The GENIUS-CHD Consortium

A new global collaboration seeks to enhance our understanding of risk and improve secondary prevention among those with established coronary heart disease. Bringing together 65 studies and more than a quarter of a million study participants, it is the most ambitious effort in this area to date.

As a cardiology community we can take great satisfaction for improving outcomes from coronary heart disease (CHD). Public health measures and improvements in treatments have consistently reduced mortality from CHD in almost all high-income countries. However, this success has conversely led to a growing number of patients living with established and chronic CHD (3M in the UK; 16M in the USA), at high risk of subsequent fatal or non-fatal events such as myocardial infarction as well as complications such as heart failure and arrhythmia. These often necessitate further hospitalization, revascularization and adjunctive, often costly, drug and device therapies.

Despite the extent of this problem, relative to our understanding of risk for *first* CHD events, we know very little about determinants of *subsequent* CHD events, beyond those related to an acute index event (LV dysfunction, arrhythmia). Secondary prevention guidelines have remained largely unchanged for over a decade, and emphasize modification of the same lifestyle and risk factors as for primary prevention of CHD. This is based on the widely accepted but unproven assumption that first and subsequent CHD events have the same pathogenesis and therefore risk factors, obviating the need for separate study.

Recent high profile failures of several new drugs have highlighted the problem of extrapolating observational findings from general populations to those with CHD (The negative Dal-Outcomes trial for example showed no post-hoc association between baseline HDL and outcomes, in contrast to the clear inverse relationship in general populations) – at enormous cost to both patients and industry.[1] This is in line with observational studies often demonstrating paradoxical or inconsistent risk factor associations with outcomes in those with and without CHD.[2-4] While lack of causality or bias may account for this, biological differences may also be at play, with recurrent event risk driven by, for example, unstable or vulnerable rather than stable plaques. These are known to differ in composition and prognosis and are likely to have different risk factor profiles.[5] Ultimately the high residual risk in apparently optimally treated patients highlights limitations of current management and indicates that there may be additional risk factors still to be identified and addressed.

In 2013, we proposed that a greater understanding of determinants of subsequent events was urgently needed to enhance secondary prevention and drive effective drug development for this growing high risk population. Importantly, this should be studied de-novo in patients with documented CHD rather than extrapolated from general populations. In particular, we argued that genetic association studies would offer unique opportunities for identifying novel molecular mechanisms that predispose to subsequent event risk, such as plaque vulnerability pathways which may be amenable to drug therapy.

In the absence of any single large resource for studying the genetic and non-genetic basis of CHD recurrence, we sought to bring together existing resources of patients with CHD at baseline, with prospective follow up and stored samples or completed genotyping. Starting with our own cohorts and enthusiastic support from

close collaborators, we formed a small grouping. It was clear however that this was insufficient and so we identified more studies from literature searches, conference presentations and collaborator contacts and reached out to other PIs from across the globe, with an open and transparent invitation. We were surprised at the unanimously positive responses from these groups who immediately shared our views and acknowledged the importance of the research and the need for close collaboration.

Thus, GENIUS-CHD came into being (www.genius-chd.org). The rather modest acronym stands for The **GEN**et**I**cs of S**U**b**S**equent CHD. Today it consists of 65 prospective studies, with more than 250K consented participants with CHD at baseline and over 45K mortality events. Studies include investigator led cohorts (e.g. angiographic or clinical CHD populations), randomized clinical trials (RCTs), or case–cohorts from larger population studies. Most have stored samples (plasma, serum, DNA), genotype data as well as a rich and deep collection of phenotype data at scale (for example lipid profiles = 200K; ECG data = 120K; angiographic phenotyping = 140K). The potential for cross-sectional studies as well as prospective studies on genetic and non-genetic exposures is clearly tremendous, and we anticipate such a global collaboration to be of significant interest to funding bodies for grants testing novel hypotheses.

[Figure 1]

The consortium is governed under a memorandum of understanding, which outlines the nature of the collaboration, governance structure and approach to analyses as well as details on publication policy and other matters. The main scientific steering committee comprises the PI or a representative from each cohort and takes all key decisions including approving new proposals, while the operational committee oversees administrative and operational aspects of the consortium. Project specific working groups (PSWGs) include those leading on an individual proposal and analyses. Further details including participating studies and committee membership are available on our website at www.genius-chd.org.

Important features of the consortium are that (1) participation is entirely voluntary as groups only participate in proposed analyses they feel are of value or they have the capacity to contribute to and (2) all data and samples belong to and remain with the PI and are not shared directly or stored centrally. This is possible because of a federated analysis approach, whereby a standardized script is generated by us or any persons leading an analysis, which is then shared (with detailed instructions using R) with all members who then run analyses locally. The outputs with summary level data are shared with the central sites at UCL and UMC Utrecht for QC and meta-analysis. For groups with limited statistical or staff capacity, the analytical team offers close support and also the option to run the analysis in its entirety using an anonymized dataset.

Currently, the consortium has successfully run its first analysis using this framework, exploring genetic association between 3 candidate loci and subsequent event risk. Data are being analyzed with a view to publication by the end of the year along with a formal design paper describing the consortium and its participants. A pathway and process for new project applications has been developed and we hope to invite new project proposals in the near future, initially from consortium members and in time from external investigators.

The scale and nature of the GENIUS-CHD consortium, also offers scope to tackle key challenges in CHD prognosis research. Firstly, CHD is a heterogenous phenotype, often used to satisfy the need for statistical power. With the sample size available, we anticipate disaggregating this into more strict CHD phenotypes including acute and stable CHD at baseline. Additionally, further stratification on variables such as time of recruitment, country and health system, LV function among others will be possible. Secondly, methodological questions around specific biases will also be addressed with advanced modelling and simulation studies. A core group of statisticians from consortium member groups are currently working to develop ways of handling and estimating the impact of survival and index event biases on planned association studies.

Despite the unprecedented size of the consortium, more cohorts are still needed, to satisfy the need to subgroup and disaggregate the CHD phenotypes without loss of power. We invite and warmly welcome all PIs with (1) any collections of patients with CHD at baseline (investigator led cohorts, RCTs, nested cohorts) and (2) prospective follow up for events and (3) baseline samples/DNA or completed genotyping to join the consortium. We are happy to consider all studies, even if the stated criteria are not fully met. Membership benefits for individual groups include (a) greater publication opportunities and routes to impact (b) access to other similar cohorts for replication of local research (c) leveraging of greater funding opportunities (d) enrichment of member cohort datasets (including genotyping) through funding acquired for consortium projects.

In summary, the GENIUS-CHD consortium is a global partnership of researchers seeking to better understand risk in those with CHD with a view to ultimately enhancing secondary prevention. It seeks to be an open and transparent entity and invites all PIs with suitable cohorts to join and collectively enhance its efforts.

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Figure 1 – Overview of the GENIUS-CHD consortium; *Approximate numbers only at the time of survey