THE UNIVERSITY *of* EDINBURGH

Project title: Causes and consequences of mutational variation in the mammalian genome

Supervisors: Peter Keightley and Konrad Lohse, Institute of Evolutionary Biology, University of Edinburgh, UK

Project Description

Spontaneous mutations are the ultimate source of genetic variation and are therefore of central importance in evolutionary biology. Understanding the nature of variation arising from spontaneous mutation is important for diverse questions, including the genetic basis of complex trait variation, the causes of inbreeding depression and the maintenance of nucleotide variation in the genome. We are recruiting a PhD student to join our team addressing such fundamental evolutionary questions.

The PhD studentship is fully funded by the European Research Council (via an Advanced Grant award), and is open to applicants from the EU. A key component of the project is an ambitious, spontaneous mutation accumulation (MA) experiment in mice, the first highly replicated MA experiment in a mammalian species. With our collaborators at the Max Planck Institute for Evolutionary Biology (Ploen, Germany) we are maintaining a large cohort of MA lines, bred by full-sib mating, for many generations in the near-absence of selection. Different lines will accumulate different spontaneous mutations and therefore diverge molecularly and phenotypically. The PhD project is expected to be within some or all of the areas described below. The project is flexible, however, and can be tailored to the interest of the successful applicant.

Applicants are strongly encouraged to contact the principal supervisor ahead of application to discuss the project.

A. The nature of variation from new mutation.

(a) Theoretically, inbred lines should harbour little genetic variation, but there are several factors which could lead to inbred lines harbouring more variation than expected. We will test this by quantifying nucleotide variation in our inbred MA line progenitors by deep genome sequencing and bioinformatic analysis. This step is a necessary for the following two studies.

(b) Variation in the mutation rate within a species have been little studied, but is fundamental for understanding the maintenance of genetic variation. We will address this question by large-scale deep sequencing and bioinformatic analysis of house mouse MA lines of different strains and potentially families of wild house mice.

(c) The relationship between nucleotide and phenotypic variation arising from mutation are largely unknown. Divergence between MA lines for complex traits quantifies the new mutational variation. We will relate the accumulation of phenotypic differences, in traits such as growth rate, reproductive fitness and gene expression, to differences in the accumulation of mutations in different genomic site classes among lines.

B. Understanding variation in diversity across the genome.

Genetic diversity in natural populations varies across the genome, but the causes of this variation are poorly understood. It is clear that variation in diversity is caused by interactions between mutation, natural selection, recombination and genetic drift. We will explore avenues of research that might help tease apart these factors. (a) Are patterns of diversity across the genome consistent between different species with different effective population sizes? It will be especially relevant to determine how diversity relates to the rate of recombination and the local density of functional genomic elements. (b) Are there signals in genomic polymorphism data, for example in the joint frequency distribution of linked sites that can differentiate between different forms of selection? We will also explore whether new computer simulation approaches can be used to efficiently model the joint effects of mutation, recombination, selection and genetic drift across the genome.

Further Information

The studentship is funded by a 5 year ERC grant, which includes a substantial budget for genome sequencing, consumables and travel to conferences.

Training is an integral part of the studentship, including attendance of bioinformatics courses and courses in population and quantitative genetics and statistics run as part of the Institute of Evolutionary Biology's MSc in Quantitative Genetics and Genome Analysis.

Prospective applicants are encouraged to contact Peter Keightley <peter.keightley@ed.ac.uk> to discuss the project in the first instance. Formal applications can be made via https://www.ed.ac.uk/biology/prospective-students/pgr/how-to-apply by 21 July 2018.