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Guest Edirorial

GENOMICS: WHERE ARE WE NOW?

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Around fourteen years ago a huge leap was made in the field of genetics – the possibility to sequence the whole human genome, 3 billion base pairs of DNA, in a rapid timeframe and at a relatively low cost. Before that, sequencing a human genome took several labs over ten year. Now several samples can be sequenced in less than a week on one machine. This has led to the development of the field of Genomics. Currently sequencing a whole human genome, or an exome, which contains the most important part, costs below 1000 Euros and 300 Euros respectively. So where are we now? Are we getting much needed answers?

Since this development of high throughput sequencing (HTS) important discoveries have been made in the field of Mendelian genetics. The genetic basis of many diseases has been uncovered at an unprecedented pace. In general, family studies are sufficient to generate these results. But there is still a percentage of tested cases where HTS (currently mainly at exome level) has not yet improved our understanding. This situation is far more difficult in complex diseases where in some conditions hundreds of genetic variants, the vast majority with small effect, interact amongst themselves and with lifestyle factors such as (smoking, drinking alcohol, diet, physical exercise), other environmental factors (such as exposure to pesticides, length of day, water quality) and also underlying physiological conditions (such as diabetes, obesity) to generate a final phenotype or outcome. Thus the effect of a genotype can be modified depending on what environmental factors are present – deciphering these effects is much more difficult particularly because over a lifetime environmental factors change.

The bottleneck right now is finding ways to analyse these large amounts of data in a way that reflects the underlying complexity. The field is complicated by the fact that there are population differences – first of all in the genome itself – every population harbours some genetic variants that are restricted to that population. This is particularly relevant for islandic populations like the Maltese where in reality the population developed from a relatively small number of founders. Secondly, lifestyle and other environmental factors vary by culture and therefore different populations, and sometimes different groups within a population, have different environmental exposures. These factors make comparing results of studies on different populations difficult.

Nevertheless, it is not always necessary to understand the full genetic contribution of a condition to develop new treatments for it. It is becoming increasingly clear that new drugs for common complex diseases can be developed when we discover the role played by a small component of this larger picture, such as a specific key protein or biological pathway. An example is the development of PCSK9 inhibitors for use in some patients with very high cholesterol levels. This potential drug target was identified through research on the genetics of familial hypercholesterolaemia (reviewed in Rosenson et al, 2018). This relatively rapid application of genetic research to clinical practice holds much promise.

Besides helping us increase our understanding of diseases and improving diagnostics, Genomics is also helping us come closer to an era of precision medicine. There will come a time where we can recognise patients who can benefit from using a drug from patients who wouldn't and tests will determine what treatment should be followed. This is already true in some fields such as breast cancer where tests done to determine properties of a tumour can modify treatment prescribed.

It is important for every population to be studied using HTS technology so that everyone can benefit from these improvements in medicine. Currently most genomes and exomes are from the developed world.

In Malta we have some major projects that are focussed on understanding the genetics and the genetic-environmental factors underlying a number of diseases – these include the Maltese Acute Myocardial Infarction (MAMI) Study and the Malta Next Generation Sequencing (NGS) Project, both projects coordinated by myself and Dr Rosienne Farrugia from the Department of Applied Biomedical Science at the Faculty of Health Sciences of the University of Malta, in collaboration with the Health Department and Mater Dei Hospital, particularly the Pathology department, respectively. In the Malta NGS Project several teams of scientists with various backgrounds (applied biomedical scientists, biologists, bioinformaticians, mathematicians), doctors, and practitioners from various fields are working on understanding the genetic basis of over 15 conditions using HTS technology. The conditions include pseudoexfoliative glaucoma, autism spectrum disorder, speech language impairment, Joubert-like syndromes, familial hypercholesterolaemia, idiopathic hypogonadotropic hypogonadism, polycystic kidney disease, hypertrophic

obstructive cardiomyopathy and myocardial infarction amongst others.

In the MAMI Study we have collected samples and lifestyle data from over 1000 participants. Plasma, serum, DNA and RNA of these individuals are banked. We are trying to raise or obtain funding to sequence all these participants – which combined with the large amount of data we have collected – over 130 variables measured (haematological, biochemical, immunological and coagulation tests) besides details on lifestyle factors recorded through interviewer-led questionnaires - are a powerful tool to improving our understanding of heart disease which is still the leading cause of death in the developed world. The department of Applied Biomedical Science also has teams working on haemoglobinopathies headed by Prof Joseph Borg and the genetics of osteoporosis (Prof Angela Xuereb and Dr Melissa Formosa), and more recently Dr David Saliba with research on cancer and the immune system.

The field of Genomics is becoming increasingly multidisciplinary. Of course working with such large numbers of research subjects and with sensitive genetic and lifestyle factors, great attention has been paid to the ethics of these projects which took some two years to develop and involved discussions with ethicists and specialists working in various fields.

Analysing such huge amounts of data at this level of complexity has led to the development of Bioinformatics – where Computing and Statistics are combined with Biology to uncover meaningful patterns from this sea of data. The Department of Applied Biomedical Science, in conjunction with the Centre for Molecular Medicine and Biobanking (CMMB), the Department of Computer Information Systems within the Faculty of Information and Communication Technology, and the Department of Statistics and Operations Research within the Faculty of Science, have started offering an MSc in Bioinformatics open to graduates with a biological, computing or mathematics background.

Finally, genetic discoveries need to be tested and confirmed generally using alternative approaches which we call 'functional work' as the functioning of protein variants arising from genetic changes is interrogated. This involves other techniques such as *in vitro* work and animal models (eg. the zebrafish).

It is an exciting era to work in the field of Genomics, a field already reaping benefits but in which there is still much more for us to understand. Investment in this field will improve healthcare and generate new industries in the fields of pharma, healthcare service providers and bioinformatics. Funding is required to enable scientists to continue working in the field and also to generate more HTS data which will help us unravel these puzzles.

Reference:

1. Rosenson R.S., Hegele R.A., Fazio S. and Cannon C.P. *The Evolving Future of PCSK9 Inhibitors.* Journal of the American College of Cardiology, Volume 72, Issue 3, July 2018. DOI: 10.1016/j.jacc.2018.04.054