Postdoc and PhD positions in SFB project ‘Polygenic adaptation’ (Vienna, AT)

Postdoc and PhD positions are available within the **Special Research Program (SFB) "Polygenic adaptation: from single selected loci to the infinitesimal model" in Vienna, Austria**. Vienna is on top of the world's most liveable cities and home to one of the largest communities of evolutionary research in Europe (www.evolVienna.at).

The SFB program is funded by the Austrian Science Fund (FWF) and brings together eight research groups at four institutions in and around Vienna with the common goal of elucidating the evolutionary genetics of adaptation of complex phenotypes: **Neda Barghi, Robert Kofler, Christian Schlötterer (Vetmeduni); Joachim Hermisson, Himani Sachdeva (Univ. of Vienna); Magnus Nordborg, Kelly Swarts (Gregor Mendel Institute); Nick Barton (ISTA)**. For young scientists, this cluster offers a unique environment for interaction and personal growth.

The SFB aims to develop a framework for understanding polygenic adaptation and to establish new standards for the analysis of adaptive polygenic traits in GWAS and experimental evolution studies. We will combine model-based conceptual work and data-driven approaches from GWAS and experimental evolution to achieve this goal. The models and methods that will be developed integrate population genetic and quantitative genetic approaches to detect, analyze, and interpret genomic patterns of the “architecture of polygenic adaptation”.

SFB – a collaborative environment for research and learning

The theoretical and empirical projects of the SFB are highly synergistic and the collaborative nature of the SFB will provide an inspiring academic environment and promote curiosity-driven research. The interaction between projects of the SFB is strongly facilitated by a long-standing track record of fruitful interactions among the PIs. The PhD students and postdocs in the SFB will benefit enormously from these tight interactions.

To ensure a good integration of experiment and theory, researchers have the opportunity to spend some time in a group from the other “camp”. These regular exchanges will improve the mutual understanding of concepts and problems, ensure that the theoretical work is guided by experiments (and vice versa) and will represent a true added value of the SFB. In addition to the formal supervisor, both PhD students and postdocs will have at least one co-advisor with complementary expertise.

Courses: The recruited early-stage researchers in the SFB will have the opportunity to acquire experience beyond their own projects and working groups.

The SFB PIs participate in joint teaching activities and representatives of all institutions are contributing to the Vienna Graduate School of Population Genetics (www.popgen-vienna.at). The PhD students will be integrated in the Vienna Graduate School of Population Genetics, which offers a 5-week introductory course that covers subjects as diverse as statistics, population genetics, *Drosophila* genetics, programming, NGS data analysis (both DNA- and RNA-Seq) and quantitative genetics.

SFB postdocs will have the opportunity to participate in the teaching in introductory course in their areas of expertise. But at the same time can attend specific modules of the introductory course together with the PhD students. This joint event will have a tremendous impact on team-building and can enable scientists from different host institutions to establish strong ties which can result in research collaborations.

The IST Graduate School offers more advanced courses in evolutionary genetics and bioinformatics (https://phd.pages.ist.ac.at/courses/), which will be available to students and postdocs in the SFB.

Monthly SFB meetings: We will have monthly SFB meetings where PhD students and postdocs can present their research. The monthly SFB meetings will provide a platform for early-stage researchers to present the progress of their research and receive helpful and constructive feedback.

Journal clubs and seminars: All SFB members will participate in weekly journal clubs and will benefit from the weekly seminar series at the Vienna Graduate School of Population Genetics and at ISTA, both of which provide opportunities for one-to-one interactions with internationally leading researchers.

Conferences: All early-stage researchers will be encouraged to present their results at national and international conferences and workshops, where they will be able to network with their peers and with more senior researchers.

Available infrastructure of research institutions of the SFB: The participating institutions in the SFB provide exceptional training infrastructure. All institutions offer access to excellent computing infrastructure, molecular biology laboratories and electronic access to all relevant journals.

OPEN POSITIONS:

Two postdoc positions are available in the groups of Joachim Hermisson and Himani Sachdeva for 2 years, each (with potential extension). Salary is according to FWF rates for postdocs (€ 4.351,90 before tax). The starting date is January 2024 (with some flexibility). Application is open until positions are filled.

Application for postdoc positions: For informal inquiries and further information, interested candidates are encouraged to contact Joachim Hermisson and Himani Sachdeva (joachim.hermisson[AT]univie.ac.at, himani.sachdeva[AT]univie.ac.at) before submitting a formal application. In this case, please send a brief statement of interest and CV.

Four PhD positions are available in the labs of Neda Barghi and Christian Schlötterer. Students will receive a monthly salary based on € 2.464,80 before tax according to FWF rates. Starting date is January 2024 or later. Application deadline: September 17, 2023.

Application for PhD positions: Only complete applications (application form, CV, motivation letter, university certificates, indication of the two preferred topics in a single pdf) received by **September 17, 2023** will be considered. Two letters of recommendation need to be sent directly by the referees. All information

about the research program and application procedures can be found at https://www.vetmeduni.ac.at/sfb-polygenic-adaptation

Postdoc positions in evolutionary modeling (Univ. of Vienna, AT)

The mathematics and biosciences group led by Joachim Hermisson and Himani Sachdeva at the University of Vienna is looking for strong and highly motivated candidates for **two postdoc positions in evolutionary modeling**.

In recent years, following the massive inflow of data from GWAS, the genetics of complex traits has become one of the main fields of study in evolutionary research. Of particular interest - but so far poorly understood - are the dynamics of such traits during adaptive evolution. How does phenotypic adaptation typically proceed? Under what conditions do we see classic signatures of selective sweeps due to large and rapid changes in allele frequencies in the underlying genes? When does adaptation occur through subtle shifts at many loci, and how could these be detected from footprints in genomic data? What is the role of linkage, and when does selection act on extended haplotypes rather than on individual loci?

In **two projects**, we want to develop models for the adaptation of complex traits. One project deals with the **change in adaptive architectures** depending on the number of alleles involved. A particular interest is "oligogenic adaptation", the poorly understood parameter range between "monogenic adaptation" (described by population genetics) and "highly polygenic adaptation" (captured by classical quantitative genetic approaches). The second project focuses on **signatures of highly polygenic adaptation** involving selection on haplotypes with many small-effect ("infinitesimal") variants, and how selection response is influenced by linkage disequilibrium in the initial population. Both projects aim to understand key phenomena through analytical theory and link to genomic data through computational and statistical modeling.

We are looking for candidates with a strong background in quantitative methods (analytical and computational modeling) in evolutionary research. Programming skills are highly appreciated. Applicants should have completed their PhD in a relevant field at the latest by the start of the position. The working language in the group is English. German skills are not essential.

PhD positions in polygenic adaptation (Univ. of Veterinary Medicine, AT)

PhD supervisor: Neda Barghi

Project 1 So what is polygenic adaptation anyway? Genetic and adaptive architecture of polygenic traits - Topic 1 Characterizing the adaptive architecture of polygenic traits

Many quantitative traits are polygenic with many underlying alleles and majority of these traits are under stabilizing selection, which stabilizes the population mean on a specific average trait value, known as the optimum. After a sudden shift in the optimum, adaptation occurs through the small frequency changes of many alleles, i.e. polygenic adaptation. Theoretical studies have predicted different phases of polygenic adaptation (1,2) which is determined based on when the new trait optimum is reached. However, in most natural and experimental populations the focal trait under selection is not known.

To tackle this problem, in this project we will explicitly shift the optimum of a trait under stabilizing selection; we will shift female body size toward larger size in replicate populations of *Drosophila simulans* through evolve and resequence (E&R). The aim of this PhD project is to identify the alleles that respond to selection on female body size in different phases of adaptation. The unique design of this experiment allows us to determine when the trait optimum is reached and characterize different phases of polygenic adaptation at the genomic and phenotypic level.

The PhD student should be interested in analyzing and integrating time-series genomic and phenotypic data. The student will have an active role in phenotyping experiments so experience in designing experiments and phenotyping is desired. Bioinformatics skills and experience in analyzing large datasets is a plus. The PhD students in topic 1 and 2 of this project will work closely together, and will interact with a technician for maintaining the experimental populations.

Topic 2 Comparison of the genetic and adaptive architectures of polygenic traits

The genetic architecture of quantitative traits comprises of all the contributing alleles and their effect sizes, i.e. genetic architecture. However, only a subset of the underlying alleles responds to selection, i.e. the adaptive architecture (3). Factors such as the distance to the new trait optimum, starting frequencies and pleiotropy determine which alleles are potentially adaptive. While the genetic architecture has been the focus of many QTL and GWA studies, the adaptive architecture of polygenic traits is not well characterized.

The aim of this PhD project is to determine the genetic architecture of a polygenic traits, *Drosophila simulans* female body size, using GWAS with 1000 individuals, and to compare the adaptive and genetic architectures of female body size. In a parallel PhD project (topic 1) *Drosophila simulans* populations are experimentally evolved for larger body size (E&R study). Availability of this dataset allows us to distinguish alleles with adaptive potential from alleles with constraints. Moreover, genome-wide association data are available for many traits in *Drosophila*. A meta-analysis of available GWAS, would facilitate identification of pleiotropic alleles which can be used to corroborate the alleles under constraints identified in this study.

The PhD student will have access to a large dataset consisting of GWAS and time-series genomic data from E&R experiments. Thus, the student should have strong bioinformatics skills and experience with handling large data sets. Background is population genetic is essential. The PhD students in topic 1 and 2 of this project will work closely together, and will interact with a technician for maintaining the experimental populations.

Project 2 Go big or go home! Genomic and phenotypic patterns of adaptation in large experimentally evolved populations

In molecular population genetics, adaptation is typically thought to occur via selective sweeps, where targets of selection have independent effects on the phenotype and rise to fixation (4). In quantitative genetics, many loci contribute to the phenotype and subtle frequency changes occur at many loci during polygenic adaptation after a shift in trait optimum. Polygenic adaptation is probably the prevalent mode of adaptation (5), but we are still lacking a solid understanding of the selection signatures under this model. Furthermore, recent theoretical and

empirical studies have shown that both selective sweep and polygenic adaptation models could result in a sweep-like genomic signature (6,7) (i.e. large allele frequency change); therefore, additional criteria are needed to distinguish the two models.

In a computer simulation study (8) we identified several distinct patterns for selective sweep and trait optimum models in experimental populations of different sizes. These features include the temporal changes in allele frequencies and phenotype, haplotype structure and (non)-parallelism among replicates. Our results showed that the combination of large and small replicate populations uncovers some distinctive patterns that can be used for developing test statistics to discriminate between the two models. Building on the results of the computer simulations we have performed an experimental evolution where 20 replicates of small (800 individuals) populations and 6 replicates of large populations (100,000 individuals) of *Drosophila simulans* were adapted to a high protein diet for more than 60 generations. The proposed project aims to test the predictions of computer simulations with empirical data.

The PhD student will have access to a large dataset consisting of time-series genomic, gene expression and fitness data for these experimentally evolved populations. Thus, the PhD student should have strong bioinformatics skills and experience with handling large data sets. The project is a great opportunity for PhD students who are interested in analyzing time-series data and combining bioinformatics methods with population genetic theory. Background is population genetic is essential.

1. Jain K, Stephan W. Modes of Rapid Polygenic Adaptation. Mol Biol Evol. 2017;34(12):3169–75.
2. Franssen SU, Kofler R, Schlötterer C. Uncovering the genetic signature of quantitative trait evolution with replicated time series data. Heredity. 2017;118(1):42–51.
3. Barghi N, Hermisson J, Schlötterer C. Polygenic adaptation: a unifying framework to understand positive selection. Nat Rev Genet. 2020;21(12),769–781.
4. Hermisson J, Pennings PS. Soft Sweeps: Molecular Population Genetics of Adaptation From Standing Genetic Variation. Genetics. 2005;169(4):2335–52.
5. Barton NH, Etheridge AM, Véber A. The infinitesimal model: Definition, derivation, and implications. Theor Popul Biol. 2017;118:50–73.
6. Barghi N, Tobler R, Nolte V, Jakšić AM, Mallard F, Otte KA, et al. Genetic redundancy fuels polygenic adaptation in *Drosophila*. PLOS Biol. 2019;17(2):e3000128.
7. Höllinger I, Pennings PS, Hermisson J. Polygenic adaptation: From sweeps to subtle frequency shifts. PLOS Genet. 2019;15(3):e1008035.
8. Barghi N, Schlötterer C. Distinct patterns of selective sweep and polygenic adaptation in evolve and re-sequence studies. Genome Biol Evol. 2020;12(6):890–904

Project 3 The extent of genetic redundancy in polygenic adaptation

Genetic redundancy facilitates adaptation and is an important characteristic of polygenic adaptation. But it is not understood how redundancy manifests at different hierarchal levels such as genomic, gene expression, metabolites, or high-order phenotypes during adaptation. Phenotypic convergence in replicate populations with heterogeneous genomic responses (1) suggests that the extent of redundancy decreases as the biological

hierarchy is higher, i.e. redundancy decreases from genetic variants to gene expression, metabolite levels and high-order phenotypes.

We have developed an accurate and high throughput method for embryo size measurement using flow cytometry (2) that allows performing selection experiments by sorting viable *Drosophila* embryos from any specified size range. We will use this method to establish an experimental framework to shift the optimum of *Drosophila* embryo size towards bigger size with different intensities, i.e. different new trait optima, in replicate populations. Given the unique design of this experiment, we can infer redundancy by estimating parallelism at different hierarchical levels by comparing selected alleles, differentially expressed genes, differential metabolites, and high-order phenotypes.

The PhD student should be interested in analyzing and integrating time-series genomic, transcriptomic, and phenotypic data. The PhD student should have strong bioinformatics skills and experience with handling large data sets. Background in population genetics is essential. The student will also have an active role in phenotyping experiments so experience in designing experiments and phenotyping is desired.

1. Barghi N, Tobler R, Nolte V, Jakšić AM, Mallard F, Otte KA, et al. Genetic redundancy fuels polygenic adaptation in *Drosophila*. Gibson G, editor. PLOS Biol. 2019 Feb 4;17(2):e3000128.
2. Barghi, N. & Ramirez-Lanzas, C. A high throughput method for egg size measurement in *Drosophila*. Sci. Rep. 13, 3791 (2023).

PhD supervisor: Christian Schlötterer

Topic 1 Understanding polygenic adaptation with reduced genetic variation

A hallmark of polygenic adaptation is that many populations contain much more adaptive variation than needed to reach a new trait optimum. This redundant architecture complicates the identification and characterization of adaptive alleles in natural populations. Furthermore, many of the contributing alleles are of very small effect such that they cannot be identified. Hence, we are left with the difficulty that polygenic adaptation is ubiquitous, but the genetic characterization seems almost impossible. This project seeks to change this situation by pursuing a novel approach: using experimental evolution we will generate time series data where recombination shuffles selected alleles. Because the complexity of a polygenic trait is dramatically reduced and the contribution of small effect loci can be determined by their joint effects in linkage blocks, the time resolved allele frequency changes will provide an unprecedented resolution of the adaptive architecture of polygenic traits.

The project provides the opportunity of two PhD positions. One PhD will be focusing on the development of Approximate Bayesian Computation (ABC) methods that are specifically tailored to capture the dynamics of time-resolved genome-wide allele frequency data. Candidates with a strong interest in large-scale computer simulations and the development of novel statistical approaches are particularly well-suited for this position. The second PhD will integrate genomic and phenotypic time-series data. The candidate will have a strong interest in empirical data analysis as well as understanding the phenotypic changes of evolving

Drosophila populations. The candidate will closely interact with technicians maintaining the experimental populations.

1. Kosheleva, K. & Desai, M.M. Recombination Alters the Dynamics of Adaptation on Standing Variation in Laboratory Yeast Populations. Mol Biol Evol 35, 180-201 (2018).
2. Burny, C., Nolte, V., Dolezal, M. & Schlötterer, C. Genome-wide selection signatures reveal widespread synergistic effects of two different stressors in *Drosophila melanogaster*. Proc Biol Sci 289, 20221857 (2022).
3. Burny, C., Nolte, V., Dolezal, M. & Schlötterer, C. Highly Parallel Genomic Selection Response in Replicated *Drosophila melanogaster* Populations with Reduced Genetic Variation. Genome Biol Evol 13(2021).

Topic 2 Characterizing the role of non-additive effects for adaptive responses

The importance of non-additive effects is a well-known controversy that started with Fisher and Wright (1,2) and has continued since (3,4). It has been argued that epistasis may facilitate adaptation because loci can interact synergistically (5,6). On the other hand, recombination shuffles alleles between backgrounds, which reduces the impact of epistasis on adaptation - at least when positive and negative epistatic interactions are present (6-8). Similarly, dominance may be less relevant for genomic selection responses because most beneficial alleles are at least partially dominant (9) and the distinction between co-dominant and dominant alleles is challenging because the allele frequency trajectories differ most at high frequencies (i.e. the trajectory of a dominant allele can well-approximate by a codominant one unless at high frequencies). Given the difficulty of evaluating the contribution of non-additive effects, in particular for the selective response during adaptation, we lack solid empirical data to resolve this long-standing debate.

This project will use experimental evolution to evaluate empirically the importance of non-additive effects for adaptation and test the hypothesis that non-additive effects are of minor importance for adaptive processes from standing genetic variation after a rapid shift in environmental conditions.

The candidate will enjoy the analysis of large genomic data sets and have a vivid interest to apply innovative approaches to address long-standing questions in population genetics.

1. Fisher, R.A. The genetical theory of natural selection, (Clarendon Press, Oxford, 1930).
2. Wright, S. Evolution in Mendelian populations. Genetics 16, 97-159 (1931).
3. Carlborg, O. & Haley, C.S. Epistasis: too often neglected in complex trait studies? Nat Rev Genet 5, 618-25 (2004).
4. Hill, W.G., Goddard, M.E. & Visscher, P.M. Data and theory point to mainly additive genetic variance for complex traits. PLoS Genet 4, e1000008 (2008).
5. Ostman, B., Hintze, A. & Adami, C. Impact of epistasis and pleiotropy on evolutionary adaptation. Proc Biol Sci 279, 247-56 (2012).
6. Hansen, T.F. Why epistasis is important for selection and adaptation. Evolution 67(2013).
7. Malmberg, R.L. The evolution of epistasis and the advantage of recombination in populations of bacteriophage T4. Genetics 86, 607-21 (1977).

8. Demuth, J.P. & Wade, M.J. Experimental methods for measuring gene interactions. Annu. Rev. Ecol. Syst. 37, 289-316 (2006).
9. Charlesworth, B. & Charlesworth, D. Elements of Evolutionary Genetics, (Roberts and Company Publishers, Greenwood Village, Colorado, 2010).

Topic 3 The role of genotype x environment interactions for adaptive responses

This project will determine how temperature adaptation is affected by the environment. Previous studies suggested that the interaction between environmental factors affects the selection response (e.g. 1,2,3). his project aims to document this interaction effect by the genome-wide selection response. Experimental evolution with two different founder genotypes will be used to study the genomic response of large experimental populations, which are adapting to a novel high temperature regime in two different environments. Based on time series genome wide allele frequency data, the genomic response to the same temperature stressor in two different environments will provide insights on the robustness of adaptive signatures.

The candidate will have a strong interest in genomic data analysis as well as understanding the phenotypic changes of evolving *Drosophila* populations.

1. Kondrashov, A.S. & Houle, D. Genotype-environment interactions and the estimation of the genomic mutation rate in *Drosophila melanogaster*. Proc Biol Sci 258, 221-7 (1994).
2. Folt, C.L., Chen, C.Y., Moore, M.V. & Burnaford, J. Synergism and antagonism among multiple stressors. Limnol. Oceanogr. 44, 864-877 (1999).
3. Pirotta, E. et al. Understanding the combined effects of multiple stressors: A new perspective on a longstanding challenge. Sci Total Environ 821, 153322 (2022).
4. Burny, C., Nolte, V., Dolezal, M. & Schlötterer, C. Genome-wide selection signatures reveal widespread synergistic effects of two different stressors in *Drosophila melanogaster*. Proc Biol Sci 289, 20221857 (2022).