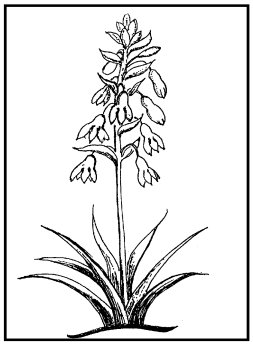
ISSN 1359-9321



Galtonia candicans

The Galton Institute

NEWSLETTER

Issue Number 81

Winter 2013 –2014

Contents

Investment in New Activities

The Council of the Institute has recently invested in two new ventures. The first of these is the latest in our series of occasional papers and is entitled '***Genetics in Medicine 1 : Conception and early life***', which appeared just before the annual conference held in November. Any member who would like to have a copy is asked to contact the General Secretary. We expect that a companion publication dealing with the same subject matter in relation to adult life will appear in the second half of 2014.

The second innovative action is to provide financial support of £500 each to travel bursaries organised and administered by the Genetics Society. These bursaries are to be given, on a competitive basis, to (up to three per year) outstanding students working for a PhD on a topic relevant to the mission of the Institute to allow them to attend appropriate conferences. Reports of their use of the bursaries will be placed in the Newsletter.

John A Beardmore

Membership and Fellowship

Initial election to membership of the Institute can be at Ordinary member or Fellow level. The Council endeavours at intervals to ensure that advancement to Fellowship is available to Ordinary members whose career development has been such as to qualify them for Fellowship. The requirement for this is possession of a PhD or an equivalent academic or professional qualification or academic or professional standing acquired through channels such as publications or high level responsibilities in appropriate organisations. Ordinary members who consider that they meet the requirement and are interested in advancement are invited to write to the General Secretary. There are no subscription implications attached to this procedure.

The Galton Institute

Conference 2014

To be held at The Royal Society on Tuesday, 4 November, 2014

GENETICS IN MEDICINE

Galton lecture to be delivered by Professor Andrew Wilkie, FRS

Admission is free but strictly by ticket
available from The Galton Institute General Secretary

Published by:

The Galton Institute
19 Northfields Prospect
Northfields
LONDON SW18 1PE

Telephone: 020-8874 7257
www.galtoninstitute.org.uk

General Secretary:
Mrs Betty Nixon

Newsletter Editor:
Dr Geoffrey Vevers

Galton Institute Conference 2013

Insect and zoonose genomes and human health

Report by

Dr Geoffrey Vevers (morning report) and Professor David Galton (afternoon report)

The annual conference of the Galton Institute held at The Royal Society on Wednesday 6th November 2013.

MORNING SESSION:

Dr Allan Spradling, Carnegie Institute of Washington

Using Drosophila to characterise the physiology and stem cell biology of the insect

Drosophila has a rapid generation turnover and has been widely used in research in this case to examine the way the gut is maintained and the results may be extrapolated to other species.

Dr Spradling explained that the midgut has about 18000 enterocytes which are maintained by about 800 stem cells; in the adult fly a few enterocytes maintain the ability to become stem cells under the stimulation of toxins or parasites. Neither the hindgut nor the Malphigian tubes have stem cells; they react to injury by becoming polyploidal. He demonstrated that polyploidal cells can divide mitotically; these polyploidal mitoses are subject to errors

Dr Allan Spradling

which can be advantageous in producing diversity.

He commented that these observations may be of relevance to mammalian repair and that methylation is an 'add-on' to stabilize states in some plants and mammals.

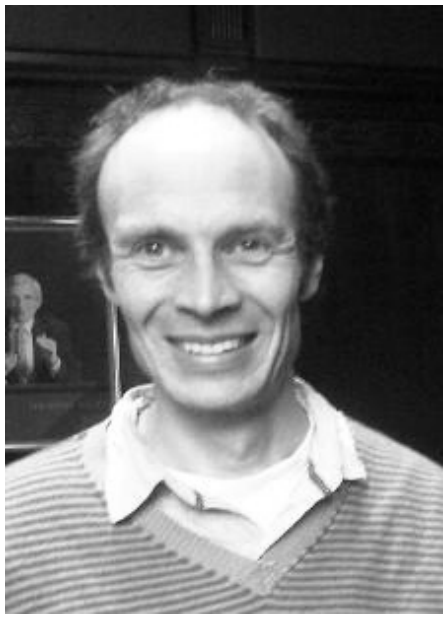
Dr Frank Jiggins of the Department of Genetics, University of Cambridge

The evolution of disease resistance in insects

The genetics basis of variation in susceptibility to infections can be studied by assessing interactions between Drosophila and viruses as well as mosquito-filarial nematode infection. Insights into the interaction between insects and viruses have identified common polymorphisms in a small number of genes, with major effects on resistance. This simple genetic basis is the result of strong selection driving major-effect resistance alleles to an intermediate frequency.

Bacterial symbionts also affect these interactions. Many species of Drosophila contain heritable *Wolbachia* bacteria which protect them against infection by RNA viruses. Shifts in susceptibilities can be caused by symbionts rapidly invading populations; the level of antiviral protection depending upon the density of the symbiosis.

Insects carrying high symbiont densities tend to survive less well



Dr Frank Jiggins

than others in the absence of infection, but survive the infections which may kill the non-carriers.

Professor Dominic Kwiatkowski, Wellcome Trust Sanger Institute, Cambridge and the Wellcome Trust Centre for Human Genetics, Oxford

Population genomics of malaria: host, parasite and vector

Global partnerships and public health interventions aim to eradicate malaria, but because of drug resistance this will have to be by a combination of drug therapies and insecticides. *Plasmodium* species reproduce every 48 hours producing 10^{10} new parasites and the mutation rate is 10^{-9}, thus one mutation every 2 days is to be expected. There is also a high rate of non-allelic recombination.

The surfin genes have been widely investigated; 25 times as many single nucleotide polymorphisms (SNPs) are found in African parasite populations than in South-East Asia so the major variance is in Africa with much transmission. Demographic processes drive variance more than evolution and recombination. Pararasitic polymorphism affects the development of drug resistance therefore polymorphic markers can indicate where drug resistance is developing. Professor Kwiatkowski also reminded us that genetic variations in the human populations affect their response to disease.

Professor Dominic Kwiatkowski

Professor David Horn, College of Life Sciences, University of Dundee

Decoding anti-trypanosomal drug efficacy and resistance

Human African Trypanosomiasis is caused by *Trypanosoma brucei* and is usually fatal if untreated. It is transmitted by the tsetse fly whose range limits the disease to sub-Saharan Africa. The disease in livestock, nagana, has an economic cost of about US $5 billion a year. Increasing resistance makes the traditional treatments even less effective.

Professor David Horn

Professor Horn and his team developed RNA interference libraries for genome-scale phenotype screening. They then developed RNA interference target sequencing for high-throughput phenotype screening using these libraries. Initial validation for over 1000 potential drug-targets was achieved and over 50 genes linked to drug action and resistance were found.

They showed that the amino acid eflornithine was taken up by the amino acid transporter AAA6. Suramin, another high molecular weight and highly charged drug, is taken up via receptor ISG75-mediated endocytosis. They were also able to demonstrate that the long-known melarsoprol-pentamidine cross-resistance is caused by the loss of function of an aquaporin (AQP2). Recently it has been shown that AQP2 mutation is involved in melarsoprol resistance in Sudan and the Democratic Republic of Congo, affecting about 30% of patients.

RNA interference target sequencing will have further applications.

AFTERNOON SESSION:
Reported by David Galton

The Galton Lecture 2013

Professor Jules Hoffmann,
CNRS Strasbourg, University of Strasbourg

The Drosophila host defence: a paradigm for innate immunity

Professor Jules Hoffmann was co-awarded the Nobel Prize for Medicine or Physiology in 2011 for his work on innate immunity. So we were very honoured to have him as our Galton Lecturer this year. He was in the unique position of being able to tell us from first-hand experience how the field of innate immunity started in the 1990s, its developments and setbacks over 20 years, leading to the universal recognition of this type of immunity throughout the animal kingdom.

He started by explaining why he chose to start with insects, particularly Drosophila. Insects comprise 80% of all living species, they destroy in average ~30% of our crops, and ~30% of humans suffer from infectious diseases transmitted by insects. But insects are quite resistant to infections themselves. The question arises as to the nature of this resistance. The story unfolds over 20 years of research and the final picture emerges that the products of bacterial or fungal infections combine with receptors, the peptidoglycan recognition proteins (PGRPs), which after degradation combine with Spaetzle proteins for binding to transmembrane receptors, the Toll proteins. This activates an intracellular signalling cascade producing NF-kB. There are response elements to NF-kB at enhancer loci on at least 7 nuclear effector genes that make bactericidal polypeptides such as drosomycin, diptericin, etc. The diptericin gene was one of the first to be cloned and found to have the NF-kB response elements; many of the others have subsequently been cloned. The evidence for the involvement of Toll receptors comes from studies of fly mutants that render the flies very susceptible to fungal and bacterial infections.

Homologues of the Drosophila immune system are found in humans. Some of the fly antimicrobial peptides e.g. drosomycin, are found on human exposed epithelial surfaces including the skin, eye, mouth, and urogenital system. Human homologues of the Drosophila Toll proteins are also found as a family of up to 7 distinct variants. As in Drosophila they are transmembrane proteins with intracellular domains that activate NF-kB, which in turn can induce up to 100 genes.

The detailed 3-D structure of Toll receptor 4 has been elucidated and shown how it binds to lipopolysaccharides (LPS). Professor Hoffmann raised the interesting idea that not only molecular products of infection can bind to Toll receptors but also the products of host tissue breakdown could too, and so contribute to autoimmune disease by activating the cytokine system. He did not overlook the fact that there may be therapeutic potentials here.

When did the innate immune system evolve? Components of the system (Toll receptors, cytokine signalling pathways and effector genes to make bacterocidal proteins) have been found in all the animal kingdom from molluscs, fishes, reptiles, birds, mammals etc. with varying degrees of complexity. However the response to viral infections in Drosophila uses a different pathway involving RNAi, dicer2 and RISC. Thus knockouts of dicer2 in flies make them very vulnerable to viral infections.

Professor Jules Hoffmann

This closed an exceptionally enjoyable and instructive lecture and we were all delighted that Professor Hoffmann had taken the time to come to London to deliver it.

Professor Francois Balloux, University College London

Reconstructing epidemics and outbreaks of human pathogens using genetic sequence data.

Professor Balloux is using genomic data to investigate the spatial genetic epidemiology of humans and human pathogens. He aims to test for possible targets of natural selection in the genome by reconstructing the spread of our ancestors around the globe in unprecedented detail, taking into account past changes in climate, food supply and the shape of continents. By knowing how and when people got to different parts of the world he will be able to distinguish which genetic variants have geographic distributions too extreme to be the results of chance effects, and thus have been likely targets for natural selection.

As examples of the use of sequence data to reconstruct past demographies of populations, he gave an introduction to the field of 'viral phylodynamics', which is the application of molecular phylogenetics specifically oriented at estimating demographic parameters of viral outbreaks and epidemics. Typical questions that are addressed in the field include the time and geographic location of an epidemic, which often represents a host jump into the human population, as well as the rate at which the pathogen population

expanded.

He illustrated these techniques by showing analyses performed on the 2009 H1N1 flu pandemic. These included the earliest estimates on the time of the host jump into humans based on the first 11 partial sequences available at the time, as well as a reconstruction of the ancestry of the eight genes of the 2009 H1N1 virus through its three hosts, human, chicken and pigs.

He then showed the same tools could be applied to bacterial infections. Using similar demographic modelling he showed how the most common UK nosocomial strain of MRSA (methicillin resistant staphylococcus aureus) emerged, evolved and spread through hospitals in the UK and could trace its likely origin to the neighbourhood of Birmingham in the mid-eighties.

Professor Francois Balloux

He then considered past plague epidemics including the Justinian Plague of (AD 541-542), the Black Death (14th century) and the Third Pandemic (1855-1959). He acknowledged the difficulty of reconstructing such old events using modern genomic samples alone, in particular as there has been an ongoing debate whether the different pandemics were caused by Yersinia pesti. However, recent progress in ancient DNA sequencing has now produced complete Y. pestis genomes from remains of people who had died during the Black Death. This demonstrates that Y. pestis was indeed the agent of previous plague pandemics and allows assigning modern plague samples as descendants of different previous plague pandemics.

Professor Andrea Crisanti,
Imperial College London
Controlling vector borne disease through genetic manipulation: its application to malaria.

Malaria is still a major health problem. Although many non-tropical countries have eradicated the disease, in the tropics $225*10^6$ people were infected and 781,000 deaths occurred in 2009. This is despite the fact that 11 countries in Africa have reduced their infection rates by ~50%. The major methods of control have been the use of insecticides and mosquito nets. In non-tropical countries the main methods of case detection, antimalarial drugs, insecticides for vector control and environmental changes such as swamp drainage have all but eradicated the disease.

Professor Crisanti is now advocating a new approach, that is to knock out the wild type Anopheles mosquito (causing ~80% of all malaria cases) using biological/genetic engineering methods. He quoted as proof-of-concept the eradication of the cassava mealy-bug by importing the wasp Apoanagyrus lopezi that lays its eggs in the mealy-bug, so protecting up to 80% of the cassava crop from destruction.

The idea for malaria is to manipulate the whole mosquito population by releasing a genetically engineered fly that after mating would render the wild type mosquito infertile. He uses a DNA restriction endonuclease gene introduced onto the X chromosome to produce transgenic flies. These flies when mating with their wild counterparts due to the endonuclease will destroy the X chromosome and so render their offspring infertile; eventually the whole population will crash as males after about 12 generations. He gave the technical details how to make the transgenic fly and has some preliminary data that this works in laboratory fly colonies using transgenic flies and normals. He is also trying to use the Y chromosome as the vehicle for the restriction endonuclease.

An interesting discussion ensued on the practicality of this idea and whether the use of a lethal transposon might be a more efficient approach; others considered these elements are too mobile and unstable for use in natural populations. Either way the use of a genetically engineered fly to destroy the wild type fly is a novel approach to an urgent problem related to world health.

The meeting was organised and chaired by Professor **Gordon Ferns** (University of Brighton), Professor **Timothy Cox** (University of Cambridge), and Dr **Branwen Hennig** (MRC International Nutrition Group).

British Society for Population Studies

Annual Conference 2013

We report another very successful annual conference, with two distinguished plenary speakers and 154 submitted papers presented over the two full days of the conference. Over 250 people travelled to Swansea to attend. Special mention should be made of the poster session, with a record 55 posters on display.

This year also saw more workshops and special sessions: a workshop on the "application of multilevel modelling"; a training session on "studying pathways between social and biological factors using modern causal inference methods: an example using data from the ONS Longitudinal Study"; a *CeLSIUS: joint hands-on training session for the 3 UK Census Longitudinal Studies;* a local government training session; a *Scottish Beyond 2011 workshop* and, last but by no means least, a career mentoring breakfast organised by the BSPS postgraduate student representative, Julia Mikolai. BSPS is very grateful to all who gave their time and expertise to bring these special sessions to Conference.

The BSPS website at www.bsps.org.uk has the full Conference programme with abstracts, available to download as a PDF. BSPS would also like to take this opportunity to thank the **Galton Institute** for their invaluable financial support again in 2013. This helps to defray the costs of plenary speakers' expenses and bursaries for student members.

Plenary 1: Professor Mary Daly, University of Oxford - Family Policy in the UK and Europe: Does it Respond to Fertility and Ageing?

The first plenary of the BSPS 2013 conference was given by Professor Mary Daly. She gave an overview of family policy models and their association with fertility, with the complexity of the linkages between policy and behaviour highlighted throughout. Despite improvements in data (notably via longitudinal studies) and the development of more sophisticated techniques of analysis, there remains a lack of consensus about the effect of policy on fertility, including questions concerning the direction of association and causal mechanisms.

The talk opened with a description of two common models of social policies, traditional ('sledge-hammer') and contemporary ('work-family balance'), and used case-studies from Europe to illustrate and compare features of these approaches.

The second part of the plenary focused on recent changes in family policy in the United Kingdom, firstly under New Labour and now under the Coalition government, comparing these policies to each other and as departures from the models of policy described in the first section of the plenary. As a result of state overhaul, support to families is a low priority currently in the UK. The UK has relatively high fertility in the European context, raising questions such as: Whether the fertility impacts of the current regime will be seen in the future? Does policy matter for fertility? and Do other routes to high fertility exist?

Whilst this plenary focused on the topic of fertility, it highlighted points concerning the complexity of analysis in making causal inference and the role of research in informing and evaluating policy issues relevant to many areas of demographic study.

Plenary 2: Professor Monica Das Gupta, University of Maryland - Demography, Gender and Kinship Systems: Perspectives from Asia

Professor Monica Das Gupta presented her thought-provoking work which focused on the demographic implications of various types of kinship systems.

She began by pointing out that many aspects of kinship systems including forms of marriage, inheritance and household formation and residence have considerable bearing on demographic outcomes. Whilst acknowledging that rigid systems may offer more social protection than other kinship systems, and that there is much variation between patrilineal systems, Das Gupta highlighted the demographic repercussions of rigid patrilineal systems in terms of marriage, childbearing and regulation, particularly focusing on its implications in terms of health outcomes for women and children.

She noted that rigidly patrilineal systems marginalise women as they are largely excluded from their parental home and are granted low autonomy in their husband's home. Women's low position in the social structure, particularly young married women, exposes them to elevated risks of ill-health and mortality. Using data from Pakistan she demonstrated that there are gender differences in the probability of consulting a doctor if ill and that within households less is spent on healthcare for women in comparison

to men. She also highlighted that rigid patrilineal systems limit the potential for adult daughters to help their parents, as for example contact with parents is limited after marriage, and that this may encourage sex selection: son preference evidenced by child sex ratios in demographic data show a striking correspondence with kinship systems.

Professor Das Gupta concluded by noting that, whilst kinship systems are persistent, there are key examples of state intervention altering kinship systems (for example South Korea and China) and by observing that norms appear to be changing in the context of increased urbanisation and education. This is for example evident through falling sex-selection in many settings in East and South Asia.

In 2014 BSPS will be at the University of Winchester for its annual conference, with the call for papers to be issued in early January 2014. BSPS hopes to see you there.

Annotating the Genome

Annual meeting of the Bloomsbury Centre for Genetic Epidemiology and Statistics, in conjunction with the South of England Genetic Epidemiology Group

The Bloomsbury Centre for Genetic Epidemiology and Statistics (BCGES, http://bcges.lshtm.ac.uk) is a joint Research Centre of University College London (UCL), the London School of Hygiene and Tropical Medicine (LSHTM) and Birkbeck, University of London. In 2013 its annual scientific meeting was held in conjunction with the South of England Genetic Epidemiology Group, an ad hoc colloquium of researchers from institutes in London, Cambridge, Oxford, Bristol, Cardiff and elsewhere. The meeting, on the theme of "Annotating the Genome", was held at LSHTM with the support of the **Galton Institute** on 11 June 2013.

The publication of results from the international ENCODE consortium in late 2012 (http://www.nature.com/encode/) was a major scientific event, revealing biological functions of large portions (up to 80%) of human DNA. This knowledge has the potential to transform genomics research, for example in starting to explain the mechanism of disease markers found by genome-wide association scans, which ultimately will lead to improved treatments for complex diseases. Currently, however, efforts to exploit this new knowledge are in their infancy. The meeting aimed to publicise the early thoughts of leaders in this field and to open up discussions on how best to exploit this knowledge in the context of our local research.

Martin Hibberd (LSHTM) opened proceedings by reviewing genome-wide association scans of infectious diseases, showing how some results were shared by non-communicable diseases such as Crohn's disease, and speculating how such diseases may be triggered by infectious agents. Andrew Smith (UCL) then described a technique, FAIRE, for identifying regions of open chromatin within genomic segments associated with disease; variants within such regions are more likely to be functionally involved in disease. Ruth Lovering (UCL) gave an overview of the Gene Ontology, a curated database of gene function that is useful for interpreting the results of genetic association studies. Emma Meaburn (Birkbeck) closed the morning by describing how DNA methylation is widely driven by sequence variation but can be specific to tissue types such as brain and blood.

After lunch, Ian Dunham (European Bioinformatics Institute) gave an in-depth description of the ENCODE project and presented some of its findings on tissue specific signals of regulation. Ben Fairfax (Oxford) described the identification of novel genetic determinants of induced innate immune responses in human primary monocytes. Leo Schalkwyk (Kings College London) presented work on DNA methylation analysis in brain tissue of Alzheimer's disease patients. Finally, Vardhman Rakyan (Queen Mary University of London) showed that an epigenetic profile could be a highly accurate marker for age, and that by modifying some epigenetic marks, cells could apparently be rejuvenated *in vitro*. Unfortunately, applying these techniques to make humans immortal is not currently anticipated.

The meeting was attended by 120 delegates who welcomed the range of topics covered. Many delegates remarked that they knew little about the subjects presented, which led to rather brief discussions following some of the talks, but the opportunity to learn about these new areas was widely appreciated. The day ended with a drinks reception that was enthusiastically attended.

Frank Dudbridge PhD
Reader in Statistical Genetics and Epidemiology,
London School of Hygiene and Tropical Medicine

The Galton Symposium Within Behaviour 2013

Behaviour 2013 is a joint meeting of the 33rd *International Ethological Conference* (*IEC*) and the Association for the Study of Animal Behaviour (ASAB)

The Galton Institute kindly funded a symposium on human ethology within Behaviour 2013, the international ethological congress held in Newcastle/Gateshead in August 2013. Behaviour 2013 was a five-day meeting with over 900 delegates from 30 countries. Its main focus was on animal behavior, but there were a number of presentations concerning human ethology, and we wanted to promote research of this kind to a wide range of biologists. The Galton Symposium formed the centrepiece of these and was specially advertised within the promotional materials. The symposium took place on the afternoon of the first full day in a 400-seat hall that was full to capacity with standing room only.

For the content of the symposium, we chose 'Sexual selection and variability in preferences in humans', following a call for proposals and a submission from Dr Anthony Little of Stirling University. This proposal seemed particularly appropriate since the research presented used techniques for measuring facial attractiveness from composites of face images, that stem directly from Francis Galton's pioneering work in this area. In his opening remarks Dr Little, who chaired the symposium, drew attention to this tradition of work and Galton's role in it. There were four talks, from Dr Little himself, Professor Ben Jones, Dr Lisa de Bruine, and Dr David Feinberg, followed by general discussion. A brief summary of the presentations is below.

Summary of the presentations

The symposium highlighted a range of recent approaches to the study of human preferences in an evolutionary framework. The speakers covered a range of topics and methodologies using, for example, sophisticated face and voice manipulation techniques as well presenting both experimental and correlational data. Three of the talks on face preferences used modern techniques based on Francis Galton's pioneering work on facial composite creation.

Little's talk *Visual cues to pathogens change mate preferences* covered the power that recent visual exposure can have over our mate preferences, asking whether visual experience of pathogen cues may mediate such variable preferences. The talk suggested that preferences can be strategically flexible according to recent visual experience with pathogen cues.

Jones and Watkins' *Systematic variation in men's dominance perceptions* addressed the importance of within-sex competition for systematic variation in men's dominance perceptions, describing a series of studies that suggest intrasexual competition has shaped both individual differences and facultative responses in men's perceptions of other men's dominance.

DeBruine's *Opposite-sex siblings decrease attraction, but not prosocial attributions, to self-resembling opposite-sex faces* presented on how experience with siblings affects human kin recognition in prosocial and mate choice contexts, providing evidence that experience with opposite-sex siblings can directly influence inbreeding avoidance mechanisms and demonstrating a functional dissociation between the mechanisms that regulate inbreeding and those that regulate prosocial behaviour towards kin.

Finally, **Feinberg's** *Women's self-perceived health and attractiveness predict their male vocal masculinity preferences in different directions across short- and long-term relationship contexts* covered individual differences in the perception of vocal attractiveness showing that self-rated attractiveness positively predicted long-term vocal masculinity preferences, whereas self-rated health negatively predicted short-term vocal masculinity preferences.

Overall, the talks demonstrated sophisticated mechanisms for variation in preferences and perception such as experience and own phenotype. Together the talks provided an interesting and important session on recent advances in evolutionary approaches to understanding variation in human mate preferences and sexual selection in humans.

The money provided by the **Galton Institute** helped defray the substantial costs of holding the conference, including venue hire, refreshments, printing programmes, and audio visual support. We would like to thank the Institute for their kind support.

Daniel Nettle
Professor of Behavioural Science
Newcastle University
daniel.nettle@ncl.ac.uk