

EAS FHSC NEWSLETTER

Issue 04, March 2018

Issue 04

From the FHSC Coordinating Centre

FHSC growth

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From the FHSC Coordinating Centre

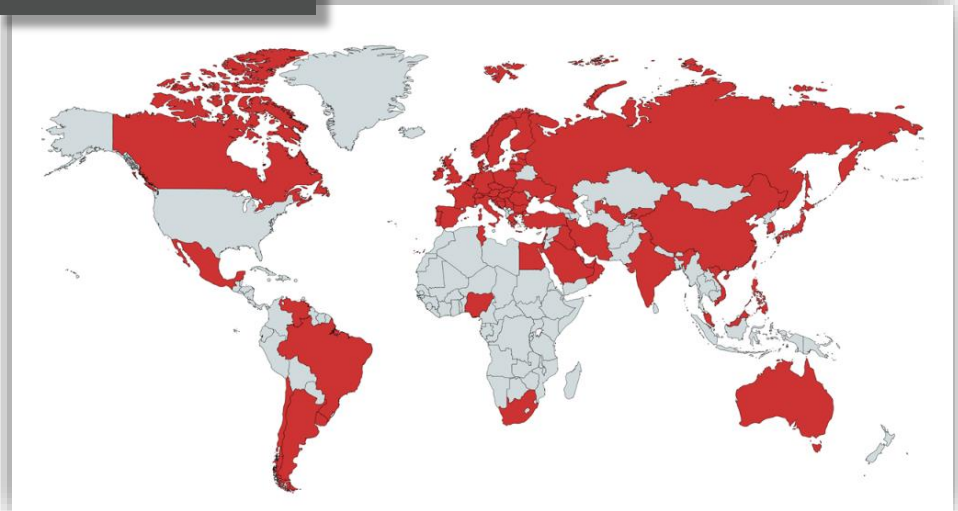
- FHSC growth
- Web Registry

From EAS FHSC Investigators

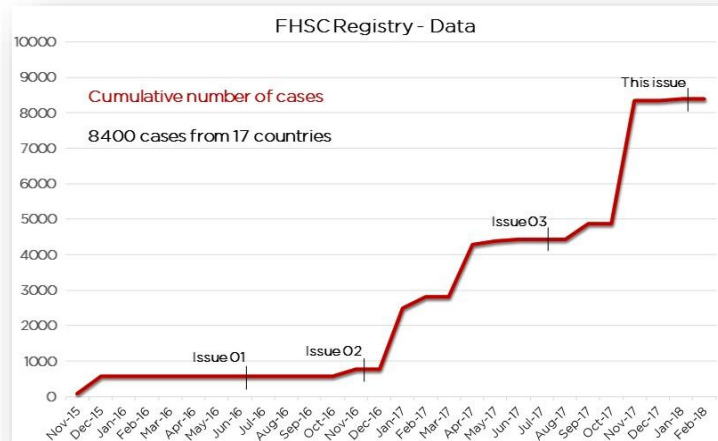
- Australia
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FHSC Steering Committee Meeting, Lisbon 2018

Publications



On its third year after its establishment the EAS FH Studies Collaboration keeps growing at a steady pace, counting a total of **81 collaborators** in **68 countries** worldwide, as per beginning of 2018. The initiative constantly attracts the interest of FH investigators in several countries, who approach the Coordinating Centre for more information or question on how to implement an FH Registry. The Registry so far comprises **8400 cases** from 17 different countries and these numbers are expected to rise sharply with the now fully working FHSC Web Registry.

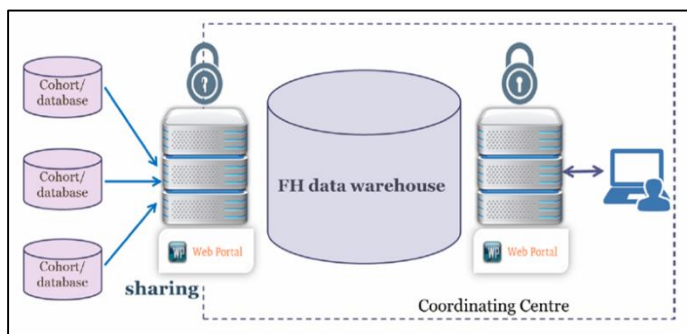


FHSC Web Registry is live

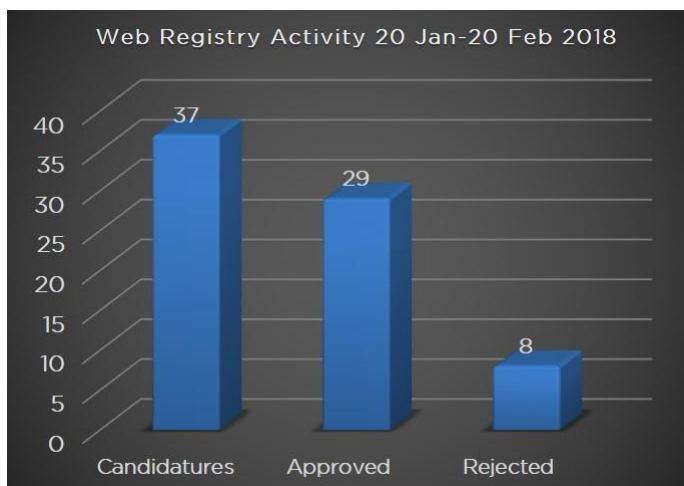
The **EAS FHSC Web Registry** has been officially launched last January, comprising a fully secured and user-friendly platform where it is possible to upload documents and share FH Data with the Coordinating Centre.

It has been a long and committing process for the IT team at Imperial College London (ICL), preliminarily presented at the past FHSC Committee meeting in Prague, 2017. Since then, excellent progress has been made through improving the encryption and the interface, aiming to offer the best possible user experience.

The Web Registry is now the main channel for Data coordination, where National Lead Investigators will be requested to upload their datasets. These Data are hosted in an internal Warehouse that has no public access and that has passed all the stages of security checks performed at ICL. To block access to external users, the registration of an applicant is checked by the Coordinating Centre and, where the requester is not a National Lead Investigator (or a close colleague previously introduced to the Coordinating Centre), their application is rejected.



Not only Data, but files, videos and document sharing will be managed through the Website. Each User account has a dedicated section where to upload documents, as well as to view files shared by the Coordinating Centre. For instance, after registration each User will be able to see their Data Sharing Agreement and Statement of Commitment already uploaded on their account.



The next important step towards the standardisation of the data sharing process is the **FHSC Data Dictionary** which is currently being finalised by the Coordinating Centre. The Data Dictionary will be the most comprehensive list of variables of interest for the project, which will serve as a guideline for Lead Investigators on sharing Data. The Data Dictionary will be also made available to all the users registered on the Website.

Australia

By Prof Gerald F. Watts & Dr Jing Pang - School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia & Lipid Disorders Clinic, Department of Cardiology, Royal Perth Hospital, Perth, Australia & The FH Australasia Network (FHAN).

FH and high Lp(a) in the coronary care unit.¹ FH and elevated Lp(a) are relatively common among patients with coronary artery disease (CAD) and screening for these conditions in the coronary care unit (CCU) is a key targeted strategy for increasing the detection. This would in turn allow systematic cascade testing of available family members for both conditions. Our studies have demonstrated that the CCU setting is a useful environment for detecting patients likely to have FH, who should then be referred to a specialist service for confirmation of the diagnosis and family screening for the condition. The combination of FH and elevated Lp(a) appears to be a 'double-whammy' for premature CAD.

Cascade screening of FH in children.² We recently demonstrated in an Australian setting that genetic testing of children of affected parents with FH is an effective means of detecting new cases of FH. From this data, we also showed that an LDL-cholesterol of ≥ 3.5 mmol/L, preferably on at least 2 occasions, can correctly classify 94.4% of screened children. Parental response to genetic testing was low. Similar to published data from other countries, only 54.8% of the FH children were started on low-dose statins but LDL-cholesterol fell by 38% in those that were treated. Future research is required to optimise cascade screening in children in an efficient and cost-effective manner, as well as to evaluate other methods of screening, such as universal testing.

FH awareness in primary care physicians in the Asia-Pacific region.³ Since FH is a public health problem, primary care physicians (PCPs) or family doctors are well placed in the community to opportunistically detect FH. We investigated several aspects of the knowledge, awareness and preferences of FH among PCPs in ten countries/regions, primarily in the Asia-Pacific Region (component of the "10 Countries Study"). The study identified important gaps, in particular, the lack of awareness of guidelines and knowledge of diagnostic features of FH. Extensive FH education, awareness programs and implementation of country-specific guidelines can help to address these gaps and to improve FH diagnosis and treatment in the region.

A primary care intervention.⁴ Supported by the National Health and Medical Research Council Partnerships for Better Health, we have devised a pragmatic intervention study that will be undertaken in 17 general practices across five states in Australia. The study will utilise an electronic data extraction tool designed specifically to identify patients with FH. We will not only investigate ways to improve the early diagnosis of FH to prevent long-term cardiovascular disease, but also develop improved, cost-effective strategies to provide better care to patients and families in the community.

The National FH Registry.⁵ We have developed a web-based registry platform for FH. According to national legislation, this registry requires fully informed consent of participants. The registry covers 30 sites across Australia and has registered over 1000 participants. The Registry collects information on people with FH and their family members which can be used to improve treatment and quality of care.



[1] Ellis, KL, Pang, J, Chieng, D, et al., Clin. Cardiol., 2018; in press.

[2] Pang, J, Martin, AC, Bates, TR, et al., J. Paediatr. Child Health, 2018; in press.

[3] Pang, J, Hu, M, Lin, J, et al., BMJ Open, 2017;7:e017817.

[4] Arnold-Reed, DE, Brett, T, Troeung, L, et al., BMJ Open, 2017;7:e017539.

[5] Bellgard, MI, Walker, CE, Napier, KR, et al., J. Atheroscler. Thromb., 2017;24:1075-1084.

Canada

By Prof Jacques Genest & Dr Isabelle Ruel.

FH in Canada. The past year was devoted to raise awareness of FH among health care providers and patients through our website www.FHCanada.net.

The Canadian FH Registry. Over 120 clinicians and scientists in 19 academic centers across Canada composed the FH Canada network. In collaboration with the Institute of Clinical Evaluative Sciences (ICES), we published the most recent estimates of the of FH (1/250 worldwide) [Akoyamen L. BMJ Open 2017 PMID: 28864697].

We estimate that more than 140,000 individuals are affected in Canada, with less than 10% diagnosed so far. As of December 2017, 3157 patients are included in the registry.

Canadian FH Definition. After extensive consultation across the country, a new definition of FH was developed and validated in Canada and uses criteria established for the Simon-Broome Registry and the Dutch Lipid Clinic Network. This definition enables physicians to make a validated diagnosis.

FH Canada Diagnostic “app”. A new tool was developed in Canada to help facilitate FH diagnosis for new patients: <http://www.circl.ubc.ca/cardiorisk-calculator.html>, the app is available free online . It provides an imputed baseline LDL-C for patients already on lipid-lowering therapy, and uses the information to make a diagnosis of FH according to the newly developed Canadian definition as well as the DLCN and Simon-Broome criteria. The tool is now available to all health care professionals; it generates a report to be saved and added to patient’s file. The validation of the algorithm used to impute baseline LDL-C is published in *Clinical Chemistry* (Ruel I, PMID: 29038147).

Molecular Diagnosis. FH Canada offers mutation analysis, including indels, for the *LDLR*, *APOB* and *PCSK9* genes using Next Generation Sequencing (NGS) technology. The aim is to create a central laboratory supported by the Health agencies.

Professional Standards of care for FH in Canada. In 2014, the Canadian Cardiovascular Society published a position statement on FH in the Canadian Journal of Cardiology (PMID: 25448461), which will be updated this year to include new data on the prevalence of FH worldwide, the information on the risk estimates for atherosclerotic cardiovascular disease in the presence of a mutation causing FH, the new Canadian definition of FH, and the availability in Canada of new drugs available to treat FH;

Public Advocacy. Promoting patient-based support and advocacy groups, through regular meetings/discussions between patients and health care professionals. The FH Canada registry also has a strong knowledge translation program.

International Collaborations. Forming alliances with international colleagues, resources and initiatives that focus on FH.



Portugal

By Dr Mafalda Bourbon, Department of Health Promotion and prevention of non-Communicable Diseases, National Institute of Health, Lisbon, Portugal

Portuguese Family Hypercholesterolemia Study.

The Portuguese Family Hypercholesterolemia Study is a research study developed and promoted by the National Institute of Health Dr Ricardo Jorge (INSA), funded by several public and private entities, which began in 1999 with the aim to identify the genetic cause of dyslipidemia in families with a clinical diagnosis of FH and promote awareness of the disorder in the country.

Program numbers. Until December 2017, 801 index cases with a clinical diagnosis of FH have been referred for this study and more than 1,800 family members were referred to the Portuguese FH Study cascade-screening program. The 801 patients studied were referred by more than 80 physicians of various specialties (paediatrics, internal medicine, cardiology, medical genetics, endocrinology, general and family medicine), from various regions of mainland Portugal and islands. The molecular study has identified up to 772 patients (319 index cases + 453 relatives), children and adults, with a potential alteration in one of the genes associated with FH, namely: LDLR, APOB or PCSK9. These individuals are currently receiving counselling and treatment according to their pathology.

Genetic tests. The mean total cholesterol found in Portuguese FH patients referenced to the Portuguese FH Study is around 300 mg/dL and LDL about 220 mg/dL, similar to the value found in other countries, and about 25% of them (36% of men, 16% of women) already have premature cardiovascular disease when they are referred for the molecular study of FH. In about 60% of the individuals studied it was not possible to find the genetic cause of their hypercholesterolemia, most probably the majority has another disease of lipid metabolism and not FH; a small percentage may have FH due to a mutation in a gene not yet identified. In addition to performing the genetic test, functional validation (functional in vitro studies) are also developed in the scope of the Portuguese FH Study, to prove that the alterations found are (or are not) the cause of FH. A total of 134 changes were found in the Portuguese population, 68 null alleles or proved functionally to be pathogenic and 49 potentially pathogenic (functional studies undergoing). The mutations found in Portugal, for the most part, have already been described in other countries. The most common mutation in the Portuguese population is p.Ala431Thr in the LDLR gene, responsible for 15% of the cases and is common in patients from the Alentejo coast. The mutation Pr_ex2 + ex8_ex12del in the LDLR gene, which leads to a deletion of a large part of the LDLR gene, is more common in the north of the country. Other 3 LDLR gene variants, (p.Asp222Asn, p.Ser177Leu, c-135C> G), account for 22% of the cases identified. In the remaining 63% of the patients, isolated (1-3 index cases) mutations were found, being 5% in APOB and 1% in PCSK9. The Portuguese FH Study also identified 10 index cases with homozygous FH, all except one with mutations in the LDLR gene.

The Portuguese FH Study has so far managed to identify about 4% of the 20,000 Portuguese estimated to have FH (based on a prevalence of 1/500); this situation of sub-diagnosis is similar in all countries, and despite the low percentage, Portugal is in the top 10 of the countries with the most cases identified. Since most countries have demonstrated to have the ability to perform the genetic diagnosis of FH, government approval and funding in each country for large-scale screening, as recommended by the World Health Organization in 1998 (WHO 1998), would be extremely important to improve the identification and prognosis of patients with FH.

Uruguay

By Dr Mario Stoll M.D., on behalf of the GENYCO Program, Cardiology Genetics Laboratory. Comisión Honoraria para la Salud Cardiovascular (CHSCV): **Early diagnosis and follow-up of patients with Familial Hypercholesterolemia in Uruguay: the GENYCO Program.**

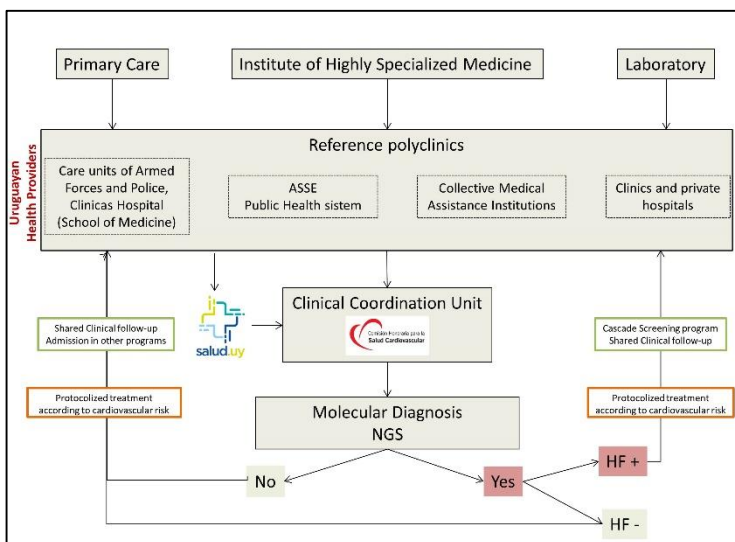
GENYCO is a National Program supported and developed by the Comisión Honoraria para la Salud Cardiovascular (www.cardiosalud.org).¹ It is oriented towards highly vulnerable individuals and families, highlighting the importance of this condition in preventive cardiology. It is a centralized registry that is being implemented in all health institutions and provides access to patients with FH and their families for clinical and genetic testing, cascade screening, proper treatment and follow up. The patients with clinical suspicion of FH arrive at the Clinical Coordination Unit (CCU) from “reference polyclinics”, by levels of LDL-c from the laboratories and from third-level care centers. The CCU selects the index cases (IC) for molecular diagnosis, carried out through the search for mutations in LDLR, APOB, PCSK9, LDLRAP1, APOE, STAP1 and polymorphism screening for polygenic HF by NGS sequencing that has become standard since 2016.

The registry includes today 805 cases with presumptive FH diagnosis in follow up from all the country; 282 are IC and 523 family members. So far, we have made progress in the identification of 215 positive cases, which corresponds to 26% of the Program population (210 positive for LDLR and 5 for ApoB). Forty different pathogenic variants were identified, all except one (ApoB P3500Q) were found in LDLR. Five of these variants were reported for the first time in Uruguay (c.-140C>A, c.-227G>C, c.789dup, c.954C>A, c.1462 Ins C). The heterogeneity of mutations found in this sample of FH is the expected in accordance with the admixture in the uruguayan population.

A software application has been developed for the communication of new cases from medical institutions to the CCU and for database management. Clinical information and the Dutch Lipid Clinic Network Score are sent to the CCU from all the country. Eventually, the CCU can request more clinical information and indicates molecular diagnosis and familial screening. A simple method for saliva collection and transportation were developed that guarantees long term gDNA stability.

We estimate a number of carriers between 6,600 to 9,100 in a total population of 3.3 million people, considering frequencies of 1/500 to 1/360, according to estimates from lipid profiles. We have obtained a positive result in 58% of the cases sent to genetic diagnosis, and an actual coverage between 8 to 11% of the expected carrier population has been clinically identified.

We found that a high rate of positive mutation carriers can be identified using a two-step selection: first in primary medical setting using scored FH criteria, followed by a second analysis at the CCU of the Program. Recently we initiated an association with the national program for Digital clinical history (Salud.uy), a unified medical record for the entire country population. The new collaboration will improve the Program capabilities for identification, diagnosis and follow-up of patients with FH in the country.



[1] The Program was created in November 2012 (Law 18.996, item 12, art. 207) followed by a Regulatory Decree (357/013) approved by the Ministry of Health, Uruguay. Participants: Ximena Reyes M.D.; Nicolás Dell’Oca M.D.; Andrés Ressa MSc.; Graciela Fernández MSc.; Mario Stoll M.D.

08 May 2018, Lisbon, Portugal

We look forward for the **EAS FHSC Steering Committee Meeting**, that this year will take place at the *Centro de Congressos de Lisboa* in Portugal immediately after the 86th EAS Congress (05-08 May, 2018). Like the past FHSC events, the attendance at the meeting is restricted to only the National Lead Investigators, and it will be the opportunity for sharing of updates, discussion with colleagues and ultimately strengthening of the FHSC network.

The program will reserve space for updates from the Coordinating Centre on the central management of the network, data sharing, scientific and technological aspects, and for updates from some of the NLIs on their activities related to FHSC. More detailed information can be found on the EAS-FHSC website. <https://www.eas-society.org/page/fhscisbon2018>



EAS FHSC Steering Committee Meeting_General Program	
12:45 - 13:30	NETWORKING LUNCH AND REGISTRATION
13:30 - 14:45	UPDATES FROM THE COORDINATING CENTRE
13:30	Welcome and introduction
13:40	Update from the coordinating centre: Management (network)
13:55	Update from the coordinating centre: Technical aspects (IT)
14:10	Update from the coordinating centre: Scientific aspects (data)
14:45 - 15:15	Break
15:15 - 17:30	UPDATES AND INITIATIVES FROM LEAD INVESTIGATORS AND PATIENTS ORGANISATIONS
15:15 - 17:00	Updates from National Lead Investigators
17:00 - 17:15	Patient Organisation: European FH Network
17:15 - 17:30	From the EAS
17:30- 17:40	CONCLUDING REMARKS
19:00 - ca. 22:00	NETWORKING DINNER

- Harada-Shiba M, Ohta T, Ohtake A, Ogura M, Dobashi K, Nohara A, Yamashita S, Yokote K; Joint Working Group by Japan Pediatric Society and Japan Atherosclerosis Society for Making Guidance of Pediatric Familial Hypercholesterolemia. *Guidance for Pediatric Familial Hypercholesterolemia 2017*. J Atheroscler Thromb. 2018 Feb 6.
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- Paquette M., Genest J., Baass A. *Familial hypercholesterolemia: experience from the French-Canadian population*. Curr Opin Lipidol. 2018 Jan 19.
- Teramoto T., Kai T., Ozaki A., Crawford B., Arai H., Yamashita S. *Treatment Patterns and Lipid Profile in Patients with Familial Hypercholesterolemia in Japan*. J Atheroscler Thromb. 2018 Jan 19.
- Pek S.L.T., Dissanayake S., Fong J.C.W., Lin M.X., Chan E.Z.L., Tang J.I., Lee C., Ong H.Y., Sum C.F., Lim S.C., Tavintharan S. *Spectrum of mutations in index patients with familial hypercholesterolemia in Singapore: Single center study* Atherosclerosis. 2017 Dec 27;269:106-116.
- Bogsrud M.P., Langslet G., Wium C., Johansen D., Svilaas A., Holven K.B. *Treatment goal attainment in children with familial hypercholesterolemia: A cohort study of 302 children in Norway*. J Clin Lipidol. 2017 Dec 6. pii: S1933-2874(17)30534-2.
- Rocha V.Z., Santos R.D. *Safety of statin treatment in children with familial hypercholesterolemia: Filling the gaps*. J Clin Lipidol. 2017 Dec 7. pii: S1933-2874(17)30532-9.
- R. H. Fairwozy, M. Futema, R. Vakili, M. R. Abbaszadegan, S. Hosseini, M. Aminzadeh, H. Zaeri, M. Mobini, S. E. Humphries & A. Sahebkar *The Genetic Spectrum of Familial Hypercholesterolemia (FH) in the Iranian Population*. Sci Rep, 2017, 7, 17087.
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If you would like to contribute to the next issues of the EAS FHSC Newsletter with any text, publication, events, etc. please contact us at:

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