, all the genotypes and its assessments will be left to each investigator's discretion. Fourth, there is no clear rationale for the duration of follow-up in this study because there is no data that we can estimate how many events will be occurred due to the rarity of these diseases. In that sense, we wanted to follow-up as much as possible, while the longest follow-up period the IRB can allow us to set is 10 years. Fifth, we do not use the universal definition of events, like an ICD 10 code. However, we will collect many information, such as date of onset, number of diseased arteries, change of electrocardiogram, elevation of cardiac enzymes, revascularization procedure, and coronary imaging in CVD. We believe that this information will make sure that the assessments of CVD are reliable.

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Competing Interests Statement

Dr. Masatsune Ogura has received lecture fees from Amgen, Astellas Pharma Inc, and Kowa. Dr. Hidenori Arai has received lecture fees from MSD, Kowa, Daiichi Sankyo, Takeda, Pfizer, UCB, Sanofi, Astelas, and Otsuka. Dr. Mariko Harada-Shiba holds shares of Liid Pharma, has received lecture fees from Amgen, Astellas, and Sanofi, has received scholarship grants from Aegerion, Recordati, and Kaneka. Dr.

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Supplemental Material

Unit	Items	choice/units
Entry	Research ID	
	Date of registration	
	Confirmation if the patient is diagnosed as either of target diseases	Yes/No
	Homozygous FH	Yes/No
	Heterozygous FH	Yes/No
	Type III hyperlipoproteinemia	Yes/No
	Familial chylomicronemia	Yes/No
	Sitosterolemia	Yes/No
	Cerebrotendinous xanthomatosis (CTX)	Yes/No
	Lecithin cholesterol acyltransferase (LCAT) deficiency	Yes/No
	Tangier disease	Yes/No
	Apolipoprotein A1 (APOA1) deficiency	Yes/No
	Abetalipoproteinemia	Yes/No
	Date of diagnosis	
	Use the National aid for intractable diseases	1. Applications are accepted, 2. Applications are denied, 3. Applications are evaluated, 4. not apply
	Registered in FAME study	Yes/No
	Informed consent	1. Reject, 2. written informed consent (baseline analysis and follow-up), 3. written informed consent (only baseline analysis), 4. Provide the chance to opt out
	Date of consent	
	Gender	
	Menstruation	
	The age of menopause	
	The year of birth	
	The month of birth	
	Age (at registration)	
Demographics	Date of measurements	
	Height	cm
	Body weight	kg
	Waist circumference	cm
	Vision test	Yes/No
	Vision	
	Systolic blood pressure (First time)	mmHg
	Diastolic blood pressure (First time)	mmHg
	Systolic blood pressure (Second time)	mmHg
	Diastolic blood pressure (Second time)	mmHg
	Physical findings	1. Achilles tendon thickness, 2. xanthoma tuberosum, 3. xanthoma planum, 4. xanthoma striata palmaris, 5. eruptive xanthoma, 6. xanthelasma palpebrarum, 7. other tendinous xanthomas, 8. arcus cornea, 9. other
	Physical findings (sitosterolemia)	1. splenomegaly
	Specific physical findings and symptoms (CTX)	1. jaundice, 2. neurologic manifestation
	Details of neurologic manifestation	1. cognitive impairment, 2. psychological symptom, 3. cerebellar symptom, 4. pyramidal sign, 5. extrapyramidal sign, 6. seizures, 7. spinalsensory disturbance, 8. peripheral neuropathy, 9. other neuropathy
	Specific physical findings and symptoms (LCAT deficiency)	1. opacity corneae, 2. edema
	Specific physical findings and symptoms (Tangier disease, and APOA1 deficiency)	1. opacity corneae, 2. Enlarged tonsils (orange-color), 3. hepatomegaly, 4. splenomegaly, 5. peripheral neuropathy
	Specific symptoms (abetalipoproteinemia) digestive symptom	Yes/No

	Details of digestive symptom	1. vomiting, 2. abdominal distension, 3. impaired development, 4. chronic diarrhea, 5. steatorrhea, 6. others
	Specific symptoms (abetalipoproteinemia) eye symptom	Yes/No
	Details of eye symptom	1. night blindness, 2. color blindness, 3. low vision, 4. blindness, 5. visual field defect, 6. retinal pigment degeneration, 7. other
	Specific symptoms (abetalipoproteinemia) neuropathy	Yes/No
	Details of neuropathy	1. reduced deep tendon reflex, 2. disturbance of vibration sense, 3. disturbance of position sense, 4. Romberg's test positive, 5. dysmetria, 6. ataxia, 7. ataxic gait, 8. dysbasia, 9. spastic paralysis, 10. contracture of skeletal muscle, 11. dysphemia, 12. other spinocerebellar symptoms, 13. autonomic symptom, 14. peripheral neuropathy, 15. other neuropathy, 16. other symptoms related to muscles
Untreated lipids	Total cholesterol	mg/dl
	LDL cholesterol	mg/dl
	HDL cholesterol	mg/dl
	Triglycerides	mg/dl
	Nutrition (infant, one year or under)	1. mother's milk, 2. formula milk, 3. both, 4. other
	LDL cholesterol (the highest value in life)	mg/dl
	LDL cholesterol (the lowest value in life)	mg/dl
	HDL cholesterol (the highest value in life)	mg/dl
	HDL cholesterol (the lowest value in life)	mg/dl
	Triglycerides (the highest value in life)	mg/dl
	Triglycerides (the lowest value in life)	mg/dl
Blood tests	Date of blood tests	
	Condition of blood tests	1. Fasting (≥ 10 hours), 2. other, 3. Unknown
	Total cholesterol (TC)	mg/dl
	LDL cholesterol	mg/dl
	HDL cholesterol	mg/dl
	Triglycerides	mg/dl
	Blood glucose	mg/dl
	Insulin	μIU/mL
	75g OGTT	Yes/No
	Insulin (0 min)	μIU/mL
	Insulin (30 min)	μIU/mL
	Insulin (60 min)	μIU/mL
	Insulin (120 min)	μIU/mL
	Blood glucose (0 min)	mg/dl
	Blood glucose (30 min)	mg/dl
	Blood glucose (60 min)	mg/dl
	Blood glucose (120 min)	mg/dl
	HOMA-IR	
	Inslulinogenic index	
	BUN	mg/dl
	Cr	mg/dl
	eGFR	mL/min/1.73m^2
	WBC	/μL
	RBC	/μL
	Ht	%
	Plt	/μL
	Total bilirubin	mg/dl
	Direct bilirubin	mg/dl
	ALT	IU/L
	AST	IU/L
	γ-GTP	IU/L

Alb	g/dl
HbAc1	%
Hb	g/dl
MCV	fl
MCHC	%
Erythrocyte morphology abnormality	Yes/No
Erythrocyte morphology abnormality detail	1. target erythrocyte, 2. difference in size, 3. erythrocyte malformation, 4. stomatocyte
Reticulocytes	
Acanthocyte	Yes/No
LCAT activity	nmol/ml/h/37℃
Free cholesterol (FC)	mg/dl
Cholesteryl ester (CE)	mg/dl
FC/CE ratio	
CE/TC ratio	
Phospholipid	mg/dl
Amylase	IU/L
Pancreatic amylase	IU/L
Lipase	IU/L
Uric acid	mg/dl
CRP	mg/dl
PT-INR	
Sedimentation rate	mm
Ca	mg/dl
IP	mg/dl
Fe	μg/dL
Folic acid	ng/mL
Vitamin B6	pg/mL
Vitamin B12	pg/mL
Vitamin A	μg/dL
25-OH-VitaminD	ng/mL
Vitamin E (α-tocopherol)	μmol/L
Vitamin E	μmol/L
Vitamin K1	ng/mL
Vitamin K2	ng/mL
TSH	mIU/L
Free T3	ng/dL
Free T4	ng/dL
ApoB	mg/dl
ApoC-II	mg/dl
ApoC-III	mg/dl
APOE	mg/dl
APOA-I	mg/dl
APOA-II	mg/dl
Lp(a)	mg/dl
Lipoprotein electrophoresis (PAG) HDL	mg/dl
Lipoprotein electrophoresis (PAG) LDL	mg/dl
Lipoprotein electrophoresis (PAG) VLDL	mg/dl
Lipoprotein electrophoresis (PAG) IDL	mg/dl
Lp-X	Yes/No
TG-rich large LDL	mg/dl
RLP-C	mg/dl
Broad-β pattern	Yes/No
LDL-MI	mg/dl

	LPL (pre-heparin)	ng/ml
	LPL (post-heparin)	ng/ml
	heparin unit	unit/kg
	Timing of blood test after heparin injection	min
	LPL activity	μmol/mL/hour
	HL activity	μmol/mL/hour
	Timing of blood test after heparin injection	min
	EPA	μg/mL
	AA	μg/mL
	EPA/AA ratio	
	HPLC-HDL	mg/dl
	HPLC-LDL	mg/dl
	HPLC-IDL	mg/dl
	HPLC-VLDL	mg/dl
	HPLC-other	mg/dl
	HPLC-total cholesterol	mg/dl
	sitosterol	μg/ml
	cholestanol	μg/ml
	lathosterol	μg/ml
	campesterol	μg/ml
	X-ray of Achilles tendon	Yes/No
Physical and imaging	Achilles tendon thickness (right)	Mm
	Achilles tendon thickness (left)	Mm
	ABI	Yes/No
	ABI (right)	
	ABI (left)	
	ECG	Yes/No
	Abnormality of ECG	Yes/No
	Details of abnormality of ECG	
	Carotid ultrasound	Yes/No
	≥ 70% stenosis (NASCET)	Yes/No
	UCG	Yes/No
	findings of UCG	1. valvular disease, 2. other
	Abdominal ultrasound	Yes/No
	Fatty liver	Yes/No
	Cirrhosis	Yes/No
	Other findings	Yes/No
	Details of other findings of abdominal ultrasound	
	Ophthalmoscopy	Yes/No
	retinal pigment degeneration	Yes/No
	Other findings	Yes/No
	Details of other findings	
	FMD	%
	Visceral fat area	cm^2
	Splenomegaly (CT or ultrasound)	Yes/No
	Head MRI	Yes/No
	atrophy	Yes/No
	location of atrophy	
	T2-FLAIR high intensity	Yes/No
	location of T2-FLAIR high intensity	
	Spinal MRI	Yes/No
	atrophy	Yes/No
	location of atrophy	
	T2 high intensity	Yes/No

	location of T2 high intensity	
	Electroencephalography	Yes/No
	epilepsy	Yes/No
	slow wave	Yes/No
	Nerve conduction study	Yes/No
	axon dysfunction	Yes/No
	Demyelinisation	Yes/No
	Bone density test	Yes/No
	lumbar vertebra	
	thigh bone	
	Urine protein/Cr ratio	
	Urine alb /Cr ratio	
	Urine protein (24 hours)	g
	Gastrointestinal endoscopy	Yes/No
	snow white duodenum	Yes/No
	Family history of coronary artery disease (<55 yr male, <65 yr female)	1. Yes, 2. No, 3. Unknown, 4. No investigation
Family history	relationship	1. parent, 2. child, 3. sibling, 4. grandparent, 5. grandchild
	Family history of FH	1. Yes, 2. No, 3. Unknown, 4. No investigation
	relationship	1. parent, 2. child, 3. sibling, 4. grandparent, 5. grandchild
	Family history of hypertriglyceridemia	1. Yes, 2. No, 3. Unknown, 4. No investigation
	relationship	1. parent, 2. child, 3. sibling, 4. grandparent, 5. grandchild
	Consanguineous marriage	1. Yes, 2. No, 3. Unknown, 4. No investigation
	Family history of sitosterolemia	1. Yes, 2. No, 3. Unknown, 4. No investigation
	relationship	1. parent, 2. child, 3. sibling, 4. grandparent, 5. grandchild
	Family history of CTX	1. Yes, 2. No, 3. Unknown, 4. No investigation
	relationship	1. parent, 2. child, 3. sibling, 4. grandparent, 5. grandchild
	Family history of low HDL-C	1. Yes, 2. No, 3. Unknown, 4. No investigation
	relationship	1. parent, 2. child, 3. sibling, 4. grandparent, 5. grandchild
	Family history of low LDL-C	1. Yes, 2. No, 3. Unknown, 4. No investigation
	relationship	1. parent, 2. child, 3. sibling, 4. grandparent, 5. grandchild
	lipids in parent	1. TC <120 mg/dl or LDL-C <70 mg/dl, 2. TC <50 mg/dl or LDL-C <15 mg/dl, 3. Unknown
	lipids in child	1. TC <120 mg/dl or LDL-C <70 mg/dl, 2. TC <50 mg/dl or LDL-C <15 mg/dl, 3. Unknown
	lipids in sibling	1. TC <120 mg/dl or LDL-C <70 mg/dl, 2. TC <50 mg/dl or LDL-C <15 mg/dl, 3. Unknown
	lipids in grandparent	1. TC <120 mg/dl or LDL-C <70 mg/dl, 2. TC <50 mg/dl or LDL-C <15 mg/dl, 3. Unknown
	lipids in grandchild	1. TC <120 mg/dl or LDL-C <70 mg/dl, 2. TC <50 mg/dl or LDL-C <15 mg/dl, 3. Unknown
	Glucose intolerance	Yes/No
Medical history	Diabetes	Yes/No
	type	1. type 1, 2. type 2, 3. other
	diabetic retinopathy (right)	A1~B5, or No
	other eye complications (right)	Yes/No
	complications (right)	1. macular disease, 2. retinal detachment, 3. rubeotic glaucoma, 4. ischemic optic neuropathy, 5. photocoagulation, 6. vitreous surgery
	diabetic retinopathy (left)	A1~B5, or No
	other eye complications (left)	Yes/No

complications (left)	1. macular disease, 2. retinal detachment, 3. rubeotic glaucoma, 4. ischemic optic neuropathy, 5. photocoagulation, 6. vitreous surgery
CKD	Yes/No
PAD	Yes/No
Hypertension	Yes/No
TIA	Yes/No
Stroke	Yes/No
Ischemic stroke	Yes/No
Cerebral hemorrhage	Yes/No
Coronary artery disease	Yes/No
age of onset	
intervention	1. PCI, 2. CABG
AS	Yes/No
Supravalvular aortic stenosis	Yes/No
Dissecting aneurysm of aorta	Yes/No
Thoracic aortic aneurysm	Yes/No
max diameter of aorta (CT)	mm
Abdominal aortic aneurysm	Yes/No
max diameter of aorta (CT)	mm
Hypothyroidism	Yes/No
Other endocrine disease	Yes/No
Acute pancreatitis	Yes/No
Gallstone	Yes/No
Diagnostic ERCP	Yes/No
Therapeutic ERCP	Yes/No
Chronic pancreatitis	Yes/No
Malfusion of pancreaticobiliary ducts	Yes/No
Pancreas divisum	Yes/No
Pancreatic tumor	Yes/No
Hepatomegaly	Yes/No
Splenomegaly	Yes/No
Lipemia retinalis	Yes/No
Blood disorder	Yes/No
Details of blood disorder	
Cataract	Yes/No
Chronic diarrhea	Yes/No
Osteoporosis	Yes/No
Prolonged Neonatal Jaundice	Yes/No
Neuropathy	Yes/No
Details of neuropathy	1. cognitive impairment, 2. psychological symptom, 3. cerebellar symptom, 4. pyramidal sign, 5. extrapyramidal sign, 6. seizures, 7. Spinal sensory disturbance, 8. peripheral neuropathy, 9. other neuropathy
Arthritis	Yes/No
Hemorrhagic diathesis	Yes/No
Loss of vision	Yes/No
Blindness	Yes/No
Dialysis	Yes/No
Nephrotic syndrome	Yes/No
Cardiomyopathy	Yes/No
Fatty liver	Yes/No
Cirrhosis	Yes/No
Hepatocellular carcinoma	Yes/No
Other liver disease	Yes/No

	Details of other liver disease	
	Hyperthyroidism	Yes/No
	Cancer	Yes/No
	Details of cancer	
	Secondary causes of hypolipidemia	Yes/No
	Details of secondary causes of hypolipidemia	
	Other specific disease	Yes/No
	Details of other specific disease	
	Antihypertensive drug	Yes/No
Medicine	class of antihypertensive drug	
	Antidiabetic drug (oral)	Yes/No
	antidiabetic drug (injection)	Yes/No
	class of antidiabetic drug (injection)	1. insulin, 2. GLP1
	Antithrombotic drug	Yes/No
	Immunosuppressive agent	Yes/No
	class of immunosuppressive agent	1. azathioprine, 2. cyclosporine, 3. other
	details of immunosuppressive agent	
	Anticancer agent	Yes/No
	class of anticancer agent	
	Antiinfective agent	Yes/No
	class of antiinfective agent	
	Hormone preparations	Yes/No
	class of hormone preparations	
	Treatments for neuropathy	Yes/No
	class of treatments for neuropathy	
	Treatments fof acne vulgaris	Yes/No
	Medications associated with pancreatitis	Yes/No
	details of medications associated with pancreatitis	
	Medications associated with hypertriglyceridemia	Yes/No
	details of medications associated with hypertriglyceridemia	
	Statin	Yes/No
	details of statin (class and dose)	
	Other lipid modifying medications	Yes/No
	details of other lipid modifying medications (class and dose)	
	Smoking habits	1. current smoker, 2. former smoker, 3. never
Lifestyle habits	peaces of smoking (daily)	
	duration of smoking	
	The age of quit smoking	
	Drinking	1. daily, 2. quit, 3. never
	days of drinking (week)	
	The age of starting drinking	
	The age of quit drinking	
	duration of drinking	
	Types and amount of alcohol	
	FH pathogenic mutation	1. Yes, 2. No, 3. No investigation
DNA	*LDLR* pathogenic mutation	1. Yes, 2. No, 3. No investigation
	PCSK9 pathogenic mutation	1. Yes, 2. No, 3. No investigation
	LDLRAP1 pathogenic mutation	1. Yes, 2. No, 3. No investigation
	APOE genetic test	Yes/No
	APOE genotype-1	
	APOE genotype-2	
	APOE phenotype test	Yes/No
	APOE phenotype-1	
	APOE phenotype-2	

	LPL pathogenic mutation	1. Yes, 2. No, 3. No investigation
	APOC2 pathogenic mutation	1. Yes, 2. No, 3. No investigation
	GPIHBP1 pathogenic mutation	1. Yes, 2. No, 3. No investigation
	LMF1 pathogenic mutation	1. Yes, 2. No, 3. No investigation
	APOA5 pathogenic mutation	1. Yes, 2. No, 3. No investigation
	ABCG5 pathogenic mutation	1. Yes, 2. No, 3. No investigation
	ABCG8 pathogenic mutation	1. Yes, 2. No, 3. No investigation
	CYP27A1 pathogenic mutation	1. Yes, 2. No, 3. No investigation
	LCAT pathogenic mutation	1. Yes, 2. No, 3. No investigation
	ABCA1 pathogenic mutation	1. Yes, 2. No, 3. No investigation
	APOA1 pathogenic mutation	1. Yes, 2. No, 3. No investigation
	ANGPTL3 pathogenic mutation	1. Yes, 2. No, 3. No investigation
	SAR1B pathogenic mutation	1. Yes, 2. No, 3. No investigation
	Other pathogenic mutation	1. Yes, 2. No, 3. No investigation
	details of other pathogenic mutation	
	Date of investigation	
Events (CVD)	Location of infarction	1. anteroseptal, 2. lateral, inferior/posterior, 4. Unclassified
	Type of angina pectoris	1. stable, 2. unstable, 3. coronary spasm angina, 4. other
	Date of onset	
	Number of diseased arteries	
	Change of ECG	Yes/No
	details of ECG change	
	Elevation of CPK or TnT	Yes/No
	PCI or CABG	Yes/No
	coronary CT or MRI	Yes/No
Events (stroke)	Type of ischemic stroke	1. lacunar, 2. atherothrombotic, 3. cardioembolic, 4. unclassified
	Date of onset	
	Symptom	Yes/No
	Details of symptom	
	Imaging	Yes/No
	type of imaging	1. CT, 2. MRI, 3. other
	results of imaging	
	Af	Yes/No
	Thrombus in left atrium	Yes/No
	Type	1. aortic valve, 3. mitral valve, 3. tricuspid valve
Events (valvular disease)	Details of valvular disease	
	TAVI	Yes/No
	Date of TAVI	
	Surgical treatment	Yes/No
	Date of surgical treatment	
	Aortic disease	Yes/No
	type of aortic disease	
	Intervention	Yes/No
	Type of PAD	
	Imaging of PAD	1. CT, 2. MRI, 3. other
	Pancreatitis	Yes/No
Events (pancreatitis)	Date of onset	
	Symptom	
	Cause of pancreatitis	
	Type	1. diabetes (new onset or worsening, 2. rhabdomyolysis, 3. dementia, 4. venous thrombosis, 5. gallstone, 6. other
Events (adverse)		