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ADELPHI GENETICS FORUM

exploring heredity and society

Adelphi Review

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All Images: ***Adelphi Genetics Forum***
Cover image:
Professor Malia Fullerton receiving the Adelphi silver dish from Professor Nicholas Wood

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EDITORIAL

Last October we were back in the familiar surroundings of the Royal Society for our Annual Conference which was very well attended thanks to a stimulating programme and a lack of train strikes. The day was devised by four of our most experienced trustees, **Dallas Swallow, Rosemary Ekong, Veronica van Heyningen** and **Elena Bochukova**. We're grateful for the huge amount of work they put into the planning of the event along with our Secretary **Betty Nixon** who worked tirelessly as ever behind the scenes. The full report of the entire conference can be found starting on page 4 and you can watch each of the talks on our website at:
https://adelphigenetics.org/events/annual-conference-2023/

On page 26, you'll find the remarkable career story of our Librarian, **Helen Middleton-Price,** while on page 30 is another brilliant book review by our tireless Treasurer, **Andrew Read**. Both articles are thoroughly entertaining.

The issue also carries adverts for two important events next year. In October, the Annual Conference is on the theme of ***'Progress and challenges of implementing genomics into practice and society—the first 20 years'*** and is once again at the Royal Society. Meanwhile in July, we hold our fifth Teachers' Conference at NOWGEN in Manchester. I hope you can attend one or both of these as we already have an impressive list of speakers. Keep an eye on our website for booking places.

Robert Johnston

The Adelphi Genetics Forum Annual Conference
Population diversity, its biological consequences and impact on disease risk
18 October 2023 at the Royal Society

This year's conference was held in the Wellcome Trust Lecture Hall of the Royal Society. The full programme along with a link to videos of the talks and podcasts is available on our website.

The President, **Professor Nicholas Wood,** opened the conference and welcomed the various speakers and all the attendees. He also thanked the organisers for all their hard work, **Professors Dallas Swallow and Veronica van Heyningen and Drs Elena Bochukova and Rosemary Ekong**.

The first session was chaired by **Professor Dallas Swallow** and the opening speaker was **Dr Garrett Hellenthall** (University College London) whose talk was entitled **"Pervasive genetic structure and signatures of recent intermixing among groups reflect historical interactions."**

Dr Hellenthall began by stating that studying the ancestral history of modern humans is difficult because it is impossible to accurately predict the dates of various events. However as humans began to move out of Africa and across the globe, there were genetic consequences that can be seen in the genome.

Human genomes are 99.9% identical in sequence but that still means that 3 million nucleotides can vary between individuals. The greatest diversity in genomes can be found in Africa since humans have been there longest while more recently populated continents show less diversity as the population has evolved from a smaller founding group who have had less time to develop. Related individuals in any population share segments of DNA

but as generations continue, the size of shared segments get smaller. It is therefore possible to compare DNA from apparently unrelated people to see how long ago they were closely related. It then becomes possible to find correlations between the geography and genetics of populations.

Detecting admixture between groups reflects known historical movements in centuries past. Examples given included the Mayans (19% Spanish and 81% Native Americans), the expansion of the Mongol Empire into Western Europe, perhaps along the Silk Road and the modern 'English' who include up to 40% Anglo Saxon DNA. Dr Hellenthall concluded by considering much older examples of admixture between ancient humans, Neanderthals and Denisovans.

Dr Garrett Hellenthall

After a coffee break, the second session was chaired by **Dr Rosemary Ekong** who introduced the next speaker, **Professor Ambroise Wonkam** (Johns Hopkins School of Medicine) who talked about **"Harnessing our common African genomes to improve health globally".**

Professor Wonkam firstly explained that he considered it his duty to convince the audience to invest in studying African population variation and divided his talk into three parts: Ancestry Ecology and Equity.

Ancestry Since modern humans arose in Africa and there is more genetic variation in Africa than the rest of the world, African genomes will be a rich source of genomic information which, in the future, can be used to improve health globally. He told us that there is much archaic human DNA found in Africans from ancient populations that never moved out of Africa. Over the last 300,000 years, there have been two waves of integration of this 'ghost' DNA; the net result of migration and admixture is highly variable

DNA amongst Africans. We already know that there is a 'susceptibility to severe Covid 19' locus on chr 3, derived from Neanderthal DNA; there may be many other similar associations waiting to be discovered in African genomes. The Human Heredity and Health in Africa (H3Africa) dataset has identified 3.4 million novel SNVs, which means there are many missing African variants in the current human reference genome.


Professor Ambroise Wonkam

Work on African genomes has identified mutations which may be useful for the development of therapies worldwide: one example of this is a PCSK9 mutation common in African Americans (2%), but rare in European Americans (<0.1%), which is associated with a 40% reduction in plasma levels of LDL cholesterol, thus identifying a potentially useful drug target. Furthermore, association studies in African populations have been shown to yield larger effect sizes in some cases, illustrating how important African genomes are to our understanding of genomic science.

Ecology The variation of climate, flora and fauna across the African continent has resulted in diverse diets, environments and infectious agents, the last of which was Professor Wonkam's particular focus, and he referred to the best-known of these: the effect of selective advantage in the autosomal recessive condition sickle cell disease (SCD), where carrier status for the S variant confers resistance to malaria. He came back to further discussion of the treatments for SCD in his last section on Equity.

Equity The key challenge is how to ensure all the data generated from African genomes benefits African people, and how the anticipated benefits of genomic research can be realised in the light of persistent world-wide inequity. H3 Africa is one effort to concentrate endeavour in Africa. However, studies such as Genome Wide Association Studies (GWAS) in Africa require rea-

gents and materials designed for African populations. For example, the Affymetrix SNP 6.0 chip, which was built using European haplotypes, would simply not capture African genomic variation, highlighting the need for appropriate population-specific analytical tools.

SCD is a particularly good example of the trans-global inequity in healthcare provision; the condition was described just 100 years ago in USA, but MRI scans of the bones of Tutankhamun indicate he had SCD; showing the condition was present in North Africa 5000 years ago. However, nowadays in Nigeria a SCD patient has just 50% chance of living to 5 years old; in the USA a patient is likely to survive to adulthood but die before 60 years. More effort needs to be expended to ensure prenatal diagnosis, management and new treatments are extended to African countries affected by SCD. Furthermore, Wonkman's group has also shown there are genetic variants that modify the SCD phenotype, including one that lowers the blood pressure in patients who have survived without treatment to adulthood in Africa, illustrating once more how study of African patients can elucidate mechanisms and identify targets for treatment.

Professor Wonkam drew our attention to the interesting case of non-syndromic deafness (i.e., deafness not associated with any other features) in Africa. The common mutation in Europeans in the gene GJB2 is not present in Africans. However, a different mutation, which first occurred in a Ghanian individual around 10,000 years ago, explains 40% of deafness in children in Ghana. There is possibly a selective advantage conferred by the Ghanian mutation, as it confers thicker skin which might make it less prone to penetration by mosquitos, thus protecting against mosquito borne diseases.

The final speaker of the morning was **Dr Gavin Band** (University of Oxford) who spoke about **"The genetics of susceptibility to malaria"**.

Dr Band described his work on the inter-relationship between the human host and parasite genetics in malaria susceptibility. His talk focussed on the human genetic factors influencing susceptibility to

malaria, and the genetics of *Plasmodium falciparum*, the most important parasite causing malaria. He mentioned that there is a third genetic aspect of malaria pathogenesis, the genotype of the mosquito transmitting the malaria parasite, but did not discuss this in his talk.

Malaria is an important cause of morbidity and mortality, and studies of human genetic variants which confer resistance to infection with this disease date back to 1949, with JBS Haldane postulating a heterozygote advantage against malaria for carriers of Sickle cell disease, confirmed by further studies by Allison in 1954.

Recent genetic association studies have investigated the possible protective effect of candidate genes such as those regulating immunity, cytoadhesion molecules and others. Only a few variants were found to be associated with malaria resistance, including of course the Sickle gene. Also associated was the DARC gene, which expresses a membrane surface protein, and has a DNA binding motif regulating production of a red cell receptor used by the p. vivax malaria parasite to enter the red cell. The DARC mutation prevents transcription of the receptor, and thus protects against vivax malaria. Kwiatkowski identified an association between malaria resistance and a cytophorin A and B duplication. The ATP2B4 gene causes expression of a GATA binding site, and the malaria protective allele doesn't express the binding site, so there is no expression of the protein. The cellular effect of the normal gene is to encourage calcium efflux from the red cell and so reduce intracellular calcium. The mutant gene increases the calcium content of the red blood cell by reducing its efflux. Malaria parasites enter the red cell by invagination within a vacuole which, in mutant red cells, would be likely to have lower concentrations of

Dr Gavin Band

calcium, which may be disadvantageous to the parasite. A further genetic association with malaria resistance is with the Dantu blood group, due to a structural duplication variant in the GYPE-GYPB-GYPA tandem genes, causing an alteration in the tension of the red blood cell membrane which may discourage parasite invasion. The risk of severe malaria in individuals with the Dantu blood group is significantly reduced.

The main host factors in malaria resistance therefore so far confirmed are HbS, determinants of blood group O, G6PD, the DARC gene, the Dantu blood group and the ATP2B4 calcium pump variant. The fact that host genetic factors can confer resistance to malaria raises the question as to whether there has been evolution of genetic factors in the parasite to avoid the protective effects of variants in the host.

The falciparium plasmodium has a genome of 23Mb containing around 5,000 genes. Studies of the malaria parasite genome were performed in the Gambia and Kenya, testing selected candidate genes in the host and most of the malaria parasite genomes in the same patients with severe malaria. The only component of the host genome showing association with parasite genomes was HbS. An association was demonstrated between HbS and non-synonymous variants in the gene for acyl-CoA synthetase family member, PfACS8, within three loci in the parasite genome. There are three pfsa genes, (1,2 and 3), two on chromosome 2 and one on chromosome 11, all in linkage disequilibrium (a very unusual finding). The pfsa negative parasite genome appeared to be associated with a significantly lower malaria infection rate in HbS heterozygotes than the pfsa positive genome, which appeared to provide no protection against severe malaria.

The heritability of malaria resistance is thought to be 20%; the variants so far identified probably explain about 2%. Many questions remain from this fascinating research: what is the mechanism of malaria resistance in the pfsa negative parasites, how do pfsa positive parasites infect HbS carriers, how does HbS protect from malaria, and how do severe and mild malaria develop in different contexts?

After lunch, the session was chaired by **Professor Anneke Lucassen** and the first speaker was **Dr Mie Rizig** (University College London) whose talk was entitled **"Ethnic variabilities in neurodegeneration: what do we know about the genetics of Parkinson's disease in African populations in comparison to other ancestry groups?"**

Dr Rizig started by mentioning the consortium, International Parkinson Disease Genomics Consortium (iPDGC), which began in 2019 to study Parkinson's disease in Africans who live in Africa and the diaspora. She defined "ethnicity" as a social concept and "ancestry" as a biological concept, as these two terms are often used interchangeably yet have different meanings. She explained that populations of African ancestry are spread over the Americas and Europe, and that slave trade over the last 5,000 years changed the African genome to the extent that it has a vast amount of diversity. Also, that aspects within the African genome, i.e. linkage disequilibrium and haplotype blocks, are very strong tools with which to study such diversity. She mentioned the Pan-African genome, constructed from individuals of African ancestry, that has DNA sequences which are missing from the first reference human genome published. She spoke generally of inequalities in genetic research which result in health inequalities, but then illustrated this point with data from other studies that show the disproportionate number of African genomes in research, 0.18% against 95% of European genomes. These disproportions inevitably result in inequalities in the benefits derived from research.

Dr Rizig went on to explain that the burden of PD is increasing due to people living longer, and that the increase in the African population will give rise to an increase in the burden of PD. Recent studies into the genetics of PD have shown that PD can run in families but can also appear where there is no history of PD. Thus, being able to understand results from genome-wide association studies (GWAS) has aided an understanding of how the different signs of PD can be linked to differences at the genetic level. GWAS has also helped produce a better understanding of its molecular background. For example, if a specific DNA change is considerably common between individuals with a con-

dition compared to those who do not have the condition. The DNA change being common in those with the condition indicates that the change could be a risk factor for that condition. Dr Rizig also mentioned that clinical studies are moving from treatments that target the signs of PD to treatments that delay or slowdown the progression of PD.

Dr Mie Rizig

The next part of Dr Rizig's talk focused on some results from the consortium's published work. Their collection included thousands of patients with PD and controls of solely African ancestry or African admixed (i.e. people with African, the Americas and Caribbean ancestry). Using GWAS, they found previously described changes at specific positions in three genes (*LRRKs*, *APOE* and *MAPT*) in samples from Egypt. However, none of these results were seen in samples from Nigeria. Whilst over 300 changes in the *GBA1* gene have previously been associated with PD in other populations, one particular change (rs3115534-G), in the part of the gene that does not code for the protein, was found only in samples of patients from Nigeria (in the Esan and Yoruba ethnic groups). This change has not been associated with PD in East Africa, in any other West African population, or non-African population! This was a striking discovery! They found that the activity of the enzyme glucocerebrosidase (a.k.a. GCase), that is produced by the *GBA1* gene, is reduced. Also, people with two copies or one copy of rs3115534-G have PD, but the extent of the symptoms varies depending on whether there are two copies or one copy of rs3115534-G. The hypothesis is that this change (rs3115534-G) increases the amount of protein, but this protein is faulty so the effect of the enzyme is reduced.

Dr Rizig and her colleagues consider that this change (rs3115534-G) is unlikely to cause Gaucher disease as the number of Gaucher disease cases in Nigeria are very low. They see this discovery as

an opportunity for new treatment options. But they are not stopping there. They will be looking for other populations with *GBA1* rs3115534-G, examining the clinical features of other PD patients with this change, finding out the implications of their observation regarding the effect on the enzyme GCase, and identifying new DNA changes in African populations that are associated with PD.

The second speaker of the afternoon was **Dr Hannah Elliott** (University of Bristol) who talked about **"Characterising epigenetic variation – a key to understanding type 2 diabetes risk in diverse populations"**.

Dr Elliott started by introducing the concept of epigenetics, the different types of DNA modifications, and specifically on DNA methylation, a repressive epigenetic mark, which her work focusses on, especially investigating DNA methylation from biobank samples of large cohorts. The role of different environmental factors' impact on DNA methylation, as well as the contribution of the underlying genetic architecture over the life course and particularly in early development was discussed. Epigenetics and its relationship with human disease examples were provided, including environmental exposures such as the Dutch famine of 1944-1945 and its links to development of type 2 diabetes. Further evidence for the role of environmental influences, likely acting via epigenetic modifications, versus underlying genetics, such as the disease discordance seen in monozygotic (genetically identical) twins, was also presented. Hannah also highlighted the difficulty in establishing if DNA methylation is causing disease or whether it's disease causing differences in DNA methylation; as well as the use of DNA methylation in disease prediction.

Dr Hannah Elliott

The next part of the talk focussed on research of type 2 diabetes in South Asian ethnicities, where the prevalence of the disease is

about six times higher compared to European populations. Major research question has been to establish if epigenetics could improve risk prediction over and above traditional risk factors including age and BMI. Dr Elliot discussed work derived from the LOLIPOP and the SABRE (Southall and Brent Revisited) cohorts, where they have identified widespread epigenetic differences in DNA methylation between UK resident self-reported South Asian and European individuals, which will be further investigated to understand the disease prevalence discordance between populations. She went on to introduce the formation of the MRC funded Diverse Epigenetic Epidemiology Partnership (DEEP), which has 20 global project partners and will investigate 13,278 population samples and analyse genetic and DNA methylation data to understand disease discordance; aiming to reducing health disparity in the UK and also in global settings.

Following afternoon tea, the President, **Professor Nicholas Wood** acted as chair for the final talk, the 2nd Adelphi Lecture (105th Galton Lecture), given by **Professor Stephanie Malia Fullerton** (University of Washington) on **"Precision medicine in a diverse world: considering the complexities"**.

Professor Fullerton introduced her talk by explaining that she had three goals: to take a retrospective look back on this issue, followed by a critical reappraisal of what we had learnt in the last few years, then making a call to reorient the ways in which we can obtain more full equity.

In 2016/2017 she (and others) had highlighted the over-representation of Europeans in genome-wide association studies (GWAs) and had cautioned that this could lead to adverse consequences. She had made the ethical case that since health equity and fair distribution is a fundamental human right, health disparities (due to sampling) are unacceptable. But ensuring equity is challenging. It is well recognised that genes play a less important role than does the environment and it is not realistic that we shall often be able to intervene, for example by editing genes.

Although between 2009 and 2016 the number of non-European

samples tested moved from 4% to 19% (largely due to the additional Asians) it was still far from representative. This was of concern for at least two reasons:

1 Disease variants are often population specific so that extrapolation from Europeans is less precise.

2 Trans-ethnic analyses suggest different associations with disease risk across groups.

Although newer projects are better, it is still not good enough.

In explicit studies to examine precision it was found that the proportion of variants of uncertain significance differs by background. The rates of false positive and false negative inferences are higher in less studied groups. This argues for the urgent incorporation of more diversity into discovery efforts and this is starting to be addressed (e.g. in the ExAC (Exome Aggregation Consortium) and TOPMed (Trans-Omics for Precision Medicine) and in addition, new recruitments (All of Us Research Programme). To do well there is a need to engage better with the community, to promote trust and thereby enhance diversity; and address past issues. It is important also to improve diversity amongst researchers and project personnel as well as recruits.

Progress has been made, but the GWAs catalogue is still far from being representative. The original argument was that fair distribution of the fruits of precision medicine requires increase in diversity because populations differ biomedically, socially and genetically; we know far less about genetic determinants of health in “non-white” population than others. She now feels that there has been an overemphasis of the inclusion of population diversity due to ancestry to the exclusion of other factors. This has led to a focus on ethnic diversity where there is consistent conflation of social and genetic heterogeneity and poor consideration of non-genetic risk factors. For example, the genome informed risk assessment-eMERGE (Electronic Medical Records and Genomics) network does not include social determinants despite original intention to do so. The PRIMED (Polygenic Risk Methods in Diverse Populations) consortium is aiming to do this but in an international setting harmonising socioeconomic factors will be a research chal-

lenge. There has been an overstated promise of public health benefit from precision medicine.

She has concluded that Polygenic Risk score is unlikely to lead to broad public health benefit because shifting high risk individuals into a lower risk category does far less than shifting the whole population into a lower risk category by encouraging everyone to change their behaviours. Misuse of such tools could exacerbate disparities. For example, high risk individuals from other causes can be mislabelled-promoting complacency. Also, rare variant interpretation requires assessment of allele frequencies which are typically measured with knowledge of ancestry but some ancestries are not represented in data bases and what about mixed ancestry? Also, the way in which ancestry data are collected is ad hoc, inconsistent and also often not related to ways in which allele frequencies are reported in data-bases. Currently there is no way of contending with this. In addition, polygenic risk scores (PRS) are very sensitive to population background and perform poorly. PRS scores are being generated that have not been validated across diverse ethnic groups, leading to ethical dilemmas about reporting.

Professor Stephanie Malia Fullerton

She then spoke of her own experience with the much smaller CSER (Clinical Sequencing Evidence-Generating Research) programme, a Consortium which aims to develop best practices for the translation of genomic sequencing into Clinical Care. This helped her to understand that enhanced clinical validity does not guarantee health equity. Numerous structural inequities include choice of candidates for testing, acceptance of offer of testing, and who will act on evidence. Barriers included cost (eg lack of insurance); organisational issues such as referral, time, social issues such as language barriers beliefs, distrust. While in a re-

search context some of these issues can be mitigated, for example by having more patient and community stakeholder involvement, it is not clear how well these inequities will realistically be overcome in the 'real world'.

Therefore, we should attend to diversity and equity across the translational cycle, learn more about gene-environment interactions in ALL populations and to achieve health equity, more research is required both into basic science and implementation-oriented efforts. There is much more work to be done.

Dallas Swallow
Rosemary Ekong
Helen Middleton-Price
Elena Bochukova
Robert Johnston

ARTEMIS TRUST GRANT

The Artemis Trust of the Adelphi Genetics Forum is seeking applications for its 2024 grant. Objectives of the Artemis Trust, as approved by the Charity Commission, are:

To preserve and protect the physical and mental health of people, particularly, but not only, those from poorer communities, in particular by:

- Assisting in the provision of fertility control and other measures to improve reproductive and sexual health; and
- Advancing education in all aspects of reproductive and sexual health.

The maximum grant available is £15,000 and full details and application form can be found on our website here: **https://adelphigenetics.org/grants-awards/artemis-trust-grants/**

The deadline for receipt of completed applications is 31st March, 2024. Notifications will be made in July and the grant will be available from 1st September, 2024

British Society for Population Studies Conference

11-13 September 2023 at Keele University

This was our 50th anniversary BSPS Conference. We had over 290 participants, with 239 presentations in 59 sessions. There was a pleasingly large contingent of presenters from outside the UK, primarily from Europe, with those from further afield including delegates from Australia and India as well as the Americas and Japan. Professor Jesman Chintsanya of the University of Malawi attended via the BSPS 'Low- and Middle-Income Countries Initiative'. The Office for National Statistics curated three sessions on Developments in Official Statistics and, in addition to the familiar strands that run at all BSPS conferences, there were sessions on Critical demography and qualitative research; Demography of disaster; Spatial modelling; Telling the story in statistics; Unintended consequences of social policy, and Demographic consequences of climate change.

There were three well-attended plenary sessions. **Professor Tony Champion** of Newcastle University offered some personal reflections from a geographical perspective whilst the second plenary was a conversation between **Professor Ridhi Kashyap** (University of Oxford), **Dr Bernice Kuang** (University of Southampton) and **Dr Louisa Blackwell** (ONS) on New and future developments in British population studies. For the last few years, BSPS has offered a plenary spot at the annual conference to the winner of the BSPS early career award, for which entries are solicited among the membership. This scheme is aimed at highlighting the achievements of early career researchers in population studies, who have the potential to make a significant contribution to population studies. This year's winner was **Dr Laura Sochas** (University

of Edinburgh) who gave an excellent talk on 'Quantitative approaches for critical & feminist population studies: Structure & heterogeneity'. Additionally, there was a postgraduate and early career breakfast event, where PhD and ECR attendees had the opportunity to pick up tips on science communication. A lively poster session in tandem with a reception on the first evening saw a pleasing amount of interaction between presenters and attendees. There were joint winners of the poster competition: Hill Kulu, Sarah Christison, Chia Liu and Júlia Mikolai on 'The war, refugees, and the future of Ukraine's population' and Oki Krisnadevi and Andrew Amos Channon on 'Inequities in access to healthcare for people with disabilities in Indonesia'.

***Plenary reports*: Plenary 1:** 'Celebrating the BSPS's first 50 years and anticipating the next: Some personal reflections from a geographical perspective'. Newcastle University Emeritus professor, **Tony Champion** delivered a plenary that reflected on how the discipline of population studies in the UK and further afield has developed and what might come in the next 50 years. Tony shared his personal journey within the field and at BSPS noting that he had been attending since 1982 in Durham and that 1973 represented the year he moved to Newcastle for a one-year position, candidly highlighting he was still there now. Tony set the context of some of the seminal texts in the field including his own edited volume with Professor Jane Falkingham, *Population Change in the United Kingdom* and two academic journals, *Population, Space and Place* and *Population Studies*. He also set of the scene of 1973 and the many changes in UK population and demography that were ongoing; life expectancies were continuing to increase, and fertility had been steadily falling for the past decade. There was also spatial change in the distribution of the population with North/South Drift and movement to urban locations. Lastly, migration was an ongoing political discussion high on the policy agenda. Remarkably, all the issues and phenomena mentioned around the birth of 1973 are still broadly prevalent in UK demography half a century later. Tony talked about the current problems that researchers are investigating in 2023, the

return of Malthusian lead debates on the impact of climate change on demography, and the social changes that have risen through the second demographic transition for example fertility shifts and changes in gender norms and the integration and adaptation (or lack thereof) of immigrants including persistent segregation.

The keynote went on to mention how through the 50 years of BSPS, researchers have tapped into new approaches, such as life course approach and increasing focus on intergenerational mechanisms. The development of tools such as GIS has also changed the way population geography can be presented and studied. Tony finished this section by looking at the next 50 years, starting with how the world will be described in 2073, could it be post-global or post-capitalist?

Professor Champion focused on three areas of interest to him, beginning with global population and its distribution. The population across the world has doubled since 1973, it continues to rise yet is projected to flatline towards the end of this century. There was discussion of how the anticipated growth will be heterogenous across areas. The population in Africa is set to boom whereas China and much of Europe will see declines in population. He also noted that the distribution will see rise to what some call the third demographic transition which is an age of widespread migration both international and internal, perhaps because of climate change. The second focus was on urbanisation and counter urbanisation, something which he has researched extensively. There was discussion over the difficulty in measuring such a phenomenon, and how the rates of urbanisation continue to change. He showed figures highlighting internal migration of students to study, but that the onward migration after studying was limited to very few urban regions.

The final focus was on internal migration, Professor Champion concluded the plenary with talking of the power of and usefulness of the census. Much of the 2021 census of England and

Wales is now available for use. He noted that there were challenges associated with Covid, students for example were generally in parental homes due to government advice which has altered age distributions. However, due to lockdowns and fewer distractions coverage of the census is better than it ever has been. Northern Ireland and Scotland data will soon be available too allowing for a full picture of the UK to be analysed. The census data will also lead to updates to longitudinal studies and there are still more outputs to come from the relevant offices. The talk was rounded off with questions and comments from the audience. Overall, it was a pleasure to listen to such an inspiring talk of the journey of our discipline over the last 50 years and what lies ahead.

Plenary 2: 'In conversation: New and future developments in British population studies' with **Mark Fransham** (chair) and panellists: **Professor Ridhi Kashyap** (University of Oxford), **Dr Bernice Kuang** (University of Southampton) and **Dr Louisa Blackwell** (ONS). The conversation began with summaries from each of the panellists about some of the key development in population studies and some of the existing challenges. Bernice spoke about improvements to methods on fertility forecasting and in particular the contribution that birth order, for example, has made to our understandings of fertility. We have found that first birth time makes a big difference and that events are interrelated and work sequentially. This all has significant policy implications. For example, supporting first time, young parents is very different to supporting those who already have children. Some of the existing challenges relate to data as people sometimes don't recall birth order well or make assumptions. Something that needs further exploration is fertility intentions. For example, in younger generations 20% of young people say they never want to have children whereas in the past it was 5%. This is a significant difference and although it could be down to a social desirability response, we need to study at how this will manifest.

Ridhi then spoke about how nowcasts differ from forecasts; these look to predict the present and overcome the traditional lag in the production of data and statistics by leveraging new kinds of signals. There are a range of ways that this is being used in econometrics, machine learning, social media and web-based data. However, although these approaches come with promise, they are also accompanied by risks. Ridhi gave the example of Google search queries which were used to track the spread of flu and were initially shown to beat official statistics by up to 2 weeks. However, it began to breakdown as it started to overpredict flu and was discontinued. This highlighted complex relationship between the true and digital worlds, and the confounding effects of algorithms. As this area of work matures, there is a move to integrate different sources of data into existing traditional data sources in order to train the predictor to something trusted and established, coming back to things like surveys or other data sources. At its core, it's integration of the old and the new and leveraging the strengths and weaknesses of different data sources, and leveraging that complementarity.

Louisa spoke about the use of dynamic data models, what we learnt from the pandemic and how to use those lessons going forward. A key issue was the need for more accurate estimates of populations at risk. The existing systems pre-pandemic didn't have the flexibility to be able to monitor the reality of the situation. For example, of the 331 local authorities it wasn’t possible to see changes in mortality by age within a local authority which is what was needed. To leverage the best possible value from admin data, we developed a dynamic population model to produce more timely population estimates. This created a real time data dashboard taking admin data and working with aggregates. This will become the national statistic next year so in many ways this time has revolutionised population statistics. Necessity is the mother of invention and this was definitely the case for the ONS during the pandemic. The panellists then spoke about the issue

of trust in science during the pandemic. Ridhi spoke about how the pandemic made demographic concepts like excess mortality, concern about denominators, age as a variable more accessible to the wider population. It spoke to the public consciences and grew an appetite for demographic knowledge.

Bernice spoke about how it was surprising that fertility recovered so quickly after the pandemic though experiences were heterogeneous. For example, for those in secure employment and finances, fertility may have increased. There was also discussion about online vs in-person surveys, interviewer retention and the importance of traditional surveys.

Louisa spoke about different innovations happening within government data, particularly around new estimates of international migration, use of linked admin data and dynamic, localised population estimates. Data science – 'what demography was before it was cool' also came up. This included consideration of using multiple data sources and interdisciplinary understandings as well as issues around data ethics of data collection and use of linked data. Demographers should be very involved in these discussions; 'we need to acknowledge the seedy parts of our history'. During the Q&A later, there were also some questions about the ethical issues of using admin linked data obtained for other purposes. The panel acknowledged this was difficult and that we need to operate within ethical boundaries. A separate question was asked about whether the panellists considered themselves data scientists.

Finally, the panel considered how international collaboration has changed in recent years: being forced to move online has made collaboration easier, better and more inclusive in some ways. We see a lot more interface across different communities now, and more of this is needed. The panel was also asked how we could track algorithmic change with private companies hiding behind intellectual property. Ridhi acknowledged that this was a big but unresolved issue; companies put out what they want and they

don't disclose how they are generating the data which is undesirable from a research perspective and we need to work together to find ways to build partnerships with different stakeholders; to share and access data so they are meaningful (giving examples of recent initiatives).

Dr Laura Sochas (University of Edinburgh) gave an insightful early career plenary talk entitled 'Quantitative Approaches for Critical and Feminist Population Studies: Structure and Heterogeneity', based largely on her doctoral work, to highlight the importance of critical and feminist perspectives in demographic research. Despite a long, but minority, tradition of critical population studies, these approaches have often been overlooked by quantitative demographers. In her talk, Dr Sochas argued that population studies should adopt a more critical stance for several pressing reasons. One of the central arguments was the need to shift attention from the individual to broader systemic issues. It was emphasised how neglecting power dynamics, institutions, and underlying structural processes places an undue burden on individuals to bring about change. Instead, the focus should be on addressing flawed systems of privilege and oppression. Dr Sochas warned of the dangers of using social categories and average effects, a common practice in demography, as they fail to capture the experiences of marginalised and less privileged groups. Referring specifically to issues of discriminatory accuracy, she stressed how talking about mean differences between groups without assessing differences in distributions can obfuscate reality. Dr Sochas went on to discuss the need to acknowledge and examine the constructed nature of social categories and attributions of categorical membership, which can essentialise complexity and lead to a loss of nuance. She also observed that the absence of critical theory in the formulation of research questions and the operationalisation of variables introduces further biases in the study of the social world.

To address these challenges and promote critical perspectives in quantitative demography, Dr Sochas drew on her own work to present a comprehensive agenda. First and foremost, she proposed

the explicit inclusion of social structure in data analysis and modelling. A practical application would be the introduction of random effects into statistical models, allowing researchers to study individuals within social structures and quantify the impact of these structures. Further, Dr Sochas spoke of the importance of advancing the modelling of distributions and heterogeneity. Methods such as decomposition were highlighted as valuable tools in this endeavour. Finally, she encouraged researchers to incorporate critical theories, such as reproductive justice, from the earliest stages of research, such as the development of research questions. As a powerful guiding analytical framework, critical theories promise a more nuanced and inclusive examination of demographic phenomena.

Dr Sochas concluded her plenary presentation by addressing the importance of reflexivity in research and by encouraging researchers to use their findings for political and emancipatory purposes. Her presentation served as a compelling call to action for demographers to embrace critical and feminist perspectives in their research: the audience was left to reflect on our role as 'researcher-activists' and the profound impact that our work can have on both the advancement of the social sciences and society at large.

We are grateful to Adelphi Genetics Forum for their support.

Micol Matilde Morellini
University of Oxford
Ilona Pinter
London School of Economics
Joseph Harrison
University of St Andrews

Conference 2024 - University of Bath from **9-11 September**

ADELPHI GENETICS FORUM

Fifth Teachers' Conference

Free conference for A-level science teachers in Manchester

On **Friday 28 June, 2024** the Adelphi Genetics Forum is holding a conference *Recent Advances in Genetics* for A-level teachers. This is being held at the Nowgen Centre in Grafton Street Manchester and is a free ticketed event with coffee/tea/lunch also being provided free. Topics included in the programme:

- Studying historical movements of populations using genetic analyses which reveal admixture between groups.
- Ethical issues of genomics in healthcare
- The principles of DNA sequencing and new DNA sequencing techniques.
- The potential applications of pharmacogenetics in the health service.
- Genetic testing for cancers.
- Genetics and forensics.

My Life in Genetics

An Interview with Dr Helen Middleton-Price
Librarian of the Adelphi Genetics Forum

Tell us a little about your early years and what first drew you into genetics

I originally took a curious mixture of subjects at A level and went on to take a BA in Psychology at Durham University. There I was frustrated at not having the background to enable me to understand the nature of the biochemical and physiological mechanisms underlying the phenomena we were studying: I didn't even know what a charged ion was, so how could I understand how a nerve impulse was generated? So, I elected to go back to 'school', and took further A levels in Physics and Chemistry, followed by a BSc in Biochemistry.

In 1984, I had just come back from a year's postgraduate research working on neurochemistry projects at the Karl Marx University in Leipzig, East Germany; as I read about the latest developments and looked around for opportunities, it seemed that genetics was the discipline where it was all happening. I was lucky enough to get a research assistantship at The Institute of Child Health (ICH)

in Marcus Pembrey's department and worked there on my PhD under the supervision of Sue Malcolm, on gene mapping studies in Charcot Marie Tooth disease.

What has been the main focus of your career?
To be honest, that isn't an easy question to answer! I did my PhD research during the great 'gene hunting' years; it was such a thrilling time to be working in the field of medical genetics. I shall never forget the excitement in 1985 when Lou Kunkel's paper on the discovery of genetic markers deleted in boys with Duchenne Muscular Dystrophy was published. Gradually at first, later in an explosion, other genes were found, and their mechanisms of action revealed: it was especially fascinating to see the genetic mechanisms explained in conditions with unusual inheritance patterns. For example, fragile X syndrome (an X-linked condition which caused intellectual impairment, yet could be transmitted by males with *normal* intelligence – the so-called 'premutation' carriers), myotonic dystrophy and Huntington disease (which both showed increasing severity – anticipation – as the gene was passed down the generations) and imprinting disorders such as Angelman syndrome and Prader Willi syndrome, where the condition was related to whether the genetic change was inherited from the mother or the father. So, at that enormously productive time in the field, I was pleased to be offered a position in the clinical genetics department at ICH/Great Ormond Street Hospital (GOSH). Although the molecular diagnosis of the condition in a family did not necessarily help the *treatment* of the patient at that time, it was invaluable to families as it would arm them with the evidence they needed to make informed life decisions. It was a privilege to be involved in the generation of data that we knew would serve patients and help their future planning.

Later, at the Science Museum and then in Manchester at the Department of Health-funded North West Genetics Knowledge Park, I became more interested in public engagement with genetics: not only helping to provide people with the tools they would need in a world of genetic information overload but also properly involving patients and members of the public with research to help ensure that we kept focused on the issues that mattered to them.

Tell us a little about your time in the US working with a charity helping to exonerate prisoners on death row

I worked for Reprieve, an organisation that works for all prisoners under threat of the Death Penalty, whether they are guilty or innocent. However, because of my background I was able to take particular interest in The Innocence Project, which works to exonerate prisoners in cases of rape and murder. Because of the rapid progress in DNA analysis, it is now possible to test archival samples that were previously regarded as too small or too degraded to subject to analysis. I had the privilege of meeting several people who had been exonerated, most notably John Thompson, who was on Death Row for 18 years, with 7 separate execution dates, before he was shown to be innocent. In 2009, I was delighted to be able to invite John to speak at The University of Manchester. John has since died, prematurely, possibly because of the many years of hardship and the extraordinary stress of his life in the US criminal justice system.

Who has been the greatest influence on your work?

Part of my PhD was spent at The Galton Laboratory under the supervision of Sue Povey, being taught by Lynne West to create somatic cell hybrids. This was a fantastic training opportunity and gave me exposure to the scientific rigor of the Galton Lab: I'd say they didn't suffer fools gladly, but they were hugely generous to me, and, more generally, to young researchers keen to learn and engage.

What do you consider to be the greatest challenges for Genetics in the coming years?

One of these must be the future potential generation of the massive amounts of data about our genomes, and the scientific, practical, and ethical implications all this entails; I would like to see the Adelphi Genetics Forum taking a cross-disciplinary approach to some of the big issues.

What roles do you think the Adelphi Genetics Forum should be playing?

In the UK, we have learned societies concerned with genetics science (Genetics Society) and the medical application of genetics (British Society of Genetic Medicine), so there is little point in us

simply duplicating what these organisations already do extremely well. The Adelphi Genetics Forum has a great opportunity to add value by bringing together not only the best science and medical research in genetics but also inviting other disciplines, examining, in particular, the sociological and ethical dimensions. I would like to see this cross-disciplinarity reflected in *all* our activities, including our grant awards, the annual conference and our schools' programmes.

Finally, tell us something about yourself that isn't widely known

I was in East Germany on 9 November 1989 when the Berlin Wall fell. I had been visiting my former colleagues and had already been on two of the Monday evening Leipzig demonstrations. It was a completely unexpected culmination of the previous couple of months: the TV (always tuned in to West German channels) was on in my friend's flat, and she just kept repeating 'this is unbelievable, unbelievable', as we watched the Berlin Wall being breached. A couple of days later I drove back over the – now open – border at Eisenach to West Germany, joining a festive queue of Trabants and Ladas, and remember seeing banners on the motorway, saying 'Bitte komm zurück' ('Please come back').

Previous contributors to the *My Life in Genetics* series:

Published in the ***Adelphi Review:***

Professor Nick Mascie-Taylor	**Issue 3**
Mr Robert Johnston	**Issue 2**
Dr Jess Buxton	**Issue 1**

Published in the ***Galton Review*:**

Professor Nicholas Wood	**Issue 15**
Professor Dallas Swallow	**Issue 14**
Professor David Galton	**Issue 13**
Professor Andrew Read	**Issue 12**
Professor Veronica van Heyningen	**Issue 11**
Professor Dian Donnai	**Issue 10**
Professor Philippa Talmud	**Issue 9**

BOOK REVIEW
Life's Edge – The Search for What it Means to be Alive - Carl Zimmer, Picador 2021

Carl Zimmer teaches science writing at Yale university and is a prolific author of science-for-the layman books. I have written before (*Galton Review* Issue 12, Spring 2020) how Zimmer has a wonderful store of anecdotes that make his books entertaining reading and would make him a wonderful pub companion. The very start of this book gives a good illustration. Have you heard of radiobes? Nor me. As Zimmer recounts, they were supposed primitive lifeforms generated in 1904 in the Cavendish Laboratory, Cambridge when John Butler Burke put pinches of radium into a sterile broth. Burke enjoyed brief fame until others tried and failed to replicate his result. This anecdote introduces his subject – what it means to be alive.

I have to confess I found the book rather hard going. Not superficially – the anecdotes keep flowing, illuminating some half-forgotten bits of science history, or unusual research activities by present-day scientists. As a novel, it is easy and entertaining reading. But I kept wondering where it was going, what was the purpose of all the anecdotes. The first section is about the life and death of whole organisms, from tardigrades to humans. There is a nice discussion of the difficulties of deciding when a brain-damaged person can be declared legally dead. But after this start, the rest of the book focuses on the question of how to recognise or define life itself, and whether a simple system like a virus can be considered alive. Surely this is a completely different subject? After all, we all agree (don't we?) that the cells of a brain-dead person on life support are alive. And he has good fun describing the knots American anti-abortion enthusiasts tie themselves into when they try to endow a fertilised egg with full human rights.

So this initial section is followed by a sort of Biology 101. A slew of chapters consider very different organisms – snakes digesting a meal, hibernating bats, foraging slime moulds, trees shedding pollen and bacteria under selection – to illustrate some general activities of living organisms. The anecdotes were interesting in themselves but to be honest, I didn't really feel they added up to a deep insight into the essential nature of life. After that, six chapters provide some history of speculations about this essential nature of life, and their gradual evolution through the idea of 'protoplasm' into present-day molecular biology. Then we progress to viruses and other half-living systems before moving on to ideas and experiments about the origin of life on earth and the search for life on other planets. We end up with an account of some tantalising experiments that might, or might not, produce some new leads into the question of how life on earth might have started.

Thus, although the book starts off with interesting discussion of the boundaries of human life, the body of the book is about the quite different question of how one might define 'life' and how it might be created. To me, the quest to produce a watertight definition of 'life' is misguided – an argument about a word, not biology. I don't think a molecular biologist would feel there is some central mystery about how cells or viruses function; the research is about how the individual parts work together to form a functioning organism. Whether a certain system might be called 'alive' or not is for me a bit of a non-question.

Maybe I am missing the point. Perhaps my atheistic and analytical mindset prevents me seeing a larger picture. Maybe people with religious inclinations would see it all hang together in a way I can't. Well, you must form your own opinion on that – but whatever you decide, you cannot fail to be impressed by Zimmer's journalistic skills and immense store of quirky anecdotes. You just may wonder whether it was all about more than a word.

Andrew P Read

ADELPHI
GENETICS FORUM

Conference 2024

The Royal Society
16 October, 2024

Progress and challenges of implementing genomics into practice and society—the first 20 years

The Adelphi Genetics Forum Conference 2024 will mark 20 years since the publication of the completed Human Genome Project in October 2004. As usual, the conference will take place at The Royal Society in London on 16 October 2024. The provisional title is *Progress and challenges of implementing genomics into practice and society – the first 20 years*. The conference aims to reflect critically on the developments in genomic medicine since 2004 and will draw on expertise from a range of disciplines. The Adelphi Forum Lecture will be given by Professor Steve Sturdy, Professor of the Sociology of Medical Knowledge at The University of Edinburgh. He is a Wellcome Trust Senior Investigator for a major project 'Making Genomic Medicine', which aimed to locate 21st century developments in genomics in their historical context.