

BMJ Open Hokuriku-plus familial hypercholesterolaemia registry study: rationale and study design

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ABSTRACT

Introduction Familial hypercholesterolaemia (FH) is an autosomal-dominant inherited genetic disease. It carries an extremely high cardiovascular risk associated with significantly elevated low-density lipoprotein (LDL) cholesterol. The diagnostic rate of this disease in some European nations is quite high, due to the presence of multiple prospective registries. On the other hand, few data—and in particular multicentre data—exist regarding this issue among Japanese subjects. Therefore, this study intends to assemble a multicentre registry that aims to comprehensively assess cardiovascular risk among Japanese FH patients while taking into account their genetic backgrounds.

Methods and analysis The Hokuriku-plus FH registry is a prospective, observational, multicentre cohort study, enrolling consecutive FH patients who fulfil the clinical criteria of FH in Japan from 37 participating hospitals mostly in Hokuriku region of Japan from April 2020 to March 2024. A total of 1000 patients will be enrolled into the study, and we plan to follow-up participants over 5 years. We will collect clinical parameters, including lipids, physical findings, genetic backgrounds and clinical events covering atherosclerotic and other important events, such as malignancies. The primary endpoint of this study is new atherosclerotic cardiovascular disease (ASCVD) events. The secondary endpoints are as follows: LDL

Strengths and limitations of this study

- This will be the first prospective multicentre cohort study in Japan to assess the risk of future atherosclerotic cardiovascular disease (ASCVD) and other clinical events among patients with familial hypercholesterolaemia (FH).
- We are performing comprehensive genetic testing for all of the participants. This will both enable us to confirm the diagnosis of FH and future ASCVD risk, and also facilitate decision-making over treatment as well as promote cascade screening among the patients' relatives. In addition, these data will help us improve the current clinical diagnostic criteria of FH in Japan, and potentially across the world.
- Although this study is conducted across a number of centres, it is not a nationwide study.

cholesterol, secondary ASCVD events and the occurrence of other diseases including hypertension, diabetes and malignancies.

Ethics and dissemination This study is being conducted in compliance 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. This study protocol has been

approved by the Institutional Review Board at Kanazawa University. We will disseminate the final results at international conferences and in a peer-reviewed journal.

Trial registration number UMIN000038210.

INTRODUCTION

Familial hypercholesterolaemia (FH) is an autosomal-dominant inherited disorder. Patients with heterozygous FH account for approximately 0.5%–0.2% of the general population, equivalent to 1 in 200–500 individuals.^{1–5} Low-density lipoprotein (LDL) receptor (*LDLR*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*), apolipoprotein B (*APOB*) and *LDLR* adaptor protein 1 (*LDLRAP1*) are the major causative genes of FH. Since FH is characterised by hyper-LDL-cholesterolemia and systemic xanthomas from infancy, it is one of the leading causes of premature coronary artery disease.⁶ Some studies suggest that early diagnosis and appropriate LDL-lowering therapies could lead to a better prognosis for FH patients.^{7–9} In that sense, several registries of this disease have been organised to validate these important suggestions, such as the Simon Broome Familial Hyperlipidaemia Registry in the UK,¹⁰ CASCADE FH Registry in the USA¹¹ and SAFE-HEART registry in Spain.¹²

For more than 50 years, our study group has been helping to clarify genotype–phenotype associations among Japanese FH patients;⁶ however, few data—and in particular multicentre data—exist regarding this issue among Japanese subjects. On the other hand, we recently established a worthwhile scheme of comprehensive FH genetic testing using next-generation sequencing.¹³ Under these conditions, we intend to organise a multicentre registry that seeks to assess comprehensively atherosclerotic cardiovascular disease (ASCVD) risks among Japanese FH patients taking into account their genetic backgrounds. We believe that such information could lead to a better understanding of this important genetic disorder, both in Japanese patients, and also in patients elsewhere in the world.

METHODS AND ANALYSIS

Overall study design

Recruitment for this prospective, observational, multicentre cohort study extends from April 2020 to March 2024. We are enrolling consecutive FH patients who fulfil the clinical criteria of the disorder in Japan from 37 participating hospitals located mostly in Hokuriku region (figure 1). Hokuriku, which comprises the prefectures of Toyama, Ishikawa and Fukui, is located in the central area of Japan's main island and is home to around 3 million people. It is of note that this region expects to see a relatively low population movement over the 5 years we have planned for follow-up, which in turn could lead to high proportion of subjects remaining in the study. A total of 1000 patients will be enrolled. Figure 1 shows the distribution of institutes that participated in this study and table 1 outlines the overall follow-up schedule. The primary

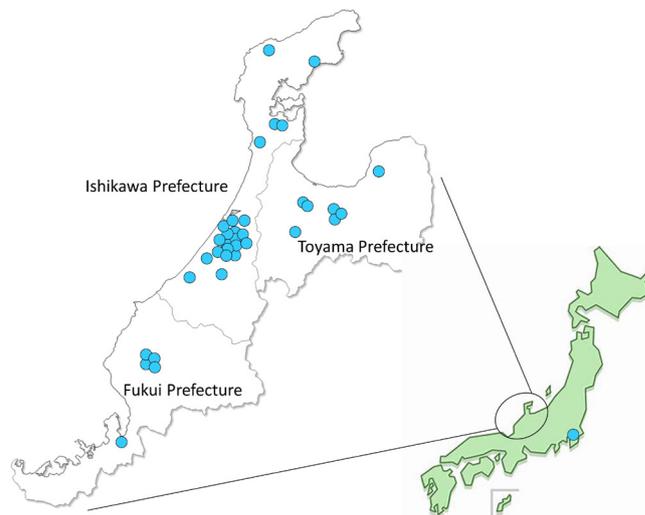


Figure 1 Participating study centres, including 37 hospitals across the Hokuriku region of Japan. Blue circles indicate the hospitals participating in this study. Thirty-one of the 37 hospitals are located in the Hokuriku region of Japan and one hospital is located in the Tokyo area.

outcome of this study is the occurrence of new onset of ASCVD events. The secondary outcomes are as follows: LDL cholesterol, secondary ASCVD events and occurrence of other diseases such as hypertension, diabetes and malignancies.

Basic variables include date of birth, gender, height, bodyweight and waist circumference. Physical findings include cutaneous xanthomas, Achilles tendon thickness (≥ 9.0 mm by X-ray) and arcus corneae. Family history includes the family history of premature coronary artery disease (male: ≤ 55 year, female: ≤ 65 year), or that of FH. Complications include hypertension, diabetes, any malignancies, ischaemic or haemorrhagic stroke or any unknown critical status. Genetic analyses include the presence and type of pathogenic mutation in FH-associated genes. Prior ASCVD include carotid atherosclerosis ($\geq 75\%$ stenotic lesion), coronary atherosclerosis ($\geq 75\%$ stenotic lesion), peripheral artery diseases ($\geq 75\%$ stenotic lesion) or aortic valve stenosis (max. velocity ≥ 3 m/s). Laboratory data include blood counts, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, lipoprotein (a), apolipoproteins, plasma glucose, HbA1c, aspartate aminotransferase, alanine transaminase, γ -glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, blood urea nitrogen, creatinine, uric acid, sodium, potassium, chloride, C-reactive protein and urinalysis. Each institution is responsible for maintaining the quality of its laboratory measurements. Events include new onset of ASCVD such as carotid atherosclerosis, coronary atherosclerosis, peripheral artery disease or aortic valve stenosis, complications including hypertension, diabetes, any malignancies, ischaemic or haemorrhagic stroke or any unknown critical status.

This study is being conducted in compliance with the Declaration of Helsinki, the Ethical Guidelines for Medical and Health Research Involving Human Subjects

Table 1 Assessment and evaluation schedule of this study

	Baseline	1 year	2 year	3 year	4 year	5 year	At events
Basic variables	X	X	X	X	X	X	X
Physical findings	X						
Family history	X						
Smoking/alcohol	X						
Medications	X	X	X	X	X	X	X
Complications	X	X	X	X	X	X	X
Genetic analyses	X						
Prior ASCVD	X	X	X	X	X	X	X
Laboratory data	X	X	X	X	X	X	X
Events						→	X

ASCVD, atherosclerotic cardiovascular disease.

and all other applicable laws and guidelines in Japan. In addition, this study protocol (V.1.0, dated 8 September 2019) has been approved by the Institutional Review Board at Kanazawa University (No. 2019–114).

Study participants

Patients diagnosed clinically with FH from April 2020 to March 2024 are being recruited, and we plan to follow-up on participants over 5 years. Of note, only participants fulfilling all inclusion criteria are being enrolled in this study (box 1) and those with either of the exclusion criteria are excluded from this trial (box 2). We are obtaining written informed consent from all participants using forms that have been approved by the IRB at Kanazawa University (see online supplementary material). Trial participants are required to understand the contents of the consent form before giving their acceptance; moreover, these forms must be dated and signed by both trial participants and investigators. On obtaining consent, the first copy of the consent form will be kept at the hospital and the other by the patient and will not be collected after the completion of this trial. Furthermore, all participants are informed that their medical care will not be affected if they refuse to enrol in the trial. They are free to withdraw their consent at any time during the study period, at their own discretion. To protect privacy, all the information will be anonymised at each institution before data are entered.

Box 1 Inclusion criteria

Patients with both of the following criteria are included.

1. Diagnosed with familial hypercholesterolaemia, according to criteria set by the Japan Atherosclerosis Society.
2. Willingness to provide written informed consent.

Patient and public involvement

This research is being carried out without patient involvement. Patients are not being invited to comment on the study design nor are they being consulted in developing patient-relevant outcomes or interpreting the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Genetic testing

We intend to sequence exons of four FH-related genes (*LDLR*, *PCSK9*, *APOB* and *LDLRAP1*) as well as other genes associated with Mendelian lipid disorders, such as ATP-binding cassette subfamily G member 5 (*ABCG5*) and ATP-binding cassette subfamily G member 8 (*ABCG8*) using the Illumina MiSeq system. The variant is defined as causal when it fulfils either of the following criteria: (a) it is registered as pathogenic/likely pathogenic in the ClinVar database; (b) minor allele frequency is <1% in the East Asian population with (i) protein-truncating variants (non-sense, canonical splice sites or frameshift) and (ii) missense variants in the *LDLR* gene that five in silico damaging scores (SIFT, PolyPhen-2 HDIV, PolyPhen-2 HVAR, MutationTaster2 and LRT) all predicted as pathogenic; (c) missense variants reported as pathogenic in the Japanese population (*PCSK9* p.Val4Ile and p.Glu32Lys) and (d) eXome-Hidden Markov Model software predicted as copy number variations in the *LDLR* gene (large duplication/large deletion). Details are described elsewhere.¹³

Box 2 Exclusion criteria

Familial hypercholesterolaemia patients with both of the following criteria are excluded.

1. Considered inappropriate to participate by their doctors in charge.

Data collection

Attending physicians and research assistants are collecting data under the supervision of the clinicians responsible for this study at each participating hospital. The primary source of the information obtained is through electronic health records at each institute. Data are recorded through electronic data capture (EDC) using the browser-based, metadata-driven EDC software REDCap.¹⁴ The proposed time frame for data collection after the initial enrolment is shown in [table 1](#).

Outcomes

The primary endpoint of this study is new ASCVD events. The secondary endpoints are as follows: LDL cholesterol, secondary ASCVD events and the occurrence of other diseases such as hypertension, diabetes or malignancies. We defined ASCVD events as fatal or non-fatal myocardial infarction; angina pectoris; ischaemic diseases including carotid atherosclerosis ($\geq 75\%$ stenotic lesion), coronary atherosclerosis ($\geq 75\%$ stenotic lesion), peripheral artery disease ($\geq 75\%$ stenotic lesion) or aortic valve stenosis (max velocity ≥ 3 m/s) and ischaemic or haemorrhagic stroke.

Data collection schedule

[Table 1](#) lists the overall data collection schedule for this study. Follow-up visits will be conducted in outpatient clinics at Kanazawa University Hospital and its affiliated institutions across the Hokuriku region of Japan. Follow-up interval, as well as the variables that are measured at certain points, will be decided according to the clinical guideline for FH¹ and the patient's condition. Nevertheless, the clinical variables listed above will be collected at least once a year during the follow-up period and collected centrally through the EDC system. We will collect data at any point when an event occurs.

Data monitoring is conducted by an independent member of staff. The trial institution is monitored after the initial enrolment of patients and subsequently every 6 months until the case report form of the last participant has been obtained. The trial database is also monitored and reviewed by the independent staff member, and data queries will be raised if necessary.

Statistical analysis

The baseline profiles are described by the mean and SD, median and quantiles (continuous variables) or proportion (categorical variables). A multivariate Cox proportional-hazards model will be used to evaluate the factors associated with new ASCVD events. In addition, this model will also be used to evaluate factors associated with LDL cholesterol, secondary ASCVD events and other complications, accounting for variables including age, gender, body mass index (baseline or its change), waist circumference (baseline or its change), hypertension, diabetes and smoking. We will compare the variables between patients with and without events using the t-test, Mann-Whitney U-test, Fisher's exact test or linear

or logistic regression adjusted by appropriate covariates stated above. Finally, $p < 0.05$ will be considered statistically significant for the primary endpoint. Statistical analysis will be performed using SAS V.9.3 or R software V.3.4.1 or above.

Patient and public involvement

Patients and the public are not being involved in the development of the research questions and outcome measures, the study's design, the assessment of interventions in the study or recruitment and conduct. We will disseminate the final results to the study participants after these are published in a peer-reviewed journal.

DISCUSSION

The Hokuriku-plus FH registry is a prospective, observational, multicentre cohort study designed to capture recent trends in clinical characteristics, genetic backgrounds, management and prognosis of patients with FH in real-world clinical practice of Japan. The registry includes all patients admitted to participating centres with FH, avoiding selection bias to elucidate a more complete picture of the clinical characteristics, medications and outcomes of patients with FH. In this study, the primary endpoint is new ASCVD events. The secondary endpoints are as follows: LDL cholesterol, secondary ASCVD events and the occurrence of other diseases such as hypertension, diabetes or malignancies. It has been shown that patients with FH are at extremely high risk for the development of ASCVD, based on their lifelong elevation of LDL cholesterol.¹⁵ Recently, we have shown that the presence of FH-mutation is associated with higher risk for ASCVD.¹⁶ In addition, we have also shown that other traditional risk factors, such as hypertension and diabetes, also exacerbate their phenotype.¹⁷ Accordingly, we are assessing such factors comprehensively in this study to further determine the impact of those factors among the patients. In addition, screening for subclinical atherosclerosis using carotid ultrasound and/or CT for FH on a regular basis (every 2 to 3 years) is recommended in our clinical practice. In this way, we believe that we can assess the development of subclinical as well as clinical atherosclerosis in FH in this study. Moreover, there are no exclusion criteria regarding the means of referral to our hospitals. We anticipate many patients with FH identified through cascade screening will be included in this study. In this way, the inclusion of patients from different age groups, and especially younger patients, will help us estimate the starting age of the development of atherosclerosis in patients with FH.

Our intention to perform comprehensive genetic testing for all patients is a strength of this study. This will both enable us to confirm diagnosis of FH and future ASCVD risk, and genetic testing will also facilitate decision-making during treatment and promote cascade screening among the patients' relatives. In addition, data from this will help us improve the present FH clinical

diagnostic criteria in Japan and potentially across the world. In this study, genetic analyses will be performed as a part of the research and the results will be returned to the patients, with genetic counselling available on request. We are also now conducting another clinical trial (Impact of Genetic Testing on LDL Cholesterol in Patients with FH (GenTLe-FH)), which aims to assess the clinical benefits of genetic testing in FH subjects.¹⁸ Our studies may provide interesting perspectives in returning genetic results with the disclosure of future ASCVD risk for patients with FH, and providing them with reliable and evidence-based treatment options to reduce their risk. We may associate our initiative in time with another Japanese FH registry, the PROLIPID-FH registry. By doing so, our shared data should be more representative of the entire country.

This study has several limitations. First, patients are not involved in the design of this study, since contacting patients for research purpose raises challenges in Japan. Involvement in the design of the registry may have otherwise provided us with useful information. Second, there will be no interaction between the registry information and physicians until the initial report is published officially. Part of the reason for this is we wanted to observe the current status/situations of FH treatments and prognoses in Japan in an unbiased manner. However, we will be providing useful feedback from this registry not only to the physicians on charge of patient care, but also to interested observers across the world through scientific papers once the determined study period is over. Finally, it is unfortunate that we cannot collect information about dietary habits and physical activity in this study. However, we will be collecting data concerning changes in body weight and waist circumference. Accordingly, we hope to be able to estimate the effects of lifestyle in patients with FH.

In conclusion, we aim to demonstrate the study design and protocol of the Hokuriku-plus FH registry. We hypothesise that patients with FH-mutation and/or other traditional risk factors are associated with a higher risk of ASCVD, and that this higher risk can be cancelled out through earlier and/or more intensive LDL-cholesterol-lowering therapies. We expect to see that a portion of the clinical-FH patients have sitosterolemia and/or are carriers of the *ABCG5* or *ABCG8* gene mutation who have different aetiology as well as different prognosis from true FH.¹⁹ Finally, this study will provide insights into the importance of clinical and genetic diagnosis of FH with extremely high cardiovascular risk.

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Data availability statement Data are available upon reasonable request. Data including detailed study protocol will be available upon official request to Dr, Hayato Tada (Email: ht240z@med.kanazawa-u.ac.jp).

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REFERENCES

- 1 Harada-Shiba M, Arai H, Ishigaki Y, *et al*. Guidelines for diagnosis and treatment of familial hypercholesterolemia 2017. *J Atheroscler Thromb* 2018;25:751–70.
- 2 Gidding SS, Champagne MA, de Ferranti SD, *et al*. The agenda for familial hypercholesterolemia: a scientific statement from the American heart association. *Circulation* 2015;132:2167–92.
- 3 Watts GF, Gidding S, Wierzbicki AS, *et al*. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. *Int J Cardiol* 2014;171:309–25.
- 4 Nordestgaard BG, Chapman MJ, Humphries SE, *et al*. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European atherosclerosis Society. *Eur Heart J* 2013;34:3478–90.
- 5 Mabuchi H, Nohara A, Noguchi T, *et al*. Molecular genetic epidemiology of homozygous familial hypercholesterolemia in the Hokuriku district of Japan. *Atherosclerosis* 2011;214:404–7.
- 6 Mabuchi H. Half a century tales of familial hypercholesterolemia (FH) in Japan. *J Atheroscler Thromb* 2017;24:189–207.
- 7 Versmissen J, Oosterveer DM, Yazdanpanah M, *et al*. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* 2008;337:a2423.
- 8 Harada-Shiba M, Sugisawa T, Makino H, *et al*. Impact of statin treatment on the clinical fate of heterozygous familial hypercholesterolemia. *J Atheroscler Thromb* 2010;17:667–74.
- 9 van der Graaf A, Cuffie-Jackson C, Vissers MN, *et al*. Efficacy and safety of coadministration of ezetimibe and simvastatin in adolescents with heterozygous familial hypercholesterolemia. *J Am Coll Cardiol* 2008;52:1421–9.
- 10 Neil HAW, Huxley RR, Hawkins MM, *et al*. Comparison of the risk of fatal coronary heart disease in treated xanthomatous and non-xanthomatous heterozygous familial hypercholesterolaemia: a prospective registry study. *Atherosclerosis* 2003;170:73–8.
- 11 O'Brien EC, Roe MT, Fraulo ES, *et al*. Rationale and design of the familial hypercholesterolemia Foundation cascade screening for awareness and detection of familial hypercholesterolemia registry. *Am Heart J* 2014;167:342–9.
- 12 Mata N, Alonso R, Badimón L, *et al*. Clinical characteristics and evaluation of LDL-cholesterol treatment of the Spanish familial hypercholesterolemia longitudinal cohort study (SAFEHEART). *Lipids Health Dis* 2011;10:94.
- 13 Tada H, Kawashiri M-A, Nomura A, *et al*. Oligogenic familial hypercholesterolemia, LDL cholesterol, and coronary artery disease. *J Clin Lipidol* 2018;12:1436–44.
- 14 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
- 15 Nordestgaard BG, Chapman MJ, Humphries SE, *et al*. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European atherosclerosis Society. *Eur Heart J* 2013;34:3478–90.
- 16 Tada H, Kawashiri M-A, Nohara A, *et al*. Impact of clinical signs and genetic diagnosis of familial hypercholesterolaemia on the prevalence of coronary artery disease in patients with severe hypercholesterolaemia. *Eur Heart J* 2017;38:1573–9.
- 17 Tada H, Kawashiri M-A, Nohara A, *et al*. Assessment of arterial stiffness in patients with familial hypercholesterolemia. *J Clin Lipidol* 2018;12:397–402.
- 18 Nomura A, Tada H, Okada H, *et al*. Impact of genetic testing on low-density lipoprotein cholesterol in patients with familial hypercholesterolemia (GenTLe-FH): a randomised waiting list controlled open-label study protocol. *BMJ Open* 2018;8:e023636.
- 19 Tada H, Okada H, Nomura A, *et al*. Rare and deleterious mutations in ABCG5/ABCG8 genes contribute to mimicking and worsening of familial hypercholesterolemia phenotype. *Circ J* 2019;83:1917–24.