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Galton Institute

Exploring Human Heredity

The Galton Review

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EDITORIAL

2018 was a busy year for the Galton Institute but 2019 promises even more. In June we shall stage our third Biennial Teachers' Conference in Manchester, covering a range of topics which should be invaluable to those teaching Biology in secondary schools. In October, our Annual Conference, organised by **Professors David Coleman, Dallas Swallow and Caroline Relton**, concerns the subject of *New Light on Old Britons* and promises to be another excellent event. Details of both conferences can be found under 'Future Events' on our website.

Also on our website are podcasts by all the speakers at the 2018 Annual Conference on *Genome Editing*. A full-house at the Royal Society in October witnessed some outstanding speakers including the Galton Lecturer, **Professor Robin Lovell-Badge**. A full report of all the talks can be found in this issue.

We also have a detailed report of the Fisher Memorial Trust meeting that took place in Edinburgh. This explored the considerable legacy of the work of RA Fisher. The event was well attended and was co-sponsored by the Galton Institute.

I'm pleased to report there are also two book reviews in this issue. **Professor Andrew Read** reviews **David Reich's 'Who we are and how we got here'** while sixth-former **Maddie Bristow** gives us her thoughts on **'Women in Science: 50 Fearless Pioneers Who Changed the World',** written and illustrated by **Rachel Ignotofsky.** I'm most grateful to both for their valuable contributions.

I also recommend the latest booklet in the series 'Genetics in Medicine'. This one concerns 'Epigenetics and Gene Regulation' and, as previously, was written by **Helen Middleton-Price, Dian Donnai and Andrew Read**. It can be viewed on our website or, if you prefer a hard copy, please contact the General Secretary.

Robert Johnston

The Galton Institute Annual Conference
Genome Editing
31 October 2018 at the Royal Society

This year's conference was one of the best attended in recent years with almost 300 delegates present to listen to a most impressive array of experts considering one of the fastest moving fields of science. The full programme is available on our website. It was organised by **Professor Anne Ferguson-Smith, FRS** and **Drs Elena Bochukova** and **Paul Hurd**. The President, **Professor Veronica van Heyningen, FRS** opened proceedings with a brief account of the aims and activities of the Galton Institute, details of which can be found at www.galtoninstitute.org.uk.

The first session, chaired by the President, began with an introduction to **'The hows and whys of genome editing'** by **Dr Kathy Niakan** (The Francis Crick Institute). She presented an overview of genome editing, and how it is enabling a broad range of potential applications in basic biology, biotechnology and medicine. She explained that all genome editing techniques first use a nuclease enzyme to cut DNA at a specific location. These double-stranded DNA breaks are then repaired by the cell using one of two main repair pathways, non-homologous end joining (NHEJ) or homology-directed repair (HDR). Depending on the approach taken, genome editing can result in the removal or insertion of a short section of DNA (NHEJ), or the introduction of a precise genetic change (HDR).

Earlier methods used zinc finger nucleases (ZFN) or transcription activator-like effector nucleases (TALENs) to target specific genes. But the more recent CRISPR (Clustered Regularly-

Interspaced Short Palindromic Repeats)/Cas9 method is 'transformative' said Dr Niakan, as it is vastly more efficient than its predecessors. The CRISPR/Cas9 system is based on a naturally occurring mechanism used by bacteria as a defence against invading viruses. It comprises a nuclease (Cas9) that is precisely directed to a target location in the genome by a guide RNA.

Dr Niakan also spoke about recent developments in the field, such as ongoing efforts to make CRISPR/Casp9 genome editing more specific and precise. Other variations of the technique involve using a 'dead' Cas9 to alter gene activity by making epigenetic rather than genetic changes.

Dr Kathy Niakan

Dr Niakan finished her introduction by highlighting some of the many applications for genome editing. These include the possibility of using 'gene drives' to tackle insect-borne diseases or invasive species that cause agricultural damage. Its potential to develop novel disease treatments is already evident, following last year's news that CAR T cells have been edited using TALENS and successfully used to treat two infants with acute lymphocytic leukaemia.

Dr Niakan then presented her own group's research on **'Exploring early human development using CRISPR-Cas9'.** She explained that there are significant differences from the mouse in the development of the early human embryo, making it important to study human embryogenesis. Her lab's work involves using CRISPR-Cas9 genome modification to mutagenize key genes in early human embryonic cells. She had been able, in early 2016, to get approval from the Human Fertilisation and Embryology Authority (HFEA) to use spare embryos to provide better

understanding of the earliest stages of human development using this new technology. Using embryonic stem cells which are pluripotent, the Niakan lab is also attempting to map the complex hierarchy of different genes that control cell activity in these early stages.

The cellular structure of the trophoblast differs in humans and mice, implantation is later in humans and the timing of the expression of transcription factors (TF), OCT4 and KLF4 is also correspondingly later in humans.

The approach taken revolves around knock-out of candidate TFs using microinjected Cas9 ribonucleoprotein complex. OCT4 appears to be critical for maintaining pluripotency and it was found that knock-out of OCT4 in humans down-regulates expression of key genes such as CDX2, which is expressed in the trophectoderm that gives rise to the placenta, and NANOG, regulator of the pluripotent inner cell mass. Examination of the break sites showed that only the target sites were highly mutagenized. There was no effect on the aneuploidy rate. In these experiments not all cells are homozygous knockouts. Sequencing across SNPs suggested patches of loss of heterozygosity in some cells. Overall the data show substantial differences between the effects of OCT4 in humans and in mice.


Professor Austin Burt

The second session, chaired by **Dr Paul Hurd**, began with **Professor Austin Burt** (Imperial College, London) discussing **'Manipulating mosquitoes for malaria control'**. He described how malaria places a huge burden on humanity with over 100,000 deaths every year. Current interventions are not effective enough, largely due to the evolution of resistance to anti-

Plasmodium drugs and insecticides. Modern gene editing techniques may well hold the answer. The most promising approach seems to be the setting up of a ‘Gene Drive’. This causes biased inheritance in which offspring will almost always inherit altered genes and therefore causing a dramatic increase in population gene frequency without any form of selection.

Much work has been carried out in the lab with conspicuous success. One technique involves a synthetic, nuclease-based driving Y chromosome that produces a male-biased sex ratio. Another method is ‘Gene Knockout by Homing’. This uses CRISPR nucleases to destroy specific genes rendering females sterile and due to ‘homing’, this rapidly spreads among the population.

Of course success in the lab does not guarantee success in the field and there are many challenges to overcome. These are technical, ecological and regulatory. The last of these may be the most challenging as mosquito populations don’t recognise national boundaries and working with so many different authorities will be a huge challenge. The goal is malaria suppression, not mosquito extinction. This is a ‘young’ science and there is still a long way to go.


Professor Daniel Voytas

The next speaker was **Professor Daniel Voytas** (University of Minnesota) who spoke on **‘Developing crops for sustainable agriculture and food security’.** He discussed his group’s work on the use of genome editing in agriculture. This includes the production of a genome-edited soybean plant to improve the nutritional profile of the oil produced from it. The new soybean oil contains around 80% oleic acid, a much higher pro-

portion than standard soybean oil, and additionally has no trans fats. This was achieved by introducing genetic changes that increase the conversion of polyunsaturated to monounsaturated fats in the plants.

Professor Voytas also discussed the regulation of genome-edited crops in America and Europe. The US Food and Drug Administration does not regulate plants with inactivated genes, single base changes or a version of a gene that already exists in a 'sexually compatible organism'. In the EU however, genome-edited plants are regarded as genetically modified organisms (GMOs), and so are subject to strict regulations.

This difference in regulatory approaches has affected development of a new strain of cassava plant. Grown widely in Sub-Saharan Africa, between 20-80% of the yield from this crop is lost due to weeds. Professor Voytas' team used genome editing to introduce gene mutations found in herbicide-resistant weeds into the cassava. But the cassava cannot be sold in Europe, an important export market, so the project is on hold. In addition to strict GMO regulations, there are also concerns about producing new crops that rely on chemical-dependent technology.

In the last part of his talk, Professor Voytas spoke about advances in 'molecular domestication', or using genome editing to introduce multiple desired traits into wild plants for cultivation as crops. This includes new ways of introducing genetic changes via new meristems, bypassing the need for tissue culture and thus speeding up the production of genome-edited plants.

The first session of the afternoon was chaired by **Dr Elena Bochukova** who introduced **Professor Richard Ashcroft** (Queen Mary University of London). His topic was **'Societal considerations on genome editing'**. He began by considering some of the

potential uses of the new technology: diagnostics, guiding of treatment decisions, somatic gene therapy, germline gene therapy, screening of potential parents. Likely limitations of genome editing include cost, efficiency and ethical constraints. He believed that many of the issues of concern regarding this latest technology are the same as those for classical 'gene therapy'. However it would seem that genome editing will prove to be cheaper and more accurate. The key area likely to be of interest to the 'general public' is human reproduction and those involved in this field will be obliged to show that it works, is safe, affordable, preferable to alternatives and is morally acceptable.

Professor Richard Ashcroft

The guiding principles of such work are that the needs and interests of parents are addressed and the welfare of the 'future person' is paramount in terms of well-being and safety. Clearly, there must also be public debate of these issues regarding population diversity, attitudes towards disabled members of society and perception of what is 'normal' reproductive choice. There will also need to be changes to UK laws and regulations although many such issues have already been considered by the Human Fertilisation and Embryology Authority when considering gene therapy.

The President then introduced **Professor Robin Lovell-Badge, FRS** (The Francis Crick Institute) who gave his Galton Lecture on **'Genome Editing to Study Regulation and Regulation of Genome Editing'.** Sex determination, an enduring interest in the speaker's illustrious career, is a process that can now be studied in novel ways using genome editing.

With current tabloid debates on gender identity, gender dysphoria, rights of transgender people, techniques for gender transformation etc., it was very interesting to hear from Professor Lovell-Badge how biology actually determines the sex of an individual. It depends, of course on which animal you are considering. For example, in crocodiles sex depends on the temperature at which the eggs are incubated. For mammals (man included) it appears surprisingly complicated to obtain a simple binary outcome – whether to become male or female.

There is a complex network of genes and transcription factors that regulate a poised balance of whether to form a male or female organism. The SRY protein, which is a transcription factor encoded by the SRY gene is responsible for the initiation of male sex determination in humans. SRY is an intron-less sex-determining gene on the Y chromosome of placental mammals and marsupials. Mutations in this gene can lead to a range of disorders of sex development with varying effects on an individual's phenotype, but a null mutation invariably leads to complete XY female sex reversal.

SRY is a member of the SOX (SRY-like box) gene family of DNA-binding proteins. When complexed with the steroidogenic factor 1 (SF1) protein it becomes a transcription factor involved in sex determination by controlling the activity of the related SOX9 gene in the early gonad.

Professor Robin Lovell-Badge

Expression of SOX9 leads to the differentiation of Sertoli cells from bipotential supporting cell precursors, which would otherwise give granulosa cells typical of ovaries in XX animals. The Sertoli

cells then instruct other cells to follow the male pathway, including germ cells, and to organise into testis cords which later develop into seminiferous tubules. If present, i.e. in an XY embryo, the SRY gene normally becomes active 6–8 weeks after fertilisation in humans. However, at least in mice, where it is possible to explore how it works in detail, it is active very transiently at the equivalent stage (about 11 days). Within just a few hours it boosts the expression of SOX9 sufficiently that the latter can then drive its own expression, acting together with SF1. This is a very time sensitive process; if there is any delay, “anti-testis” factors prevent SOX9 expression, resulting in ovary development.

Recent work has examined the very long and complex regulatory region adjacent to the SOX9 coding region, and defined a new “enhancer” sequence, which maps a long way upstream that turns out to be essential for SRY action. When this is deleted in mice, XY female development ensues. Mutations affecting the equivalent enhancer in humans are now implicated in disorders of sex development.

Unfortunately, **Professor Jennifer Doudna, FRS** was unable to attend this year’s conference and instead a video presentation she sent on **‘Genome editing: history and future’** was played.

The final talk of this very successful day was chaired by **Professor Anne Ferguson-Smith, FRS** and was given by **Professor Emma Morris** (Royal Free Hospital, London) on the topic of **‘Genome editing in the clinic: the Holy Grail’**. She first reviewed gene therapy methods that have been used to date, describing some of the hazards. Treatments include the replacement of non-functional genes or introductions that provide novel function. Viral vectors, which can be transient, long-lasting or permanent, have been used and can be transfected into somatic cells ex vivo or injected directly. For example, haematopoetic stem cell

Professor Emma Morris

transplantation is used for a variety of disorders including blood cancers and primary immunodeficiency and genetic modification of stem cells (mainly haematopoetic) using viral regulatory promotors driving transgene expression, is now being used. However the first gene therapy using such vectors transfected into haematopoetic cells for SCID (severe combined immune deficiency disease) resulted in development of T-cell leukaemia a few years later in 5/12 successfully treated SCID patients, apparently due to insertional mutagenesis. Nevertheless this vital experience led to important modifications, but the risk of potential hazards of this kind of therapy has to be balanced with the benefits.

Professor Morris then focussed her talk on research aimed at retargeting autologous T-cells to recognise tumour antigens, ie immunotherapy. There has been highly successful development of genome engineered T-cells made using recombinant retroviral vectors with chimaeric antigen receptors (CARs), directed to antigens specific to the particular cancer cells growing in the patient. Recent developments show that T-cells with their own T-cell receptor inactivated by editing, work better than those just transfected with CARs. While hundreds of clinical trials involving gene therapy are going on, genome editing itself, which involves specific editing of the patients own genome is still in its infancy, with just 6 active Phase 1 trials world-wide (including Hurler's disease, thalassaemia and haemophilia as well as the use of gene edited T-cells).

Dallas Swallow
Jess Buxton
David Galton
Robert Johnston

100 years of quantitative genetics theory and its applications: celebrating the centenary of Fisher 1918

October 2018, Royal College of Surgeons, Edinburgh

Ronald A. Fisher's 1918 paper, entitled "The correlation between relatives on the supposition of Mendelian inheritance" and published in the Transactions of the Royal Society of Edinburgh, set the foundations for the study of the genetics of quantitative traits. 100 years later, we celebrate Fisher's contribution and reflect on the advances made since this classical paper first emerged.

Prior to R.A. Fisher's famous contribution, the genetic basis of evolutionary change was vigorously disputed between biometricians and Mendelians. In support of Darwin's theory of evolution by natural selection, biometricians believed evolution to be a continuous process, having developed much of modern statistical methods such as regression and correlation to describe the inheritance of biometric (continuous or quantitative) traits. After the rediscovery of Mendel's work on inheritance, the Mendelians argued against these views by vehemently supporting discontinuous evolution via Mendelian (discontinuous) traits controlled by the segregation of major genetic factors. The first attempts to reconcile the two opposing schools of thought were made independently by George Udny Yule in 1902 and Wilhelm Weinberg in 1910, whose studies were largely overlooked by both biometricians and Mendelians, blinded by the ongoing conflict. It was only in 1918 that the first comprehensive synthesis of Mendelism and biometry was put forth by Fisher.

Fisher (1918) presented the mathematical relationships between the principles of biometric measures of *heredity* (correlations between relatives), Mendelian *inheritance* of genetic factors and Darwinian evolution. He believed biometric heredity to be a special case of Mendelian segregation of genetic factors, and there-

fore reformulated it in terms of the Mendelian principles of inheritance, such that variation in a single trait could result from the segregation of one or multiple Mendelian factors. We now refer to Mendelian factors as loci, and to traits as Mendelian if determined by a few loci with clear-cut segregation of alleles, or as quantitative if determined by so many loci that segregation at individual loci cannot be observed.

Traits can be determined by several components, including those with a genetic basis and those without (often described as environmental components). Among the genetic components is the *additive genetic* component which describes how the genotype of a parent affects the phenotype of its offspring. The magnitude of these components cannot be directly measured for a given individual. Instead, by comparing phenotypes among related individuals, the cause of phenotypic variation can be tracked. These statistical tools were introduced by biometricians to describe whether differences between individuals could be ascribed to differences between their parents. In his 1918 paper, Fisher coined the term *variance,* and extended these statistical tools to an *analysis of variance* framework to show that the (co)variance among traits can be decomposed into different components, such as between and within-family components (which include genetic and environmental components) and that these components could be quantified. Strikingly, the within-family variance estimates were largely consistent with those expected under a scenario with a large number of additive Mendelian factors, suggesting that traits are often determined by multiple loci.

The concepts introduced by Fisher (1918) opened the horizon to an explosion of studies in genetics and evolutionary biology that resulted in a large body of theoretical and empirical work. Among these studies are those concerned with fundamental aspects of evolution, such as the genetic architecture of traits and the effect of evolutionary forces on different components of the phenotype. More applied studies have been concerned with topics such as ani-

mal and plant breeding, and have contributed to much of the theory of quantitative genetics as well as to practical advances.

The meeting started with an introduction by the lead organiser, **Brian Charlesworth** (University of Edinburgh, UK), about RA Fisher and some of the key concepts introduced by his work that are still widely used to this day. This was followed by a series of talks representative of the diversity of topics that have developed from Fisher's classical 1918 paper. There were speakers from several countries, of which 7 were invited speakers: **Nick Barton** (Institute of Science and Technology, Austria), **Josephine Pemberton** (University of Edinburgh), **Sharon Browning** (University of Seattle), **Heather Cordell** (University of Newcastle), **Ed Buckler** (Cornell University), **Richard Mott** (University College London) and **Jarrod Hadfield** (University of Edinburgh). 4 were early career speakers: **Josselin Clo** (University of Montpellier), **Chandana Basu Mallick** (Roslin Institute), **Himani Sachdeva** (IST, Austria) and **Daniel Crouch** (University of Oxford). The meeting closed with a Fisher Memorial Lecture, introduced by the Chairman of the Fisher Memorial Trust, **Sir Walter Bodmer** (University of Oxford), and given by **Michael Goddard** (University of Melbourne). Additionally, there were 9 contributed posters: **Juliane Friedrich** (Roslin Institute), **Emanuele Giorgi** (Lancaster University), **Richard Oppong** (University of Edinburgh), **David Clark** (University of Edinburgh), **Jing Chen** (University of Birmingham), **Keira Johnston** (University of Glasgow), **Anna-Margarete Staehler** (University of St Andrews), **Sandy Ayoub** (University of London) and **Gabriela Gomes** (Liverpool School of Tropical Medicine).

Fisher (1918) realised that most traits are likely to be determined by many *independently inherited* loci with additive effects. Fisher arrived at this conclusion given the similarity between his estimates with those expected under the "infinitesimal model", which describes the extreme case where traits are determined by an indefinite number of loci, each contributing a small fraction of the pheno-

typic variance. Nick Barton presented an exhaustive analysis of the generality of the infinitesimal model in predicting the inheritance of quantitative traits. By formulating the infinitesimal model in terms of the distribution of phenotypes in a population, rather than the distribution of additive effects of the underlying loci, he showed that phenotypes *within* families are normally distributed without making assumptions about the distribution of phenotypes *across* the population. This work showed the infinitesimal model to preserve its generality in the presence of selection, drift, mutation, population structure and epistasis. Himani Sachdeva later spoke about the effects of selection and recombination on the introgression (exchange of genetic material between divergent gene pools) of blocks of linked loci, by assuming an infinitesimal model that considers *linkage*.

One of the main applications of the analysis of genetic variance into its different components introduced by Fisher (1918) is the estimation of additive genetic values and variance components given the genetic relatedness between individuals of a population. Estimating the relatedness between closely related individuals can be performed using pedigree information or from DNA sequence similarity. However, the task becomes more difficult among distantly related individuals: the effect of missing individuals in pedigrees becomes more significant as the distance between individuals increases and tests of sequence similarity among individuals become less powerful at detecting shared ancestry. Sharon Browning and Heather Cordell presented sophisticated computational methods for estimating the relatedness between individuals, using coalescent theory and genetic marker data to estimate the identity by descent (IBD) of genetic variants among individuals. From the notion that recombination breaks down linkage between loci and causes the decay of haplotypes (blocks of linked loci) over time, these methods use the frequency and length of shared haplotypes to inform about IBD. For example, long and common haplotypes are likely to be more identical

by descent than those that are short and rare.

In experimental populations, whether in farm or in laboratory settings, reasonably good information about the genetic relationships between individuals as well as the environment experienced by them, is attainable. The next step is then to use this information to predict breeding (additive genetic) values and components of phenotypic variance, which can then be used to predict the response to selection using genomic selection. Animal and plant breeders were the first to make use of such predictions for artificial selection of traits and genetic improvement. Michael Goddard is one of the world leaders in quantitative genetics applied to animal breeding. Over the years, his work has made great contributions to the genetic improvement of cattle by making use of theoretical genetic considerations for the development of cost-efficient breeding programs. Michael presented the Fisher Memorial Lecture, where he spoke about how the use of densely distributed single nucleotide polymorphism (SNP) data has revolutionised our understanding of the genetic architecture of traits, i.e. the number and effects of loci that determine traits. SNP data allow us not only to estimate the additive genetic variance of a quantitative trait but also to detect large effect loci. Consistent with Fisher's ideas, the immense SNP data that has been collected across numerous populations and species has shown most quantitative genetic variation to be caused by many polymorphisms with small effects. Mutations typically have weak or almost neutral effects on the phenotype, and those that have large effects are often deleterious and thus removed by selection. It is only in rare instances that these large effect mutations can be favoured by selection. Focusing on maize, one of the largest production crops worldwide, Ed Buckler spoke about how we can use machine learning tools and functional information to estimate breeding values more accurately and thus to predict the response to artificial selection over time.

The study of quantitative traits in wild populations is more compli-

cated. The environment in these populations is uncontrolled and the genetic relationships among individuals are hard to determine. Josephine Pemberton, one of the pioneers of quantitative genetics in the wild, spoke about the challenges involved in estimating variance components in such populations, and described advances in using these to predict the effects of selection. Using two wild animal populations from islands off the coast of Scotland, the Soay sheep on St Kilda and the red deer on the Isle of Rhum, a joint effort by a large team of researchers has assembled detailed pedigrees using micro-satellite-based parentage as well as genomic inference, and has collected a vast amount of genomic and phenotypic data. Focussing on *fitness* itself as a quantitative trait, the Pemberton group has made advances in understanding the causes of differences in fitness between individuals and genetic variation within populations, showing how conventional approaches to predicting the effects of selection can be misleading.

Traits that are subject to selection are to some degree causative of fitness, and often described in terms of indirect genetic effects (IGE) on fitness. Jarrod Hadfield spoke about how the kin selection models developed by William Hamilton in 1964 are in essence a special case of IGE models. These models describe a process by which an individual's fitness benefits from the fitness of its relatives. As such, a social interaction (e.g. altruism) that *directly* benefits a relative's fitness thus *indirectly* benefits its own. Indirect genetic effects can come at a cost and it is the balance between the costs and benefits that determines the degree to which an individual can benefit from the indirect genetic effects of a correlated trait (e.g. a social interaction). These models assume that social interactions are determined by single traits, but break down when they are determined by multiple traits. Using a framework developed by Lande (1979) for selection on multiple correlated traits, Jarrod showed how the evolution of social interactions can be modelled when they are determined by multiple quantitative traits. As Fisher proposed, most quantitative traits are determined by

many loci of small effect. However, different loci can have different magnitudes of effect and large effect loci can sometimes be detected. Chandana Basu Mallick and Daniel Crouch spoke about the detection of major effect loci affecting two human traits. Chandana presented her work on the genetic basis of hair shape, using the mouse as a model for quantitative trait locus validation. For over 100 years, the mouse has been a powerful model system for the study of human genetics, due to the high genomic similarities between the two species as well as the ease of genomic manipulation in mice. A locus with a major effect on hair shape is present in humans, associated with genetic variation within European and East Asian populations. Chandana described knock-out experiments in mice that confirm that this gene (*Prss53*) is involved in the control of hair-shape. Daniel presented his work on the genetic basis of human facial features, using a novel approach to Genome Wide Association Mapping. Using phenotypic data on several facial features, three loci with major effects were detected in the UK population.

Virtually any genetic or environmental variable can affect the expression of a quantitative trait. In most quantitative genetic studies, phenotypic variance is decomposed in an additive genetic component, other non-additive genetic components and an environmental component. Recent work by Richard Mott has shown that additive genetic variance in a trait can be caused by genetic variants other than SNPs. He showed how structural variants, including transposable element insertions, can be detected by treating read counts from short-read sequences as a quantitative trait. When applied to the model plant species *Arabidopsis thaliana*, structural variants were found to contribute significantly to heritable variation in quantitative traits.

The magnitude of additive genetic variance in a population is determined by the joint effect of the evolutionary forces of drift, selection, mutation and migration. Consequently, features of popula-

tions that affect these forces indirectly influence such variance. Josselin Clo spoke about his work on the effects of *self-fertilization*, which occurs when an individual mates with itself, on the magnitude of additive genetic variance. The study found selfing in plant populations to reduce the additive genetic variance and total genetic variance of quantitative traits and consequently to reduce the potential of populations to respond to selection.

The meeting was attended by approximately 200 people, including PhD students, early career researchers and senior researchers, many of whom are renowned scientists whose contributions have greatly marked the field of quantitative genetics. Filled with intense scientific discussions, the meeting radiated excitement and curiosity. In moments of reflection throughout the meeting it became clear to me, and perhaps to most attendees, how much we owe to Ronald A. Fisher's work.

The meeting was sponsored by the Fisher Memorial Trust, the Genetics Society, the **Galton Institute**, the London Mathematical Society and the Royal Statistical Society.

Jessica G King

BOOK REVIEW
David Reich: *Who we are and how we got here*
Oxford University Press pp 334.

Many years ago, my lab tried to extract DNA from a group of Egyptian mummies in the Manchester Museum. The museum wanted to know whether they were a family group. We thought we could answer that question by extracting DNA and typing it for the HLA tissue-type genes. We failed comprehensively. We weren't the only people, perhaps fired by *Jurassic Park*, to mount naïve efforts at isolating ancient DNA. It required years of painstaking

work by Svante Pääbo and his group in Leipzig to show how, with extreme precautions and dedicated ultra-clean facilities, it was possible to obtain minute quantities of genuinely ancient DNA from archaeological specimens.

Subsequent technical developments have made the whole process somewhat easier. David Reich has led the pack in generating the resulting flood of data on ancient genomes – now numbering at least 4000 and rapidly growing. Not only ancient humans, but ancient dogs, ancient crops and ancient pathogens are revealing their secrets (anyone for genuine Black Death DNA?). He collaborated with Pääbo in his ground-breaking work on the Neanderthal genome, and then set up a lab at Harvard to extract and sequence ancient DNA on an industrial scale. This book does exactly what its rather splendid title promises.

In the first of the three sections of his book, Reich covers Pääbo's work on our deep history, revealing the relationship of *Homo sapiens* to our Neanderthal and Denisovan cousins. It's a thrilling story – but Reich's main interest is in more recent history, using ancient DNA to unravel population origins and movements over the past 10,000 years. This is the topic of the main, second, section of the book. Archaeologists can identify cultural changes – the emergence of the Bell Beaker culture in the early Bronze age, for example – but they have no way of knowing whether this was a settled society adopting new ways, or a replacement by outside people bringing their own culture. The DNA studies tell an unambiguous story of extensive population movements, mixing and replacements. For example, the people who built Stonehenge were almost completely replaced by a different population within a few hundred years of completing the monument.

These studies are fascinating to anybody who is curious about history, but they also have political implications. In the final section of his book Reich addresses these and related matters head-on. Nationalists like to believe they represent a proud ancient

people, guardians of their ancestral homeland for untold millennia. DNA usually tells us otherwise. Pity the poor Nazis: their *deutsche Volk* arrived from central Asia relatively recently and mixed with all sorts of non-Aryans.

A further important implication is the way these studies touch on the sensitive topic of race. Ever since Lewontin showed that within-population genetic differences far outweighed between-population differences, surely something anybody who is not a hermit must have noticed. There has been a comforting assumption that between-population differences don't exist, or at least are negligible. People have been warned off studying group differences. Reich quotes the American political scientist Jacqueline Stevens demanding that such studies should be banned. But group differences do exist and Reich steers a careful course between Stevens' head-in-sand attitude and endorsing racism. He argues that "if as scientists we wilfully abstain from laying out a rational framework for discussing human differences, we will leave a vacuum that will be filled by pseudoscience, an outcome that is far worse than anything we could achieve by talking openly." Not every reader will want to take their speculations on this as far as Reich does, but this is an important topic and he discusses it lucidly and fearlessly.

In short, this is a wonderful book that deals authoritatively with matters that surely interest everybody, and does it in a way that can be understood by anybody who can follow our Galton booklets. Highly recommended.

Andrew P Read
Emeritus Professor of Human Genetics
University of Manchester

BOOK REVIEW

Women in Science: 50 Fearless Pioneers Who Changed the World

Written and illustrated by Rachel Ignotofsky

Hachette Children's Group **pp128** .

Shortlisted for the Royal Society's Young People's Book Prize 2018

The immediacy of new technology has changed the way we access information. Younger people are less likely to sit and watch a long documentary, as it's so much easier to watch a short, targeted YouTube video to gather the same - if not more - information. Author and illustrator Rachel Ignotofsky has successfully applied this approach to her book. It provides an overview of the advancements in STEM (science, technology, engineering and maths) made by women since the 19th Century, in a concise and visually appealing way. All 50 of the individual biographies have illustrations of characters, equipment, and doodles alongside extra facts. The text is also broken up with timelines, intricate diagrams, and hard-hitting stats about the underrepresentation of women in STEM throughout history. This makes the book accessible to a variety of ages and reading abilities.

At the end of the book, Ignotofsky states that her overarching goal is to inform the readers about the unmentioned innovators of our today. Moreover, she hopes to inspire the female scientists and engineers of future generations to pursue their passions and to utilise their inquisitive traits. However, I would recommend this book to all ages of both genders, in particular those interested in history, STEM, or even beautiful illustrations. Not only does it introduce you to (or remind you of) some great science facts, processes and theories; but it reveals the gripping, scarcely-told stories of women who worked in the shadows of their male counterparts.

The author's passion for STEM subjects and history is gloriously portrayed, leaving the reader with a sense of pride and inspiration, but also anger at the skewed representation of scientific advance-

ments. My A level Biology textbook lists the brilliance of Watson and Crick in their discovery of DNA structure, but it fails to mention that they looked at Rosalind Franklin's work and published her findings within their own. They later achieved the Nobel Prize, with Rosalind dying before the work was recognised as hers.

The quality of the text and illustrations is undeniable, but the book can be difficult to navigate. The names aren't in alphabetical or career-related order, so it may take a while to find who you are looking for. Regardless, I thoroughly enjoyed reading this book, since I had never previously heard of most of the women. It filled gaps in my knowledge that I never knew I had. Although, it also made me wish that my science and maths teachers were better artists! I highly recommend this book to all young aspiring scientists, technicians, engineers, and mathematicians.

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African Society of Human Genetics 10th Scientific Meeting

Held in conjunction with the H3Africa Consortium and the National Society of Human Genetics of Egypt, November 2017, Cairo. Conference theme: Human Genetics and Genomics in Africa - challenges for both rare and common genetic disorders.

The tenth meeting of the African Society of Human Genetics (AfSHG) took place in Cairo ten years to the month after its fifth scientific meeting which was also held in Cairo. The spotlight in 2017 was on genetic disorders, a relatively neglected area of human genetics on the African continent where many countries lack the infrastructure or trained personnel to deliver clinical genetics services. This is a challenge, but one the AfSHG is willingly taking on through its hallmark approach of shared experience, collaboration and friendship.

Over 450 delegates from 38 countries, 19 of which were African, participated in the conference. The increasing global interest in African Genetics research and its role in health research and services was reflected in the contributions from delegates from European and Asian countries as well as the USA. Over half (54%) of participants were female.

During the opening ceremony, the audience was addressed by **Professors Amal Mohamed** (Chair of the Local Organising Committee), **Mona Abdel Razek** (Head of the Human Genetics and Genome Research Division at the National Research Center, Cairo), **Samia Temtamy** (President of NSHG), **Michele Ramsay** (president of the AfSHG), **Ambroise Wonkam** (representing H3A) and **Mahmoud Sakr** (President of the National Research Centre, Cairo). Inspirational talks were delivered by internationally renowned researchers on a range of topics including medical genetics and diagnostics, democratizing data-driven medicine, African genetic diversity in the dawn of precision medicine, stem cell medicine and genetics, ethics and bio-banking in African settings as well as sessions on infection, cancer, genetic blood disorders and neurogenetics. The programme included oral presentations selected from submitted abstracts.

The development of early career researchers (ECRs) has been an integral part of the AfSHG mission since the Society's inception and the AfSHG ECR forum was held, as has become traditional, the day before the start of the main scientific meeting. This event provided PhD students and less experienced post-doctoral scientists with the opportunity to present their work to each other and to a group of more senior investigators who offered support and mentorship. Prizes were awarded for the best talks and posters. The ECRs then attended the main meeting where the programme included workshops specifically for them. Topics included next generation sequencing pipelines and data control, single variant and gene based analysis and gene co-expression network analysis and differential expression analysis. The Galton Institute's generous

support enabled the attendance of three African ECRs, selected for funding on the basis of the quality of their research abstract submissions.

Since the AfSHG was inaugurated in 2003, its scientific meetings have catalysed the formation of national Societies of Human Genetics in countries that have hosted the meetings (e.g. Senegal and Cameroon as well as Rwanda which will host the 11th AfSHG meeting in September 2018) as well as countries such as Mali and the Democratic Republic of Congo that are developing active genetics programmes in spite of challenging circumstances such as lack of infrastructure and trained health professionals. There are now seven national Societies with only the Southern African Society of Human Genetics existing before 2003. The AfSHG meeting in Cairo provided a forum where members of these Human Genetics Societies came together to report on their activities and to share progress, expertise and solutions thus providing support while addressing wide-ranging and complex challenges that African genetics researchers and clinicians face.

The aims of the AfSHG are to expand genetic and genomic research in Africa across the whole continent, to integrate its work with the work of other relevant societies, to increase collaboration both within the continent and externally, to increase awareness of human genetics and genomic research, to promote the development of effective public policy and to improve the translation of genetic knowledge into clinical practice throughout Africa. Given the logistical demands of working across the world's second largest continent and our limited Society resources, our scientific meetings are vital to enable us to meet these goals. We are extremely grateful for the on-going support of the **Galton Institute** through the award of a conference grant.

Melanie Newport
University of Sussex
On behalf of the African Society of Human Genetics

41st Research Students' Conference in Probability and Statistics 24-27 July 2018, Sheffield, UK

The RSC annual conference is held for PhD students researching any area of probability or statistics. This year's conference consisted of 90 talks by students across a huge array of topics such as Ecology, Statistical Biology, Stochastic Processes, Big Data and Bioinformatics. We had attendees from UK, France, Turkey, Germany, Pakistan and New Zealand.

Day one of the conference consisted of our four invited speakers: **Professor Ruth King** (Edinburgh), who discussed a Bayesian approach to population ecology, **Professor Peter Diggle** (Lancaster), who spoke about the modelling of spatial-temporal point processes, **Professor Richard Wilkinson** (Sheffield), gave an overview of uncertainty quantification and reliability, and **Dr Cécile Mailler** (Bath), gave us a tour through the history and applications of Póly Urn processes.

Days two and three were filled with our students' talks taking over three lecture halls in the University of Sheffield. We had a large variety of presentations from rare data modelling to modelling phenomena using differential equations.

The RSC provides a platform for students to present their work, get comfortable asking questions to speakers and network with their peers and future collaborators. With this in mind we put on a number of social activities for the attendees such as a wine reception, conference dinner, BBQ, climbing, trampolining and a cocktail masterclass!

Day three concluded with our wine reception which doubled as the poster session in which we had 50 research posters presented. The audience consisted of our students, the staff of the Prob-

ability and Statistics department of the University of Sheffield as well as our 2018 sponsors. Here students could have prolonged discussion about their work, which is often harder to do during a talk. It was here where we also handed out the prizes for the three best talks and best poster as voted for by the students.

In the past few years attendance at the RSC has dropped significantly from 111 in 2015 to 87 in 2016 and 68 in 2017. We therefore decided to increase our advertising campaign, open registration early and close later, reduce the registration fee as much as we could by searching for sponsors, as well as advertising attendance and childcare grants to attendees. We are happy to report that we had 134 attendees at this year's conference. As a product of the effort put in to increase students, we noticed that the percentage of females was 50%; given that the proportion of females in science is considerably lower than this we were very proud.

The 2018 RSC was a roaring success with fantastic feedback from the students. A key part of its success was down to the sponsors who made it all possible. We'd like to thank the **Galton Institute** for its support which allowed us to offer childcare grants to 3 students and attendance grants to a further 10 students who otherwise may not have been able to attend.

Mark Yarrow
University of Sheffield

2019 - DATES FOR YOUR DIARY

Galton Institute Teachers' Conference
26 June, 2019 in Manchester

Galton Institute Conference — *New Light on Old Britons*
30 October, 2019 at The Royal Society, London