Procardis: genome wide association studies of disease

What is involved in such a study, and what potential ethical issues are there?

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Issues in Research Ethics

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Precocious Coronary Artery Disease

the ETHOX centre

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Introduction

- In the first Procardis podcast I discussed why there is a particular interest in ethical issues in genetics research
- The Procardis project is an example of genomics research, where information from the genome – from across the whole spread of DNA in each individual – is being examined with the aim of improving our understanding of disease
- The aim of this talk is to explain in a little more detail what such a project, and similar projects, involve, in order to explain in a little more detail some of the ethical and social questions that arise with such scientific projects

Genomics research is taking place in a variety of different kinds of project

- **Case control studies**: In Procardis: samples were collected from cases and controls, and also from small family groups
- Genomics research can also be part of **birth cohort studies**, such as **ALSPAC** and the 1958 National Child Development Study (the 58 birth cohort study)

  http://www.bristol.ac.uk/alspac/

  http://www.cls.ioe.ac.uk/

- **Longitudinal studies** follow recruits for a number of years
- The **Framingham heart study** is a well known example of a longitudinal study based in a town in the US: http://www.framinghamheartstudy.org/
- As are the famous UK **Whitehall studies** also – heart disease which also includes genomics: http://www.ucl.ac.uk/whitehallII/
- Biobank projects such as UK biobank typically look at a range of diseases:

  http://www.ukbiobank.ac.uk/

- Procardis is not a longitudinal study

What’s involved for Procardis recruits

- Recruits from a number of European countries – Italy, Sweden, Germany, UK
- Patients and controls
- In some cases, groups of three people from the same family – family trios
- Health information given, measures such as blood pressure, and a sample of blood
- Blood tested for various traits including lipids, and DNA extracted

- Recruits are all volunteers
- Recruits gave informed consent to research on genetics of cardiovascular disease
- Procardis has a number of partners including various universities and also some commercial partners
- Recruits told that there may possibly be some commercial outcomes but that they would not benefit
- And that they would not be given any individual results from the study, although some were given immediate results such as measurements of blood lipids.

- Procardis has been performing genome-wide association (GWA) scans on the DNA.
- Many such GWA studies have been undertaken in recent years
- Falling costs and increasingly sophisticated technology have boosted the power of these studies considerably in recent years
- In a GWA study, typically there are thousands of recruits.

Genome-wide association studies

A genome-wide association scan looks at a large number of points of information across an individual's DNA looking for Single Nucleotide Polymorphisms (SNPs: pronounced 'snips')

DNA is made up of many, many different molecules strung together. A nucleotide is one of these molecules: each of us has roughly 3 billion (3 000 000 000) of these in our genome – in our DNA.

A Single Nucleotide Polymorphism is simply a variation in one of these nucleotides – (polymorphism simply meaning that there is more than one form of a nucleotide – some have one form, some have another)

SNPs are points of variation where some individuals in the population have different patterns of DNA.

These SNPs may produce variations between individuals, such as differences in hair colour, or, importantly, differences in susceptibility to diseases.

In a GWA project such as Procardis, a million SNPs are examined for each individual. That is, out of the roughly 3 billion points along each person's genome, one million points of possible variation between people are sampled

In future work of this type, as the technology becomes cheaper and more powerful, more and more of each individual's genome can be sampled – some research now is looking at the whole of the genome of each individual

- Cases of those with cardiovascular disease are then compared to controls:
- If some forms of SNPs are more common in cases than in controls, or vice versa, this *may* help explain why some experience disease and others do not.
- However, there is still much work to be done to work out which SNPs are significant and a great deal of painstaking work into the underlying biology is being undertaken by Procardis scientists – once significant SNPs have been found, it's necessary to look at where they are in the genome and at whether they might be related to a gene of interest
- Much work in Procardis and similar projects is looking at the underlying biology
- Some of the work accompanying such investigation involves looking at mouse models of disease

Why so many recruits in genomics research?

- Because so many different points along the DNA are being looked at, and cases compared with controls, there's a high possibility that some of the associations found will simply be random
- If only a few people were examined, it might be found simply by fluke that those in the disease group had an association with something that was not actually anything to do with the disease
- So the larger the study size, the smaller the chance that any general association found really indicates a causal relation with the disease of interest
- Also: this research needs to be replicated to show the results are real and not the result of chance.
- This research is dogged by 'winners' curse' – the phenomenon that the first results showing an association is significant often tend to show that it has greater significance than later studies. For this reason too research needs to be replicated.

Sharing data

- It’s common for researchers to share data
- This increases the power of the study by making any associations more likely to be truly causal
- Data from one population group may be usefully compared with data from another population group
- But to share data in this way it’s important to preserve mechanisms to protect privacy and confidentiality of recruits
- It is often useful to use archived data
- Sharing data also means efficiency – why recruit more people when there’s already blood and DNA to be used?
- Some also argue that those motivated to contribute to medical research are likely to wish full use to be made of their samples and data
- But doing the research can use up the samples
- And it’s important to compare ‘like with like’ – making sure the information on the samples such as clinical measurements is consistent

Limitations on sharing data

- The consent agreements of some studies may limit sharing data
- Some consent agreements limit the type of disease that research – ethics committees may then require that to use for other research may require going back for further consent
- Others give broader consent, or relate to a broad disease category – e.g. cardiovascular disease is linked to lipid levels, to type II diabetes, to body mass index, and to inflammation
- Some consent agreements rule out commercial involvement
- Some consent agreements rule out returning results to recruits – others may require it
- Sharing data in genomics may mean that effectively it's hard or impossible to withdraw one's data from a study – if it's already been used and results published
- There may be some concerns about sharing data across international borders in different legal jurisdictions

Genomics research and populations

- Some genomics research looks at large family collections – extended families where the disease of interest is found in some members
- Some also looks at particular population groups where there may be particular disease patterns
- Certain diseases may be more prevalent in different populations, or different forms may be prevalent in different populations
- For example, cardiovascular disease is more prevalent in European populations than in Japanese populations
- Within Europe, there are differences in the prevalence of cardiovascular disease between north and south, and east and west
- Some of these differences may be due to genetic factors, or to other factors such as lifestyle, environment, diet, and patterns of tobacco and alcohol use.
- Large studies which take into account the geography and ancestry of recruits are needed to untangle all these factors.

- Many people have been concerned about ethical issues in genetics and race, especially following Nazi abuses and 20th C eugenics
- Genomics research routinely takes note of ancestry – to exclude confounding factors that may provide false signals – genetic ancestry is looked at for methodological reasons
- Procardis research is primarily in European populations – now also doing work in conjunction with populations originating from south Asia
- Genomics research which is only conducted in one population may not generalise well to different population groups
- So failure to take ancestry groups into account may mean that research findings will be less robust and outcomes may be less relevant to certain groups
- For genomics research to proceed equitably, research on different population groups will be needed.
- Concerns have been raised that genetic research results may stigmatise certain clearly identifiable, or isolated population groups.

Outcomes of research

- Screening for genetic risk – it's already the case that come commercial DTC companies include cardiovascular risk scores
- But some recent work shows that even including all the findings to date about genetic risk factors for cardiovascular disease does not improve risk scoring accuracy above conventional measures
- So is DTC "money for old rope"?
- More likely that work to understand underlying molecular biology will be more fruitful
- Work is looking at different forms of disease, and different expressions in different tissues
- Cardiovascular disease is strongly linked to socio-economic status: for reasons of equity, strategies for its treatment and prevention need to take these factors into account hand in hand with examining genetic factors

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Website: www.procardis.org