

Genetic analysis of quantitative traits in medaka fish and humans

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About

Code to render PDF:

```
bookdown::render_book("book", bookdown::pdf_book())
```

Code to render PDF with different fonts:

First make the bookdown::pdf_book: entry in _output.yml first.

Then...

```
bookdown::render_book("book")
```

To clean up the references:

```
citr::tidy_bib_file(rmd_file = c("book/index.Rmd",
                                 "book/01-Introduction.Rmd",
                                 "book/02-MIKK_genome.Rmd",
                                 "book/03-Pilot.Rmd",
                                 "book/04-MIKK_F2.Rmd",
                                 "book/06-Fst.Rmd",
                                 "book/07-references.Rmd"),
messy_bibliography = "book/book.bib",
file = "book/tidy_references.bib")
```

Test to understand which commands are creating errors:

```
bookdown::render_book("book",
bookdown::pdf_book(pandoc_args = "--listings",
latex_engine = "xelatex",
biblio_style = "apalike",
csl = "chicago-fullnote-bibliography.csl",
```

```
includes = rmarkdown::includes(in_h
documentclass = "book",
sansfont = "Georgia",
monofont = "AndaleMono",
highlight = "pygments"))
```

citation_package = "natbib" throws an ugly error, and ends up removing all references in the document.

Weirdly, fonts only change if they go in index.Rmd.

0.1 bs4_book

```
bookdown::render_book("book",
bookdown::bs4_book(css = "style.css",
theme = list("primary" = "#52002E"),
repo = list("base" = "https://github.com/rstudio/bookdown"))
includes = rmarkdown::includes(in_h
footnotes_inline = T,
bibliography = "book.bib"))
```

This is a *sample* book written in **Markdown**. You can use anything that Pandoc's Markdown supports; for example, a math equation $a^2 + b^2 = c^2$.

0.2 Usage

Each **bookdown** chapter is an .Rmd file, and each .Rmd file can contain one (and only one) chapter. A chapter *must* start with a first-level heading: # A good chapter, and can contain one (and only one) first-level heading.

Use second-level and higher headings within chapters like:
A short section or ### An even shorter section.

The index.Rmd file is required, and is also your first book chapter. It will be the homepage when you render the book.

0.3 Render book

You can render the HTML version of this example book without changing anything:

1. Find the **Build** pane in the RStudio IDE, and
2. Click on **Build Book**, then select your output format, or select “All formats” if you’d like to use multiple formats from the same book source files.

Or build the book from the R console:

```
bookdown::render_book()
```

To render this example to PDF as a bookdown::pdf_book, you’ll need to install XeLaTeX. You are recommended to install TinyTeX (which includes XeLaTeX): <https://yihui.org/tinytex/>.

0.4 Preview book

As you work, you may start a local server to live preview this HTML book. This preview will update as you edit the book when you save individual .Rmd files. You can start the server in a work session by using the RStudio add-in “Preview book”, or from the R console:

```
bookdown::serve_book()
```


Chapter 1

Introduction

1.1 A brief history of genetics

Humankind has long sought to understand the basis of biological variation. What gives rise to the wondrous variety of life forms on Earth? Why do individuals of a particular species differ from one another? How do children inherit traits that are similar to those of their parents, yet on the whole remain distinct from both their parents and their siblings? And are the traits we care about – our health, our intelligence, our ability to thrive in a changing world – pre-determined from birth, or continuously pliable throughout our lives?

1.1.1 Ancient Greece

Around 500 BC, the Ancient Grecian Pythagoras applied his understanding of triangles to this question, proposing the theory known as “spermism”. He posited that hereditary information was passed down from parent to child via male sperm, with the female only providing the nutrients that would allow it to grow, and, like the theorem that bears his name, that these two sides of the “triangle” the length of the third side: the characteristics of the child.¹

¹Siddhartha Mukherjee, *The Gene: An Intimate History* (Simon and Schuster, 2016), <https://books.google.com?id=XvAsDAAAQBAJ>.

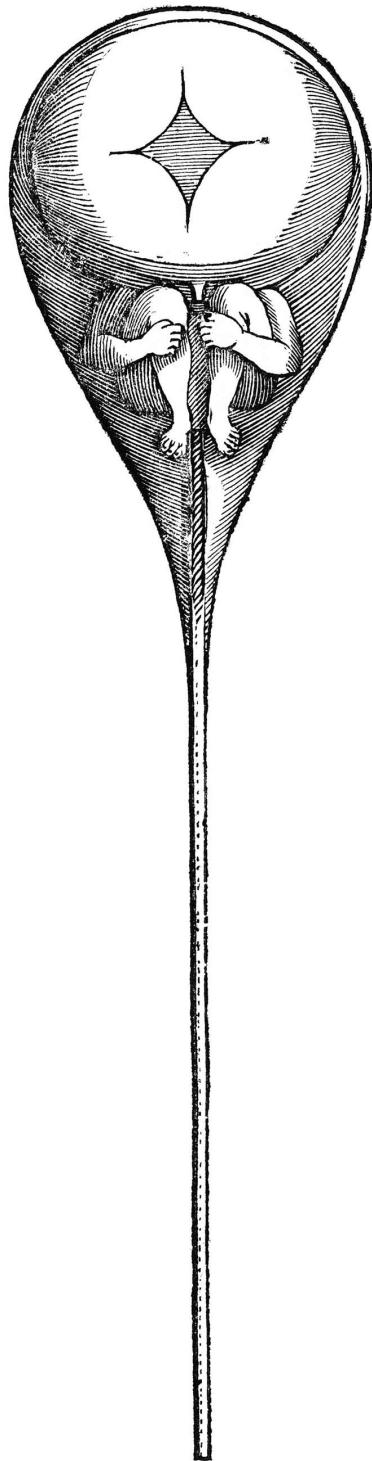
Over a century later, in 380 BC, Plato extended this metaphor in *The Republic* to argue that this principle could be applied to perfect humanity, by breeding perfect combinations of parents.

Aristotle joined the discussion with his treatise *Generation of Animals*, where he noted cases where human skin colour and other traits could skip generations, and thus hereditary information must not only be transmitted through sperm. He suggested an idea of “movement” – the transmission of information – from the father’s sperm, which sculpts the mother’s menstrual blood in the same way a carpenter carves a piece of wood.²

1.1.2 Medieval times

In medieval times, the prevailing theory was that a tiny human – a homunculus – sat within the sperm, waiting to be inflated upon its introduction to a woman’s uterus. However, this would require a homunculus to sit within another homunculus, *ad infinitum*, like Matryoshka dolls, all the way back to the Biblical first man, Adam. Even the inventor of the microscope, Nicolaas Hartsoeker, thought he saw one in a sperm he was studying.

²Mukherjee.



1.1.3 Charles Darwin and Gregor Mendel

In 1831, a young Charles Darwin boarded the HMS *Beagle* to embark on an expedition to collect specimens from South America. After collecting a huge number of fossils from the along the eastern coast and shipping them back to England, the *Beagle* spent 5 weeks touring through the 18 volcanic islands of the Galàpagos, where Darwin collected

1.1.4 Breeding programs in agriculture

Chapter 2

Genomic variations in the MIKK panel

This project was carried out in collaboration with Felix Loosli's group at the Karlsruhe Institute of Technology (KIT), and Joachim Wittbrodt's group in the Centre for Organismal Studies (COS) at the University of Heidelberg.

This chapter sets out my contributions to the the following pair of papers published in the journal *Genome Biology*, on both of which I am joint-first author:

- Tomas Fitzgerald et al.¹
- Adrien Leger et al.²

¹“The Medaka Inbred Kiyosu-Karlsruhe (MIKK) Panel,” *Genome Biology* 23, no. 1 (February 21, 2022): 59, <https://doi.org/10.1186/s13059-022-02623-z>.

²“Genomic Variations and Epigenomic Landscape of the Medaka Inbred Kiyosu-Karlsruhe (MIKK) Panel,” *Genome Biology* 23, no. 1 (February 21, 2022): 58, <https://doi.org/10.1186/s13059-022-02602-4>.

2.1 The Medaka Inbred Kiyosu-Karlsruhe (MIKK) panel

Biological traits are the product of an interaction between an organism's genes and its environment, often described as the relationship between "nature and nurture".³ This is especially true for complex traits such as behaviour, which I investigate in Chapters 3 and 4.

It is unfeasible to explore the relationship between genes and environment experimentally in humans due to the insufficient ability to manipulate either set of variables. Researchers accordingly resort to using model organisms, with which it is possible to control for both. The genetics of model organisms may be controlled to a degree by establishing inbred strains through the repeated mating of siblings over successive generations. Eventually, as the individuals within each line inherit the same same haplotype from their related parents, they become almost genetically identical to one another, with the added benefit that their genotypes can be replicated across time in subsequent generations. This utility has led to the establishment of "panels" of inbred strains for several model organisms including the thale cress (*Arabidopsis thaliana*),⁴ common bean (*Phaseolus vulgaris L.*),⁵ tomato (*Lycopersicon esculentum*),⁶ maize (*Zea mays*),⁷ nema-

³ Robert Plomin and Kathryn Asbury, "Nature and Nurture: Genetic and Environmental Influences on Behavior," *The ANNALS of the American Academy of Political and Social Science* 600, no. 1 (July 1, 2005): 86–98, <https://doi.org/10.1177/0002716205277184>.

⁴ Joy Bergelson and Fabrice Roux, "Towards Identifying Genes Underlying Ecologically Relevant Traits in *Arabidopsis Thaliana*," *Nature Reviews Genetics* 11, no. 12, 12 (December 2010): 867–79, <https://doi.org/10.1038/nrg2896>.

⁵ William C. Johnson and Paul Gepts, "Segregation for Performance in Recombinant Inbred Populations Resulting from Inter-Gene Pool Crosses of Common Bean (*Phaseolus Vulgaris L.*)" *Euphytica* 106, no. 1 (March 1, 1999): 45–56, <https://doi.org/10.1023/A:1003541201923>.

⁶ Vera Saliba-Colombani et al., "Efficiency of RFLP, RAPD, and AFLP Markers for the Construction of an Intraspecific Map of the Tomato Genome," *Genome* 43, no. 1 (February 2000): 29–40, <https://doi.org/10.1139/g99-096>.

⁷ Anis M. Limami et al., "Genetic and Physiological Analysis of Germination Efficiency in Maize in Relation to Nitrogen Metabolism Reveals the Importance of Cytosolic Glutamine Synthetase," *Plant Physiology* 130, no. 4 (December 1, 2002): 1860–70, <https://doi.org/10.1104/pp.009647>.

2.1. THE MEDAKA INBRED KIYOSU-KARLUHE (MIKK) PANEL¹⁵

tode (*Caenorhabditis elegans*)⁸, fruit fly (*Drosophila melanogaster*)⁹ and mouse (*Mus musculus*)¹⁰.

Although the mouse is an appropriate model for humans due to their orthologous mammalian organ systems and cell types, inbred strains of this organism descend from individuals that had already been domesticated, and therefore do not represent the genetic variation present in wild populations. Furthermore, the large panels of inbred mice such as the Collaborative Cross (CC)¹¹, Diversity Outcross (DO)¹² and B6-by-D2 (BXD)¹³ are derived from only a small number of individuals. As gene-environment studies seek to ultimately understand their effects on traits “in the wild” (such as with humans), there is accordingly a need for a panel of inbred vertebrates that represents the genetic variation present in natural populations.

The medaka fish (*Oryzias latipes*) has been studied as a model organism in Japan for over a century¹⁴ and is gaining recognition elsewhere as a powerful genetic model for vertebrates¹⁵. In addition to possessing a number of desirable traits that are characteristic of model organisms (including their small-size, short reproduction time, and high fertility), medaka are also – uniquely among

⁸Kathryn S. Evans et al., “From QTL to Gene: C. Elegans Facilitates Discoveries of the Genetic Mechanisms Underlying Natural Variation,” *Trends in Genetics* 37, no. 10 (October 1, 2021): 933–47, <https://doi.org/10.1016/j.tig.2021.06.005>.

⁹Trudy F. C. Mackay and Wen Huang, “Charting the Genotype–Phenotype Map: Lessons from the *Drosophila Melanogaster* Genetic Reference Panel,” *WIREs Developmental Biology* 7, no. 1 (2018): e289, <https://doi.org/10.1002/wdev.289>.

¹⁰Michael C. Saul et al., “High-Diversity Mouse Populations for Complex Traits,” *Trends in Genetics* 35, no. 7 (July 1, 2019): 501–14, <https://doi.org/10.1016/j.tig.2019.04.008>.

¹¹David W. Threadgill et al., “The Collaborative Cross: A Recombinant Inbred Mouse Population for the Systems Genetic Era,” *ILAR Journal* 52, no. 1 (January 1, 2011): 24–31, <https://doi.org/10.1093/ilar.52.1.24>.

¹²Karen L Svenson et al., “High-Resolution Genetic Mapping Using the Mouse Diversity Outbred Population,” *Genetics* 190, no. 2 (February 1, 2012): 437–47, <https://doi.org/10.1534/genetics.111.132597>.

¹³Jeremy L. Peirce et al., “A New Set of BXD Recombinant Inbred Lines from Advanced Intercross Populations in Mice,” *BMC Genetics* 5, no. 1 (April 29, 2004): 7, <https://doi.org/10.1186/1471-2156-5-7>.

¹⁴Joachim Wittbrodt, Akihiro Shima, and Manfred Schartl, “Medaka — a Model Organism from the Far East,” *Nature Reviews Genetics* 3, no. 1, 1 (January 2002): 53–64, <https://doi.org/10.1038/nrg704>.

¹⁵Mikhail Spivakov et al., “Genomic and Phenotypic Characterization of a Wild Medaka Population: Towards the Establishment of an Isogenic Population Genetic Resource in Fish,” *G3 Genes|Genomes|Genetics* 4, no. 3 (March 1, 2014): 433–45, <https://doi.org/10.1534/g3.113.008722>.

vertebrates – resilient to inbreeding from the wild.

Since 2010, the Birney Group at EMBL-EBI, in collaboration with the Wittbrodt Group at COS, University of Heidelberg and the Loosli Group at the Karlsruhe Institute of Technology (KIT), have been working to establish the world’s first panel of vertebrate inbred strains – now known as the Medaka Inbred Kiyosu-Karlsruhe Panel (**MIKK panel**). The MIKK Panel was bred from a wild population caught near Kiyosu in Southern Japan, and now comprises 80 inbred, near-isogenic “lines”.¹⁶

The MIKK Panel was created to map genetic variants associated with quantitative traits at a high resolution, and to explore the interactions between those variants and any environmental variables of interest. The purpose of the companion papers Fitzgerald et al.¹⁷ and Leger et al.¹⁸ was to introduce the MIKK panel to the scientific community, and describe the genetic characteristics of the MIKK panel that would make it a useful resource for other researchers who wish to explore the genetics of quantitative traits in vertebrates. My contributions to these papers involved visualising the inbreeding trajectory of the panel (Chapter 2.2.2), exploring the evolutionary history of the MIKK panel’s founding population (Chapter 2.2.3), measuring the levels of homozygosity across the panel (Chapter 2.2.4), assessing its allele-frequency distribution and rate of linkage disequilibrium (LD) decay (Chapter 2.2.5), and characterising the structural variants present in a smaller sample of lines using Oxford Nanopore long-read sequencing data (Chapter 2.3).

¹⁶Fitzgerald et al., “The Medaka Inbred Kiyosu-Karlsruhe (MIKK) Panel.”

¹⁷

¹⁸“Genomic Variations and Epigenomic Landscape of the Medaka Inbred Kiyosu-Karlsruhe (MIKK) Panel.”

2.2 Genomic characterisation of the MIKK panel

2.2.1 MIKK panel DNA sequence dataset

For the preparation of Fitzgerald et al.¹⁹, 79 of the 80 extant MIKK panel lines – together with several wild Kiyosu samples and individuals from the established *iCab* medaka strain – had their DNA sequenced from brain samples using Illumina short-read sequencing technology. Tomas Fitzgerald from the Birney Group at EMBL-EBI then aligned these sequences to the *HdrR* medaka reference and called variants to produce the **MIKK Illumina call set** in the form of a .vcf file containing single nucleotide polymorphism (SNP) and small insertion-deletion (INDEL) calls for each line. To avoid allele frequency biases introduced by the 16 pairs/triplets of “sibling lines” (see 2.2.2), I removed each pair’s arbitrarily-labelled second sibling line from the variant call set, leaving 63 MIKK panel lines (**MIKK non-sibling call set**), and used only those calls for the analyses in Chapters 2.2.4 and 2.2.5.

For the preparation of Leger et al.²⁰, 12 MIKK panel lines had their DNA sequenced from brain samples using Oxford Nanopore Technologies (ONT) long-read sequencing technology. Adrien Leger from the Birney Group at EMBL-EBI then aligned these sequences to the *HdrR* medaka reference, and called variants to produce the **MIKK ONT call set** in the form of a .vcf file containing structural variants calls for each line with tags for insertions (INS), deletions (DEL), duplications (SUP), inversions (INV) and translocations (TRA). The work described below used these variant call sets as the primary datasets.

¹⁹“The Medaka Inbred Kiyosu-Karlsruhe (MIKK) Panel.”

²⁰“Genomic Variations and Epigenomic Landscape of the Medaka Inbred Kiyosu-Karlsruhe (MIKK) Panel.”

2.2.2 Assessing the inbreeding trajectory of the MIKK panel

The MIKK panel was bred from a wild population of medaka found in the Kiyosu area near Toyohashi, Aichi Prefecture, in southern Japan.²¹ From this wild population, the Loosli Group at KIT set up random crosses of single mating pairs to create 115 ‘founder families’. For each founder family, they then set up between two and five single full-sibling-pair inbreeding crosses, which resulted in 253 F1 lines. Lines derived from the same founder family are referred to as ‘sibling lines’. Over the course of the next eight generations of inbreeding, they used only one mating pair per line. I generated Fig. 2.1A and B from the inbreeding data provided by the Loosli Group. Fig. 2.1A shows the number of lines that survived over the course of the first 14 generations of the inbreeding program, and the various causes for the termination of other lines. Fig. 2.1B shows the average fecundity levels of the surviving lines at generation F16. In addition, the Birney Group at EMBL-EBI generated morphometric data for the MIKK panel lines to demonstrate the distribution of physical phenotypes across the MIKK panel. I used this data on relative eye diameters to generate Fig. 2.1C.

2.2.3 Introgression with northern Japanese and Korean medaka populations

To explore the evolutionary history of the MIKK panel’s founding population, we sought to determine whether there was evidence of introgression between that southern Japanese population, and northern Japanese and Korean medaka populations. To this end, I used the 50-fish multiple alignment from Ensembl release 102 to obtain the aligned genome sequences for the established medaka inbred lines *HdrR* (southern Japan), *HNI* (northern Japan), and *HSOK* (Korea), as well as the most recent common ancestor of all three

²¹Spivakov et al., “Genomic and Phenotypic Characterization of a Wild Medaka Population.”

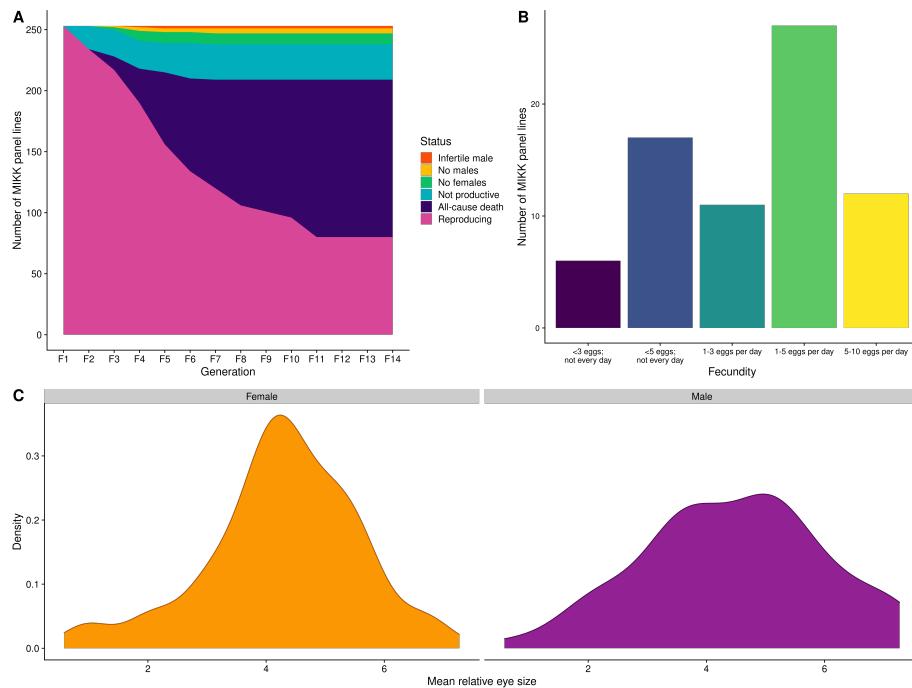


Figure 2.1: Inbreeding, fecundity and eye size in the MIKK panel lines. **A:** Status of all MIKK panel lines during the first 14 generations of inbreeding, showing cause of death for non-extant lines. **B:** Average fecundity of MIKK panel lines in generation F16, as measured during peak egg production in July 2020. **C:** Distribution of mean relative eye size for female and male medaka across all MIKK panel lines.

strains.²² Using the phylogenetic tree provided with the dataset, and the *ape* R package,²³ I identified the most recent common ancestor of those three strains. For each locus with a non-missing base for *HdrR*, I assigned the allele in that ancestral sequence as the ‘ancestral’ allele, and the alternative allele as the ‘derived’ allele, and then combined that dataset with the MIKK Illumina call set and variant calls for the southern Japanese *iCab* strain (see 2.2.1).

I then carried out an ABBA BABA analysis to calculate a modified ‘ad-mixture proportion’ statistic \hat{f}_d ²⁴ as a measure of the proportion of shared genome in 500-kb sliding windows between the MIKK panel and either *iCab*, *HNI*, or *HSOK* (Fig. 2.2), using the scripts provided by the first author of Martin, Davey, and Jiggins²⁵ on their GitHub page.²⁶

Based on the genome-wide mean \hat{f}_d , the MIKK panel shares approximately 25% of its genome with *iCab*, 9% with *HNI*, and 12% with *HSOK*. These results provide evidence that the MIKK panel’s originating population has more recently introgressed with medaka from Korea than with medaka from northern Japan. This supports the findings in Spivakov et al.²⁷, where the authors found little evidence of significant interbreeding between southern and northern Japanese medaka since the populations diverged. Although the proportional difference between *HNI* and *HSOK* is small, this further supports the general finding that northern and southern Japanese medaka strains show low levels of interbreeding that may be a result of geographical isolation or genome divergence.²⁸

²²“Index of /Pub/Release-102/Emf/Ensembl-Compara/Multiple_alignments/50_fish.epo/,” accessed January 25, 2022, https://ftp.ensembl.org/pub/release-102/emf/ensembl-compara/multiple_alignments/50_fish.epo/.

²³Emmanuel Paradis and Klaus Schliep, “Ape 5.0: An Environment for Modern Phylogenetics and Evolutionary Analyses in R,” *Bioinformatics* 35, no. 3 (February 1, 2019): 526–28, <https://doi.org/10.1093/bioinformatics/bty633>.

²⁴Simon H. Martin, John W. Davey, and Chris D. Jiggins, “Evaluating the Use of ABBA–BABA Statistics to Locate Introgressed Loci,” *Molecular Biology and Evolution* 32, no. 1 (January 1, 2015): 244–57, <https://doi.org/10.1093/molbev/msu269>.

²⁵Simon martin, *Simonhmartin/Genomics_general*, 2022, https://github.com/simonhmartin/genomics_general.

²⁷“Genomic and Phenotypic Characterization of a Wild Medaka Population.”

²⁸Takafumi Katsumura et al., “Medaka Population Genome Structure and Demographic History Described via Genotyping-by-Sequencing,” *G3*

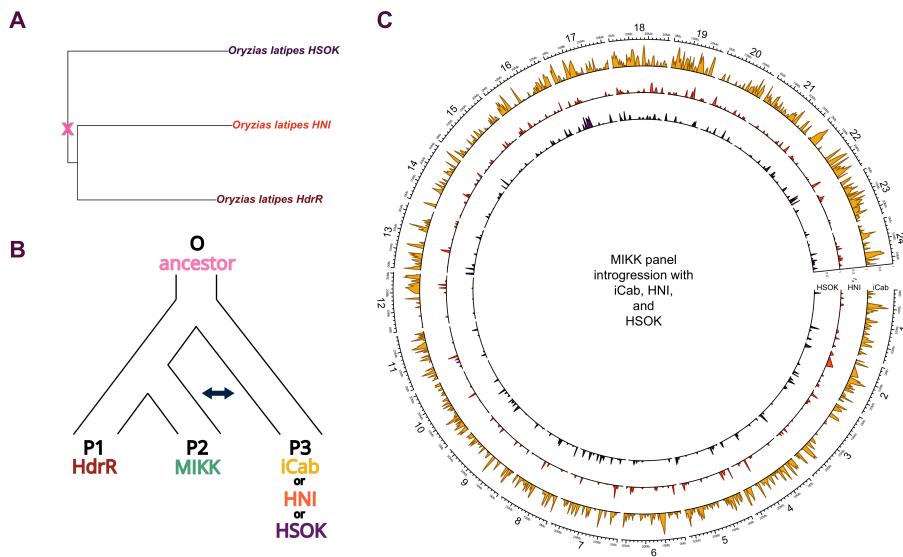


Figure 2.2: Figure 2: ABBA-BABA analysis. **A.** Phylogenetic tree generated from the Ensembl release 102 50-fish multiple alignment, showing only the medaka lines used in the ABBA-BABA analysis. **B.** Schema of the comparisons carried out in the ABBA-BABA analysis. **C.** Circos plot comparing introgression (\hat{f}_d) between the MIKK panel and either *iCab* (yellow), *HNI* (orange), or *HSOK* (purple), calculated within 500-kb sliding windows using a minimum of 250 SNPs per window.

2.2.4 Nucleotide diversity

As a means of assessing genetic diversity in the MIKK panel, I calculated nucleotide diversity ($\hat{\pi}$) within 500-kb non-overlapping windows across the genome of the 63 lines in the MIKK non-sibling call set (see 2.2.1), and compared this to the nucleotide diversity in 7 wild medaka from the same Kiyosu population from which the MIKK panel was derived. Mean and median nucleotide diversity in both the MIKK panel and wild Kiyosu medaka were close to 0, and slightly higher in the MIKK panel (mean: MIKK = 0.0038, wild = 0.0037; median: MIKK = 0.0033, wild = 0.0031). The patterns of varying nucleotide diversity across the genome are shared between the MIKK panel and wild Kiyosu medaka, where regions with high levels of repeat content tend to have higher nucleotide diversity ($r = 0.386$, $p < 0.001$) (Fig. 2.3). I also calculated $\hat{\pi}$ for each line individually, and as expected, levels of $\hat{\pi}$ around the (XX/XY) sex determination region of 1:-16-17 Mb are elevated in all lines relative to the consistently low levels found in most other chromosomes.

The higher level of $\hat{\pi}$ observed within specific regions on several chromosomes – such as chromosomes 2, 11, and 18 – correspond closely to the regions we identified as containing large (>250 kb) inversions that appear to be shared across at least some of the MIKK panel (Fig. 2.4). These regions are also enriched for large deletions and duplications.²⁹ Inversions cause permanent heterozygosity,³⁰ and duplications and deletions may have increased the density of called SNPs in these regions,³¹ so the observed depressions in homozygosity at these loci may be the result of such large structural variants that are present in the MIKK panel’s genomes.

Overall, this analysis confirms that the MIKK panel shows similar

Genes|Genomes|Genetics 9, no. 1 (January 1, 2019): 217–28, <https://doi.org/10.1534/g3.118.200779>.

²⁹Leger et al., “Genomic Variations and Epigenomic Landscape of the Medaka Inbred Kiyosu-Karlsruhe (MIKK) Panel.”

³⁰Ary A. Hoffmann, Carla M. Sgr’o, and Andrew R. Weeks, “Chromosomal Inversion Polymorphisms and Adaptation,” *Trends in Ecology & Evolution* 19, no. 9 (September 1, 2004): 482–88, <https://doi.org/10.1016/j.tree.2004.06.013>.

³¹David Fredman et al., “Complex SNP-related Sequence Variation in Segmental Genome Duplications,” *Nature Genetics* 36, no. 8, 8 (August 2004): 861–66, <https://doi.org/10.1038/ng1401>.

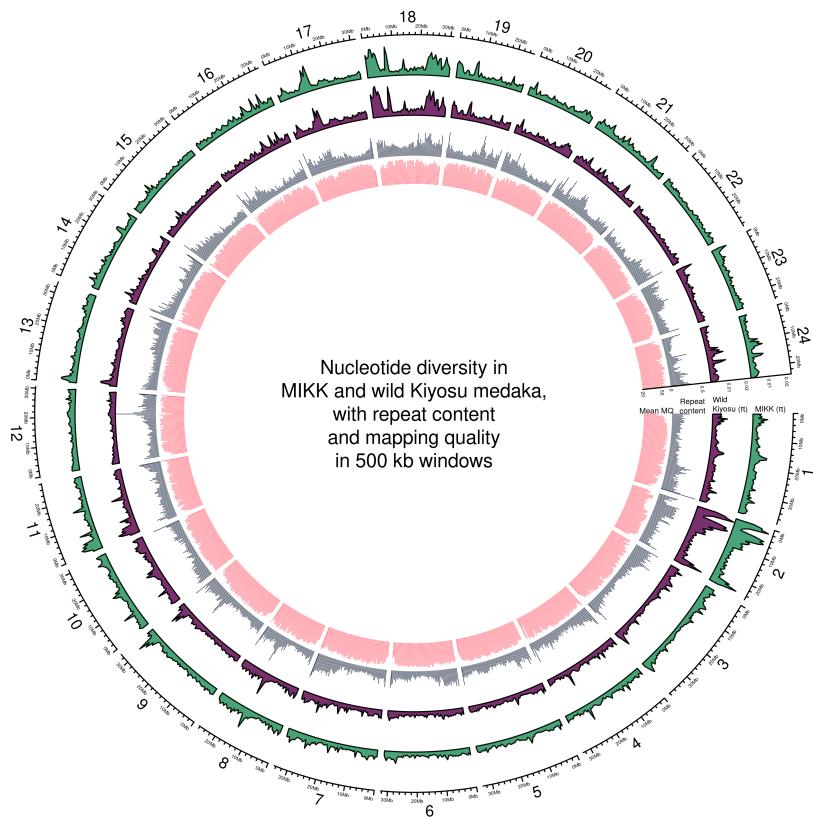


Figure 2.3: Circos plot with nucleotide diversity ($\hat{\pi}$) calculated within 500-kb non-overlapping windows for 63 non-sibling lines from the MIKK panel (green) and 7 wild Kiyosu medaka samples from the same originating population (purple); proportion of sequence classified as repeats by RepeatMasker (blue); and mean mapping quality (pink).

levels of homozygosity compared to classical laboratory inbred medaka strains, and possesses a strong increase in isogenic genotypes compared to wild medaka from the original wild population.

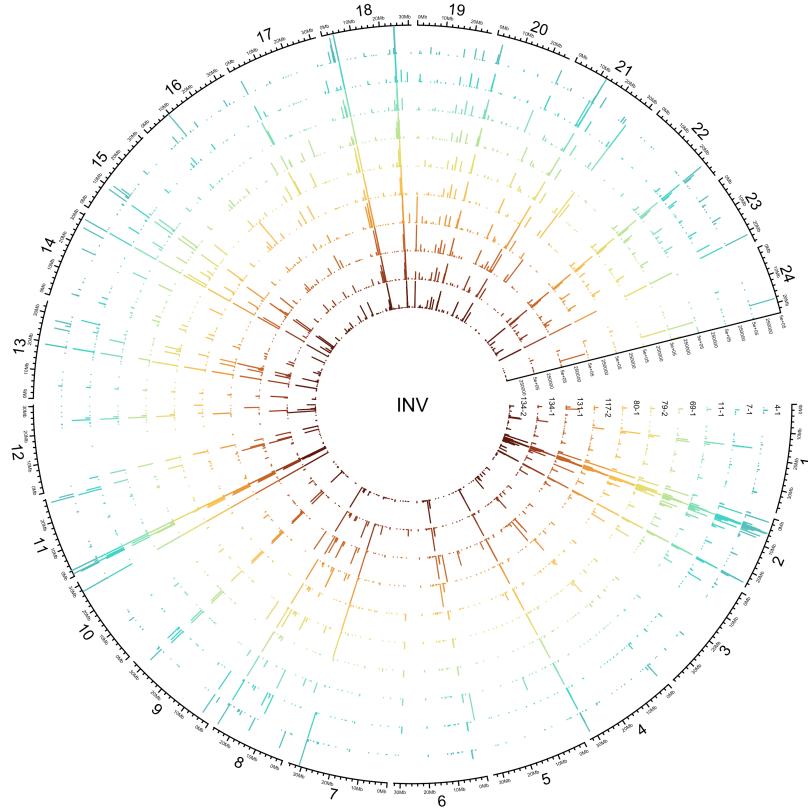


Figure 2.4: Inversions identified in 9 MIKK panel lines using a combination of Oxford Nanopore Technologies long-read and Illumina short-read sequences (see Chapter 2.8 below).

2.2.5 LD decay

I analysed the MIKK panel's allele frequency distribution and linkage disequilibrium (LD) structure to assess their likely effects on genetic mapping. To remove allele-frequency biases introduced by the

presence of sibling lines in the MIKK panel, I used only the MIKK non-sibling call set (see Chapter 2.2.1).

To assess how accurately one may be able to map genetic variants using the MIKK panel relative to a human dataset, I compared the MIKK panel's minor allele frequency (MAF) distribution and LD structure against that of the 2,504 humans in the 1KG Phase 3 release.³² To prepare the “1KG call set”, I first downloaded the .vcf files for each autosome from the project's FTP site (<ftp://ftp.1000genomes.ebi.ac.uk/voll/ftp/release/20130502/>), then merged them into a single VCF using GATK.³³ I then used PLINK³⁴ to calculate the minor allele frequencies for all non-missing, biallelic SNPs in both the MIKK non-sibling and 1KG call sets (N SNPs = 16,395,558 and 81,042,381 respectively) (Fig. 2.5A). As expected, the 1KG and MIKK panel calls are similarly enriched for low-frequency variants, albeit to a lesser extent in the MIKK panel, which is likely due to its smaller sample size.

To determine the rate of LD decay in the MIKK panel and compare it to that in the 1KG sample, for both the MIKK non-sibling and 1KG call sets, I used PLINK to compute r^2 on each autosome for all pairs of non-missing, biallelic SNPs with MAF > 0.10 within 10 kb of one another (for 1KG and the MIKK panel respectively ~ 5.5M and ~ 3M SNPs, with a total number of pairwise r^2 observations of 204,152,922 and 146,785,673). I then grouped the r^2 observations for each pair of SNPs based on their distance from one another into non-overlapping bins of 100 bp in length, and calculated the mean r^2 in each of those bins to generate Fig. 2.5B using the mean r^2 and left boundary of each bin.

Based on the 1KG calls under these parameters, LD decays in humans to a mean r^2 of around 0.2-0.35 at a distance of 10 kb, whereas the

³²“A Global Reference for Human Genetic Variation,” *Nature* 526, no. 7571 (2015): 68–74, <https://doi.org/10.1038/nature15393>.

³³Aaron McKenna et al., “The Genome Analysis Toolkit: A MapReduce Framework for Analyzing Next-Generation DNA Sequencing Data,” *Genome Research* 20, no. 9 (January 9, 2010): 1297–1303, <https://doi.org/10.1101/gr.107524.110>.

³⁴Christopher C Chang et al., “Second-Generation PLINK: Rising to the Challenge of Larger and Richer Datasets,” *GigaScience* 4, no. 1 (December 2015): 7, <https://doi.org/10.1186/s13742-015-0047-8>; Shaun M Purcell and Christopher C Chang, *PLINK* 1.9, n.d., www.cog-genomics.org/plink/1.9/.

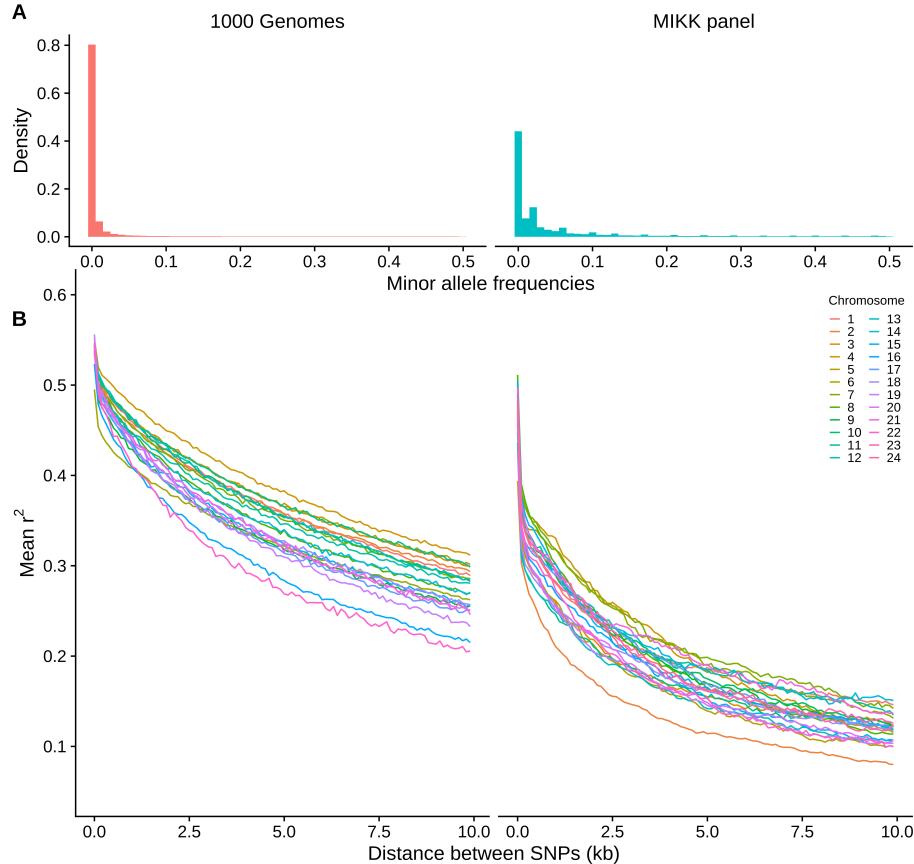


Figure 2.5: Minor allele frequency distributions and LD decay for biallelic, non-missing SNPs in the 1000 Genomes Phase 3 variant calls ($N = 2,504$) (1KG), and the MIKK panel Illumina-based calls excluding one of each pair of sibling lines ($N = 63$), across all autosomes (1KG: chrs 1-22; MIKK: chrs 1-24). **A:** Histogram of allele frequencies in the 1KG and MIKK panel calls. **B:** LD decay for each autosome, calculated by taking the mean r^2 of pairs of SNPs with MAF > 0.1 within non-overlapping 100 bp windows of distance from one another, up to a maximum of 10 kb. LD decays faster on chromosome 2 for the MIKK panel due to its higher recombination rate.

MIKK panel reaches this level within 1 kb, with a mean r^2 of 0.3-0.4 at a distance of ~100 bp. This implies that when a causal variant is present in at least two lines in the MIKK panel, one may be able to map causal variants at a higher resolution than in humans. We note that LD decays faster in chromosome 2 of the MIKK panel relative to the other chromosomes. This suggests that it has a much higher recombination rate, which is consistent with the linkage map described in Kiyoshi Naruse et al.³⁵, showing a higher genetic distance per Mb for this chromosome. This higher recombination rate in chromosome 2 may in turn be caused by its relatively high proportion of repeat content (Fig. 2.6).

2.3 Structural variation in the MIKK panel

As an alternative to the variation pangenome approach described in Leger et al.³⁶, I explored the structural variants (SVs) present in 9 of the MIKK panel lines in a reference-anchored manner, similar to many human studies. Differences in SVs between panel lines is another important class of genetic variation that could cause or contribute to significant phenotypic differences. Here we used ONT data obtained for 9 of the 12 selected lines allowing us to characterise larger SVs in the MIKK panel and to create a more extensive picture of genomic rearrangements compared to available medaka reference genomes. Adrien Leger from the Birney Group at EMBL-EBI first called structural variants using only the ONT long reads, producing a set of structural variants classified into five types: deletions (DEL), insertions (INS), translocations (TRA), duplications (DUP) and inversions (INV). I then “polished” the called DEL and INS variants with Illumina short reads to improve their accuracy. The polishing process filtered out 7.4% of DEL and 12.8% of INS variants, and adjusted the breakpoints (i.e. start and end positions) for 75-77% of DEL

³⁵“A Detailed Linkage Map of Medaka, *Oryzias Latipes*: Comparative Genomics and Genome Evolution,” *Genetics* 154, no. 4 (April 1, 2000): 1773–84, <https://www.genetics.org/content/154/4/1773>.

³⁶“Genomic Variations and Epigenomic Landscape of the Medaka Inbred Kiyosu-Karlsruhe (MIKK) Panel.”

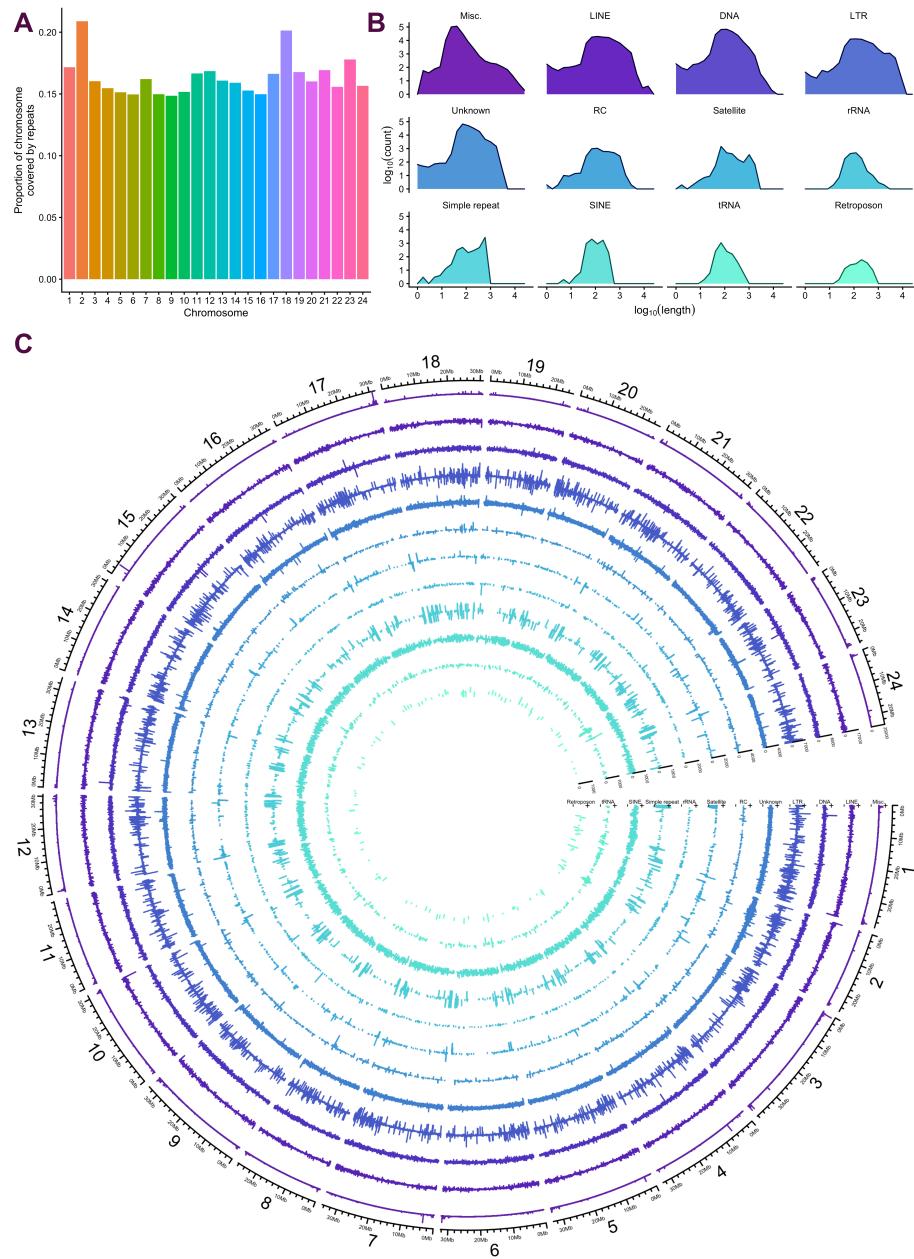


Figure 2.6: Repeat content in the *HdrR* genome based on RepeatMasker results obtained by Jack Monahan. A. Proportion of repeat content per-chromosome. B. \log_{10} of repeat lengths and counts per repeat class. “Misc” includes all repeats assigned to their own specific class, for example “(GAG) n ” or “(GATCCA) n ”. C. Circos plot showing repeat length (radial axes) by locus (angular axis) and repeat class (track).

and INS variants in each sample by a mean of 23 bp for the start position, and 33 bp for the end position. This process produced a total of 143,326 filtered SVs.

The 9 “polished” samples contained a mean per-sample count of approximately 37K DEL variants (12% singletons), 29.5K INS variants (14%), 3.5K TRA variants (9%), 2.5K DUP (7%) and 600 INV (7%) (Fig. 2.7D). DEL variants were up to 494 kb in length, with 90% of unique DEL variants shorter than 3.8 kb. INS variants were only up to 18.8 kb in length, with 90% of unique INS variants shorter than 2 kb. DUP and INV variants tended to be longer, with a mean length of 19 and 70.5 kb respectively (Fig. 2.7A). Fig. 2.7E shows the per-sample distribution of DEL variants across the genome. Most large DEL variants over 250 kb in length were common among the MIKK panel lines. A number of large DEL variants appear to have accumulated within the 0-10 Mb region of chromosome 2, which is enriched for repeats in the *HdrR* reference genome (Fig. 2.6).

SVs were generally enriched in regions covered by repeats. While only 16% of bases in the *HdrR* reference were classified as repeats (irrespective of strand), those bases overlapped with 72% of DEL, 63% of DUP, 81% of INV and 35% of TRA variant regions. However, repeat bases only overlapped with 21% of INS variants. We also assessed each SV’s probability of being loss-of-function (pLI)³⁷ by calculating the logarithm of odds (LOD) for the pLI scores of all genes overlapping the variant (Fig. 2.7B,C). 80,857 out of 134,088 DEL, INS, DUP and INV variants overlapped at least one gene, and 9% of those had a score greater than 10, indicating a high probability that the SV would cause a loss of function. Two INS variants on chr2 had an outlying LOD score of 57 as a result of overlapping medaka gene ENSORLG00000003411, which has a pLI score of 1 – the highest intolerance to variants causing a loss of function. This gene is homologous with human genes *SCN1A*, *SCN2A* and *SCN3A*, which encode sodium channels and have been associated with neuronal and sleep disorders. We did not find evidence that longer SVs tended to have

³⁷Monkol Lek et al., “Analysis of Protein-Coding Genetic Variation in 60,706 Humans,” *Nature* 536, no. 7616, 7616 (August 2016): 285–91, <https://doi.org/10.1038/nature19057>.

a higher probability of causing a loss of function (**Fig. 2.7B**).

We compared these polished INS and DEL calls with the high-quality graph-based alternative paths and large-scale deletions, respectively (see section titled *Novel genetic sequences and large-scale insertions and deletions in the MIKK panel* in Leger et al.³⁸). We found that 2 of the 19 regions covered by graph-based alternative paths, and 4 of the 16 regions covered by graph-based deletions, had no SVs that overlapped those regions at all, which suggests they would have been missed entirely when using a reference-anchored approach alone.

With the exception of one alternative path on chromosome 20, the alternative paths were not captured by INS variants, which only covered up to 63% of the bases in each region, and in many cases substantially less. On the other hand, for 8 of the 16 graph-based deletions, the DEL variants covered at least 85% of the bases in those regions. The other 8 graph-based deletions were either not at all covered by DEL variants, or only slightly. This indicates that the reference-based approach is better at detecting large-scale deletions than alternative paths (“insertions”), but still misses around half of such variants relative to the graph-based approach.

2.4 Conclusions

Taken together, these analyses show that the MIKK panel is highly homozygous, with LD characteristics that will favour high-resolution genetic mapping relative to humans. In the future, the SV analysis performed on a subset of the MIKK panel will be expanded across the entire panel, which will permit the inclusion of both large- and small-scale variants in genetic linkage studies. I proceeded to use the MIKK panel to analyse bold/shy behaviours, as I describe in Chapter 4, with a view to carrying out an F2-cross linkage study to identify genetic variants associated with differences in the behaviours of an individual, and the extent to which they transmit those behaviours to their social companions. However,

³⁸“Genomic Variations and Epigenomic Landscape of the Medaka Inbred Kiyosu-Karlsruhe (MIKK) Panel.”

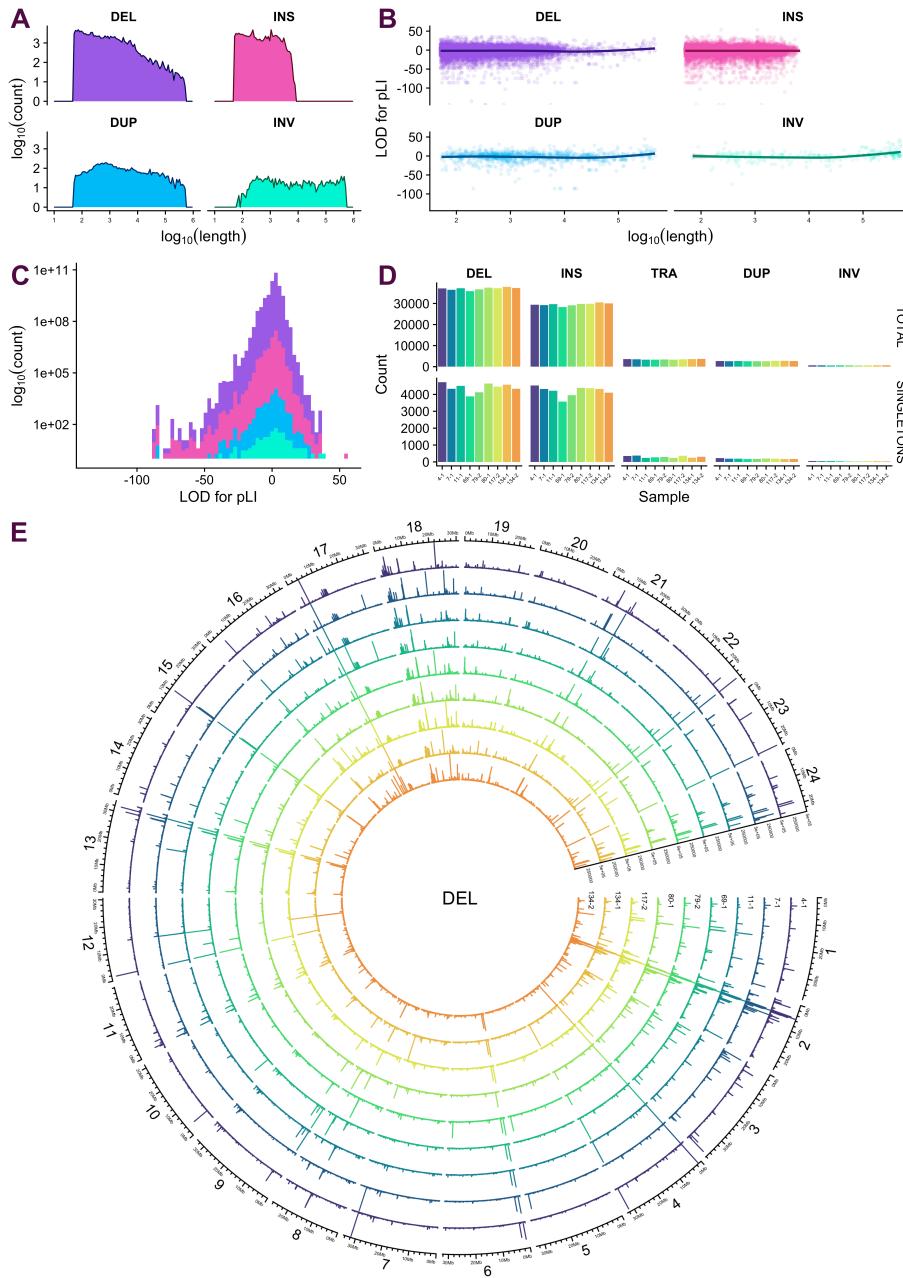


Figure 2.7: Polished SVs in 9 MIKK panel lines sequenced with ONT. DEL: deletion; INS: insertion; TRA: translocation; DUP: duplication; INV: inversion. A. Aggregate \log_{10} counts and lengths of distinct SVs by type, excluding TRA. B. pLI LOD scores in distinct SVs by SV type. C. Histogram of LOD scores by SV type. D. Total and singleton counts of SV types per sample. E. Circos plot showing per-sample distribution and lengths of DEL variants across the genome.

before carrying out this study, we first ran a “pilot” study on 5 previously-established inbred lines to validate our behavioural assay. This is the subject of the following chapter.

Chapter 3

Classification of bold/shy behaviours in 5 inbred medaka lines

Chapter 4

Bold/shy behaviours in the MIKK panel

Chapter 5

Variation in the frequency of trait-associated alleles across global human populations

5.1 Background

Humans have long sought to use genetic information to predict an individual's likely value for a given trait, in our own species and for other organisms (Chapter 1). As seen in previous chapters, an individual's phenotypic value at a given point in time is the product of complex interactions between their genome and their environment, beginning from embryonic development and continuing throughout their lifetimes.

It is now clear that “complex” traits such as height, intelligence, and behaviour are highly polygenic, meaning that they are genetically influenced by hundreds or thousands of genetic variants, each exerting a small effect in one or the other direction along the trait’s

spectrum.¹

A richer understanding of the cumulative effect of genetic variants on any trait allows for the prediction of the value that an individual is most likely to have for that trait. Of all human traits, diseases are particularly salient; in 2018, the global healthcare industry was valued at US\$8 trillion, and predicted to increase to US\$12 trillion by 2022.² This strong financial imperative complements the moral imperative to reduce suffering, together driving the question of how to use genetic information to improve human health.

Recent technological developments have made it possible to sequence human genomes at scale, and it is thought that by combining detailed genetic information with other environmental and phenotypic information (such as lifestyle or clinical factors), clinicians could move towards the practice of “precision medicine”, where interventions could be tailored to their patients’ unique risk profiles.³ The use of genetic information to predict individuals’ values for a trait of interest entails the construction of metrics known as “polygenic scores” (PGS). When the trait is a disease, PGS is commonly known as polygenic risk scores (PRS), or genetic risk profiling, but I will use the term PGS to encompass both disease and non-disease traits.

¹G. Sella and N. Barton, “Thinking About the Evolution of Complex Traits in the Era of Genome-Wide Association Studies.” *Annual Review of Genomics and Human Genetics*, 2019, <https://doi.org/10.1146/annurev-genom-083115-022316>.

²“The \$11.9 Trillion Global Healthcare Market: Key Opportunities & Strategies (2014-2022) - ResearchAndMarkets.com,” June 25, 2019, <https://www.businesswire.com/news/home/20190625005862/en/The-11.9-Trillion-Global-Healthcare-Market-Key-Opportunities-Strategies-2014-2022---ResearchAndMarkets.com>.

³Naomi R. Wray, Michael E. Goddard, and Peter M. Visscher, “Prediction of Individual Genetic Risk to Disease from Genome-Wide Association Studies,” *Genome Research* 17, no. 10 (January 10, 2007): 1520–28, <https://doi.org/10.1101/gr.6665407>.

5.1.1 Polygenic Scores (PGS) and Genome-Wide Association Studies (GWAS)

5.1.1.1 PGS

PGS using genetic information alone show modest yet reliable accuracy for the prediction of complex traits:⁴ the correlations between PGS and the trait value as measured by R^2 have reached 0.24 for height,⁵ and 0.12-0.16 for educational attainment.⁶ For a variety of health-related traits, PGS improve predictions beyond non-genetic clinical models – these traits include blood pressure, breast cancer,⁷ prostate cancer,⁸ and type I diabetes.⁹

PGS scores can further be combined with lifestyle and clinical factors to improve the accuracy of predictions for diseases such as cardiovascular disease.¹⁰

⁴Alicia R. Martin, Masahiro Kanai, et al., “Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities,” *Nature Genetics* 51, no. 4, 4 (April 2019): 584–91, <https://doi.org/10.1038/s41588-019-0379-x>.

⁵Loic Yengo et al., “Meta-Analysis of Genome-Wide Association Studies for Height and Body Mass Index in []700000 Individuals of European Ancestry,” *Human Molecular Genetics* 27, no. 20 (October 15, 2018): 3641–49, <https://doi.org/10.1093/hmg/ddy271>.

⁶Aysu Okbay et al., “Polygenic Prediction of Educational Attainment Within and Between Families from Genome-Wide Association Analyses in 3 Million Individuals,” *Nature Genetics*, March 31, 2022, 1–13, <https://doi.org/10.1038/s41588-022-01016-z>.

⁷Paige Maas et al., “Breast Cancer Risk From Modifiable and Nonmodifiable Risk Factors Among White Women in the United States,” *JAMA Oncology* 2, no. 10 (October 1, 2016): 1295–1302, <https://doi.org/10.1001/jamaoncol.2016.1025>.

⁸Fredrick R. Schumacher et al., “Association Analyses of More Than 140,000 Men Identify 63 New Prostate Cancer Susceptibility Loci,” *Nature Genetics* 50, no. 7, 7 (July 2018): 928–36, <https://doi.org/10.1038/s41588-018-0142-8>.

⁹Seth A. Sharp et al., “Development and Standardization of an Improved Type 1 Diabetes Genetic Risk Score for Use in Newborn Screening and Incident Diagnosis,” *Diabetes Care* 42, no. 2 (January 11, 2019): 200–207, <https://doi.org/10.2337/dcl8-1785>.

¹⁰Amit V. Khera et al., “Genome-Wide Polygenic Scores for Common Diseases Identify Individuals with Risk Equivalent to Monogenic Mutations,” *Nature Genetics* 50, no. 9, 9 (September 2018): 1219–24, <https://doi.org/10.1038/s41588-018-0188-z>; Iftikhar J. Kullo et al., “Incorporating a Genetic Risk Score Into Coronary Heart Disease Risk Estimates,” *Circulation* 133, no. 12 (March 22, 2016): 1181–88, <https://doi.org/10.1161/CIRCULATIONAHA.115.020109>; Pradeep Natarajan et al., “Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prevention Setting,” *Circulation* 135, no. 22 (May 30, 2017): 2091–101, <https://doi.org/10.1161/CIRCULATIONAHA.116.024436>; Martine Paquette et al., “Polygenic Risk Score Predicts Prevalence of Cardiovascular Disease in Patients with Familial Hypercholesterolemia,” *Journal of Clinical Lipidology* 11, no. 3 (May 1, 2017): 725–732.e5, <https://doi.org/10.1016/j.jacl.2017.03.019>; Emmi Tikkannen et al., “Genetic Risk Prediction and a 2-Stage Risk Screening Strategy

Beyond trait prediction, PGS have also been harnessed by evolutionary biologists to test whether a set of causal variants are evolving across populations or over time. Jeremy J Berg et al.¹¹ and Michael D Edge and Graham Coop¹² found that this tends to occur through small, coordinated shifts in their allele frequencies.

5.1.1.2 GWAS

PGS are calculated for an individual by summing trait-associated alleles identified by genome-wide association studies (**GWAS**), as weighted by the alleles' effect sizes.¹³ GWAS aim to identify genetic variants associated with traits by comparing the allele frequencies of individuals who share similar ancestries, but differ in the trait in question.¹⁴ As of 2021, over 5,700 GWAS have been performed for more than 3,830 traits.¹⁵

However, most GWAS have been performed with individuals of European ancestry, despite only constituting 16% of the present global population. Although the proportion of participants in GWAS from a non-European background increased from 4% in 2009 to 16 % in 2016),¹⁶ as of 2019, 79% of all GWAS participants recorded in the GWAS Catalog were of European ancestry, and the proportion of non-European individuals has remained the same or reduced since late 2014.¹⁷ This bias extends to PGS studies, where as of 2019, only 67% of them included only participants of European ancestry, with

for Coronary Heart Disease," *Arteriosclerosis, Thrombosis, and Vascular Biology* 38, no. 9 (September 2018): 2261–66, <https://doi.org/10.1161/ATVBAHA.112.301120>.

¹¹"Reduced Signal for Polygenic Adaptation of Height in UK Biobank," ed. Magnus Nordborg et al., *eLife* 8 (March 21, 2019): e39725, <https://doi.org/10.7554/eLife.39725>.

¹²"Reconstructing the History of Polygenic Scores Using Coalescent Trees," *Genetics* 211, no. 1 (January 1, 2019): 235–62, <https://doi.org/10.1534/genetics.118.301687>.

¹³L. Duncan et al., "Analysis of Polygenic Risk Score Usage and Performance in Diverse Human Populations," *Nature Communications* 10, no. 1, 1 (July 25, 2019): 3328, <https://doi.org/10.1038/s41467-019-11112-0>.

¹⁴Emil Uffelmann et al., "Genome-Wide Association Studies," *Nature Reviews Methods Primers* 1, no. 1, 1 (August 26, 2021): 1–21, <https://doi.org/10.1038/s43586-021-00056-9>.

¹⁵Uffelmann et al.

¹⁶Alice B. Popejoy and Stephanie M. Fullerton, "Genomics Is Failing on Diversity," *Nature* 538, no. 7624, 7624 (October 2016): 161–64, <https://doi.org/10.1038/538161a>.

¹⁷Martin, Kanai, et al., "Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities."

another 19% including only East Asian ancestry participants, and only 3.8% with cohorts of African, Hispanic, or Indigenous ancestry.¹⁸

It is therefore unsurprising that PGS scores are far better at predicting disease risk in individuals of European ancestry than in those of non-European ancestry.¹⁹ For example, Martin, Gignoux, et al.²⁰ found that height was predicted to decrease with genetic distance from Europeans, despite robust evidence that West Africans are as tall as Europeans on average. Indeed, the predictive accuracy of PGS scores decays with genetic divergence of the GWAS “independent” or “test” sample from the “discovery” or “training” sample, as established in both humans,²¹ and livestock.²²

These differences in representation cause PGS scores to have a lower accuracy for individuals of non-European ancestry. For example, compared to PGS scores for those of European ancestry, PGS scores across multiple traits for individuals of African ancestry are ~64-78% less accurate,²³ and for individuals of South-Asian ancestry ~37% less accurate, and ~50% less accurate for individuals of East-Asian ancestry.²⁴

¹⁸Duncan et al., “Analysis of Polygenic Risk Score Usage and Performance in Diverse Human Populations.”

¹⁹Alicia R Martin, Christopher R Gignoux, et al., “Human Demographic History Impacts Genetic Risk Prediction Across Diverse Populations,” *The American Journal of Human Genetics* 100, no. 4 (2017): 635–49, <https://doi.org/10.1016/j.ajhg.2017.03.004>; Martin, Kanai, et al., “Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities.”

²⁰“Human Demographic History Impacts Genetic Risk Prediction Across Diverse Populations.”

²¹Martin, Gignoux, et al.; Martin, Kanai, et al., “Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities.”

²²Samuel A. Clark et al., “The Importance of Information on Relatives for the Prediction of Genomic Breeding Values and the Implications for the Makeup of Reference Data Sets in Livestock Breeding Schemes,” *Genetics Selection Evolution* 44, no. 1 (February 9, 2012): 4, <https://doi.org/10.1186/1297-9686-44-4>; David Habier et al., “The Impact of Genetic Relationship Information on Genomic Breeding Values in German Holstein Cattle,” *Genetics Selection Evolution* 42, no. 1 (February 19, 2010): 5, <https://doi.org/10.1186/1297-9686-42-5>; M. Pszczola et al., “Reliability of Direct Genomic Values for Animals with Different Relationships Within and to the Reference Population,” *Journal of Dairy Science* 95, no. 1 (January 1, 2012): 389–400, <https://doi.org/10.3168/jds.2011-4338>.

²³Duncan et al., “Analysis of Polygenic Risk Score Usage and Performance in Diverse Human Populations”; Martin, Kanai, et al., “Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities.”

²⁴Martin, Kanai, et al., “Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities.”

5.1.2 Contributors to PGS non-transferability

What explains this disparity in predictive value? A number of factors may be responsible, including:

1. The failure of GWAS to identify causal variants that either do not exist or are not identifiable within the “discovery” sample.²⁵
2. The sample populations may differ in linkage disequilibrium (LD) – the correlation structure of the genome – which would change the estimated effect sizes of the causal variants, even when the causal variants themselves are the same.²⁶
3. Allele frequencies of the causal variants, and the distribution of the effect sizes of the causal variants, may differ between populations.²⁷
4. The environments and demographies may differ between populations. These differences are often correlated with genetic divergence due to geography, making it difficult to determine whether the associations are driven by the differences between population in their genetics, or their environments.²⁸

The first three factors can degrade predictive performance even in the absence of biological and environmental differences. On the other hand, environmental and demographic differences can drive forces of natural selection can in turn drive differences in causal genetic architecture.²⁹

²⁵Martin, Kanai, et al.

²⁶Martin, Kanai, et al.

²⁷Martin, Gignoux, et al., “Human Demographic History Impacts Genetic Risk Prediction Across Diverse Populations”; Marco Scutari, Ian Mackay, and David Balding, “Using Genetic Distance to Infer the Accuracy of Genomic Prediction,” *PLOS Genetics* 12, no. 9 (September 2, 2016): e1006288, <https://doi.org/10.1371/journal.pgen.1006288>.

²⁸Martin, Kanai, et al., “Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities”; Sini Kerminen et al., “Geographic Variation and Bias in the Polygenic Scores of Complex Diseases and Traits in Finland,” *The American Journal of Human Genetics* 104, no. 6 (June 6, 2019): 1169–81, <https://doi.org/10.1016/j.ajhg.2019.05.001>.

²⁹Martin, Kanai, et al., “Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities.”

Differences in LD and allele frequencies between populations can explain 70-80% of the loss of PGS relative accuracy for traits like body mass index and type 2 diabetes.³⁰

I discuss each of these factors in turn

5.1.2.1 Failure to discover causal variants

The power to discover a causal variant through GWAS depends on the variant's effect size and frequency in the study population.³¹ That is to say, the stronger the variant's effect, or the more common it is, the more likely it is to be discovered. Rare variants tend to have stronger effect sizes,³² likely due to purifying selection,³³ and tend not to be shared across populations.³⁴

There are several issues that can affect the discoverability of causal variants through GWAS, including the technology used for genotyping, the selection of the cohort, and the necessary exclusion of genotypic outliers.

With respect to genotyping technologies, GWAS often use data from SNP microarrays. These do not sequence the whole genome, but rather a selection (from several hundred thousand to millions) of

³⁰Ying Wang et al., “Theoretical and Empirical Quantification of the Accuracy of Polygenic Scores in Ancestry Divergent Populations,” *Nature Communications* 11, no. 1, 1 (July 31, 2020): 3865, <https://doi.org/10.1038/s41467-020-17719-y>.

³¹Martin, Kanai, et al., “Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities”; P. C. Sham et al., “Power of Linkage Versus Association Analysis of Quantitative Traits, by Use of Variance-Components Models, for Sibship Data,” *The American Journal of Human Genetics* 66, no. 5 (May 1, 2000): 1616–30, <https://doi.org/10.1086/302891>.

³²Kyoko Watanabe et al., “A Global Overview of Pleiotropy and Genetic Architecture in Complex Traits,” *Nature Genetics* 51, no. 9, 9 (September 2019): 1339–48, <https://doi.org/10.1038/s41588-019-0481-0>.

³³Ju-Hyun Park et al., “Distribution of Allele Frequencies and Effect Sizes and Their Interrelationships for Common Genetic Susceptibility Variants,” *Proceedings of the National Academy of Sciences* 108, no. 44 (November 2011): 18026–31, <https://doi.org/10.1073/pnas.1114759108>.

³⁴Simon Gravel et al., “Demographic History and Rare Allele Sharing Among Human Populations,” *Proceedings of the National Academy of Sciences* 108, no. 29 (2011): 11983–88, <https://doi.org/10.1073/pnas.1019276108>; 1000 Genomes Project Consortium et al., “A Global Reference for Human Genetic Variation,” *Nature* 526, no. 7571 (2015): 68.

genetic markers intended to present common genomic variation,³⁵ which accordingly tend to neglect rare genetic variants.³⁶ To increase the density of genotypes, which would increase the likelihood of refining the association signal and identifying causal variants, researchers often “impute” variants that aren’t sequenced directly.³⁷ The imputation process involves “phasing” the study genotypes onto the genotypes of a “reference panel.”³⁸ However, if the reference panel does not sufficiently represent the populations in the study sample, they are likely to miss or incorrectly impute those genotypes.³⁹ This is particularly problematic for African populations, which are far more genetically diverse than European populations,⁴⁰ making it difficult to capture a sufficient range of variation.

The neglect of rare variants can be overcome by using next-generation sequencing technologies such as whole-genome sequencing (WGS) and whole-exome sequencing (WES); the former seeks to sequence the full genome, and the latter of only targets the coding regions of the genome. However, these methods are more expensive, although as their costs continue to decrease, their application in large-scale GWAS is likely to become more widespread.

Alignment issues

A second issue is the selection of GWAS cohorts, which can introduce selection and collider biases.⁴¹ For instance, the UK Biobank, which contains genetic and phenotypic data on 500,000 participants recruited between 2006 and 2010, tend to be older, female, healthier, and wealthier than non-participants.⁴²

³⁵Eleonora Porcu et al., “Genotype Imputation in Genome-Wide Association Studies,” *Current Protocols in Human Genetics* 78, no. 1 (2013): 1.25.1–14, <https://doi.org/10.1002/0471142905.hg0125s78>.

³⁶Uffelmann et al., “Genome-Wide Association Studies.”

³⁷Porcu et al., “Genotype Imputation in Genome-Wide Association Studies.”

³⁸Shane McCarthy et al., “A Reference Panel of 64,976 Haplotypes for Genotype Imputation,” *Nature Genetics* 48, no. 10, 10 (October 2016): 1279–83, <https://doi.org/10.1038/ng.3643>.

³⁹Martin, Kanai, et al., “Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities.”

⁴⁰Consortium et al., “A Global Reference for Human Genetic Variation.”

⁴¹Uffelmann et al., “Genome-Wide Association Studies.”

⁴²Anna Fry et al., “Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population,” *American Journal of Epidemiology* 186, no. 9 (November 1, 2017): 1026–34, <https://doi.org/10.1093/aje/kwx311>.

A third issue is the “quality control” step that is required during the GWAS process.⁴³ To avoid confounding from population stratification, which can lead to overestimated heritability and biased PGS, GWAS cohorts are filtered to include only those with similar ancestries – or relative genetic homogeneity – by clustering individuals through principal component analysis (PCA) of their genotypes. I elaborate on the issue of population stratification in section 5.1.2.4 below.

5.1.2.2 Differences in LD

Because GWAS SNP markers are often not the causal variants themselves, but merely in physical proximity to them, the estimated effect size of a SNP marker depends on the extent to which it is in LD with the causal variant.⁴⁴ To illustrate the problem, if a SNP has an LD r^2 with a causal variant of 0.8 in the discovery population and 0.6 in the target population, it would explain $25\% = (1 - 0.6/0.8)$ less trait variation in the target population, and would therefore be less predictive.⁴⁵

Differences in effect-size estimates may typically be small for most regions of the genome, but as PGS sum across these effects, they aggregate these population differences.⁴⁶ Previous empirical and simulation studies have shown that accuracy of PGS scores decay with increased genetic differentiation (F_{ST}) and LD differences between populations.⁴⁷

1093/aje/kwx246.

⁴³Uffelmann et al., “Genome-Wide Association Studies.”

⁴⁴Hakhamanesh Mostafavi et al., “Variable Prediction Accuracy of Polygenic Scores Within an Ancestry Group,” ed. Ruth Loos, Michael B Eisen, and Paul O'Reilly, *eLife* 9 (January 30, 2020): e48376, <https://doi.org/10.7554/eLife.48376>; Jonathan K. Pritchard and Molly Przeworski, “Linkage Disequilibrium in Humans: Models and Data,” *The American Journal of Human Genetics* 69, no. 1 (July 1, 2001): 1–14, <https://doi.org/10.1086/321275>.

⁴⁵Wang et al., “Theoretical and Empirical Quantification of the Accuracy of Polygenic Scores in Ancestry Divergent Populations.”

⁴⁶Martin, Kanai, et al., “Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities.”

⁴⁷Habier et al., “The Impact of Genetic Relationship Information on Genomic Breeding Values in German Holstein Cattle”; Pszczola et al., “Reliability of Direct Genomic Values for Animals with Different Relationships Within and to the Reference

It was demonstrated in simulations that using LD information from an external reference panel as a prior to infer the posterior mean effect size of a genetic variant can improve PGS predictive accuracy.⁴⁸

Genetic divergence between populations can be measured by F_{ST} , and the correlation between true and predicted phenotypic values decays approximately linearly with respect to F_{ST} .⁴⁹

5.1.2.3 Differences in allele frequencies

Causal variants can differ in both frequency and effect size between different ancestry groups, e.g. for lactase persistence, or skin pigmentation.⁵⁰ If a causal allele is rare in the GWAS discovery population, even if it is discovered (see 5.1.2.1) it is likely to have noisy effect size estimates, and therefore likely to inaccurately estimate its effect size in a different population where it exists at a higher frequency.

Differences in allele frequencies between populations can arise through random genetic drift, or be driven by selective pressures towards the trait optima for a given environment.⁵¹

Chapter 5 will explore the differences in allele frequencies across populations for all polygenic traits in the GWAS Catalog, and demonstrate that with few exceptions – including skin pigmentation, and HIV viral load – the differences in allele frequencies between populations tends to be small. And therefore, the

Population”; Scutari, Mackay, and Balding, “Using Genetic Distance to Infer the Accuracy of Genomic Prediction”; Wang et al., “Theoretical and Empirical Quantification of the Accuracy of Polygenic Scores in Ancestry Divergent Populations.”

⁴⁸Bjarni J Vilhjálmsson et al., “Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores,” *The American Journal of Human Genetics* 97, no. 4 (2015): 576–92.

⁴⁹Scutari, Mackay, and Balding, “Using Genetic Distance to Infer the Accuracy of Genomic Prediction.”

⁵⁰Kaustubh Adhikari et al., “A GWAS in Latin Americans Highlights the Convergent Evolution of Lighter Skin Pigmentation in Eurasia,” *Nature Communications* 10, no. 1, 1 (January 21, 2019): 358, <https://doi.org/10.1038/s41467-018-08147-0>.

⁵¹Arbel Harpak and Molly Przeworski, “The Evolution of Group Differences in Changing Environments,” *PLOS Biology* 19, no. 1 (January 25, 2021): e3001072, <https://doi.org/10.1371/journal.pbio.3001072>.

5.1.2.4 Differences in environment

Genes interact with the environment to create phenotypic values.⁵² Yet when it comes to the differences in mean values between groups (i.e. populations) for traits that carry social benefit – such as intelligence – there is ongoing debate about what proportion of the variance that we observe between populations is genetic.

- The second issue is the same as what often affects the interpretation of the slippery biological concept of heritability. “Heritability” in its genetic sense describes the proportion of variance in a trait that is attributable to genetic factors. Because it is a *proportion* of variance, when studying a population that is subject to greater environmental variation, the variance attributable to genetic factors will proportionately reduce. Conversely, when studying a population where the environment is held constant, the heritability for that trait will approach 1. PGS also measure the proportion of variance within a population that is explained by genetics, and the higher that proportion, the more accurate the predictions will be. So in the same way as heritability, increases in the amount of environmental variance in a population will reduce the proportion of variance explained by genetics.
- The third issue is the confounding that different environments often have with population structure.⁵³ For example, in East Asia, there is a greater proportion of individuals of East-Asian ancestry than there is of European ancestry, and *vice versa* in Europe. Those East-Asian individuals will therefore tend to share more of their genetic background with each other than with Europeans, and that “population structure” will be correlated with the different environments that exist in East Asia compared to Europe. This makes it difficult to determine whether it is the environment or the population structure that is driving the differences between those populations.

⁵²Plomin and Asbury, “Nature and Nurture.”

⁵³Berg et al., “Reduced Signal for Polygenic Adaptation of Height in UK Biobank.”

5.2 Analysis

In this chapter I explore the distribution of F_{ST} scores for loci associated with 587 traits, a subset of the GWAS Catalog that passed our criteria for suitable polygenic traits (see Chapter 5.2). Using high-coverage sequence data for 2,504 individuals from the 1000 Genomes Project phase 3 release, for each trait in the GWAS Catalog we calculated the distribution of F_{ST} across all approximately-unlinked SNPs associated with it (trait SNPs), and compared these F_{ST} distributions with the F_{ST} distributions of random-selected SNPs that were matched to the trait SNPs by their allele frequencies in European populations (control SNPs). Our results show that traits related to the physical correlates of “race” (such as skin-pigmentation, eye colour, and hair shape) tend to have relatively high F_{ST} values – signifying relatively high variance in allele frequencies between populations – whereas traits related to intelligence (such as self-reported EA, mathematical ability, and cognitive function measurement) tend to have lower F_{ST} values that are similar to those of most polygenic traits such as height and body mass index.

5.2.1 Datasets

5.2.1.1 1000 Genomes

As the reference for human genomic variation across diverse populations, we used the New York Genome Center high-coverage, phased .vcf files⁵⁴ for the 2,504 individuals described in the 1000 Genomes phase 3 release.⁵⁵ We then annotated those .vcf files with human SNP IDs from dbSNP release 9606.⁵⁶

⁵⁴“Index of /Vol1/Ftp/Data_collections/1000g_2504_high_coverage/Working/20201028_3202_phased/,” accessed March 24, 2022, http://ftp.1000genomes.ebi.ac.uk/vol1/ftp/data_collections/1000G_2504_high_coverage/working/20201028_3202_phased/.

⁵⁵Consortium et al., “A Global Reference for Human Genetic Variation.”

⁵⁶Elizabeth M. Smigielski et al., “dbSNP: A Database of Single Nucleotide Polymorphisms,” *Nucleic Acids Research* 28, no. 1 (January 1, 2000): 352–55, <https://doi.org/10.1093/nar/28.1.352>.

5.2.1.2 GWAS Catalog

We used the R package *gwasrapidd*⁵⁷ to query all traits in the GWAS Catalog⁵⁸ as of 9 August 2021 ($N_{TRAITS} = 3,459$). For 541 of these traits, no matching variant IDs could be pulled out from the 1000 Genomes VCFs, leaving $N_{TRAITS} = 3,008$.

5.2.2 Linkage disequilibrium

To obtain the “trait SNP” dataset, for each trait, we sought to isolate the SNP closest to each of its true causal variants, and exclude the SNPs in linkage disequilibrium (LD) with them. To this end, we used PLINK 1.9⁵⁹ to “clump” the SNPs associated with each of the remaining 3,008 traits, using an “index” SNP p-value threshold of 10^{-8} ,⁶⁰ r^2 threshold of 0.1,⁶¹ and base window size of 1 Mb. This process left us with 2,045 traits with at least one index SNP that met the p-value threshold. The index SNPs for each trait formed our set of trait SNPs, and Figure 5.1 shows the counts of unique SNP IDs associated with each trait before and after clumping. In order to target relatively polygenic traits, we further filtered out traits with fewer than 10 trait SNPs, leaving $N_{TRAITS} = 587$.

5.2.3 Control SNPs

To obtain our “control SNP” dataset, we assigned each trait SNP to one of 20 bins based on its minor allele frequency in European

⁵⁷Ramiro Magno and Ana-Teresa Maia, “Gwasrapidd: An R Package to Query, Download and Wrangle GWAS Catalog Data,” *Bioinformatics* 36, no. 2 (January 15, 2020): 649–50, <https://doi.org/10.1093/bioinformatics/btz605>.

⁵⁸Jacqueline MacArthur et al., “The New NHGRI-EBI Catalog of Published Genome-Wide Association Studies (GWAS Catalog),” *Nucleic Acids Research* 45, no. D1 (January 4, 2017): D896–901, <https://doi.org/10.1093/nar/gkw1133>.

⁵⁹Chang et al., “Second-Generation PLINK”; Purcell and Chang, *PLINK 1.9*.

⁶⁰Orestis A. Panagiotou, John P. A. Ioannidis, and Genome-Wide Significance Project, “What Should the Genome-Wide Significance Threshold Be? Empirical Replication of Borderline Genetic Associations,” *International Journal of Epidemiology* 41, no. 1 (February 2012): 273–86, <https://doi.org/10.1093/ije/dyr178>.

⁶¹W. G. Hill and Alan Robertson, “Linkage Disequilibrium in Finite Populations,” *Theoretical and Applied Genetics* 38, no. 6 (June 1, 1968): 226–31, <https://doi.org/10.1007/BF01245622>.

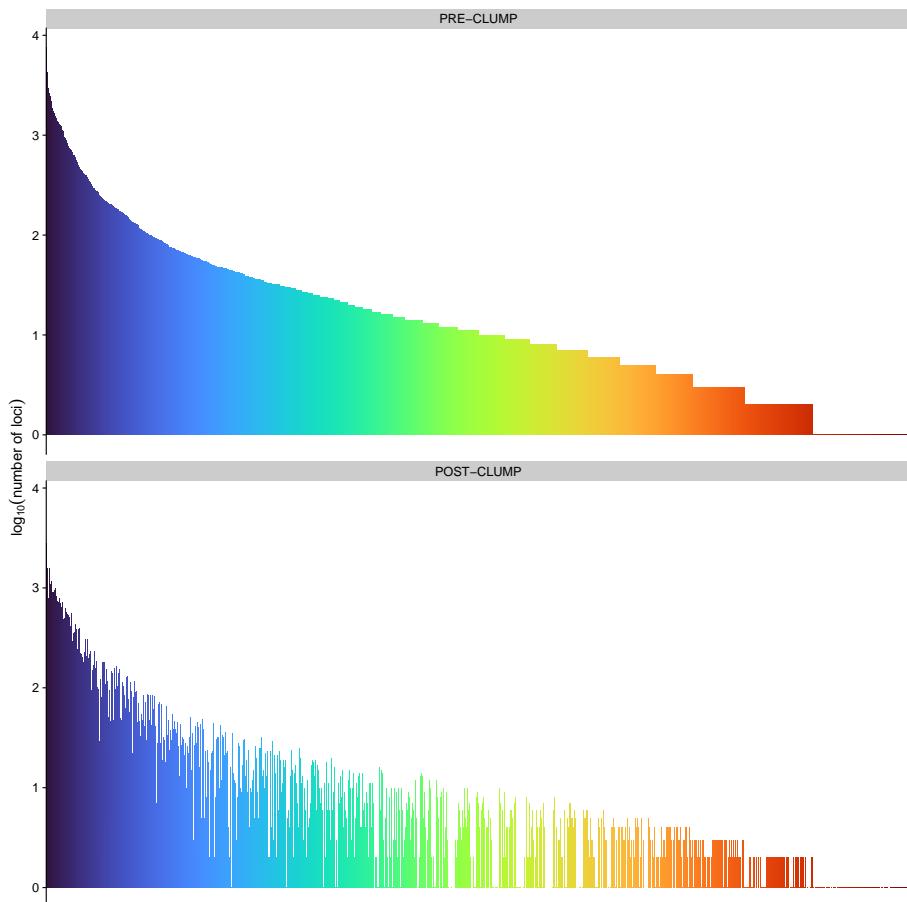


Figure 5.1: \log_{10} counts of associated SNPs for each trait before and after the clumping process, which involved: a) excluding all SNPs with a p -value greater than 10^{-8} ; and b) starting with the SNPs with the lowest p -values (“index” SNPs), excluding all other SNPs within a 1 Mb region of the index SNP with an LD r^2 of more than 0.1.

populations (as provided in the original 1000 Genomes .vcf files under the column header ‘INFO/AC_EUR’). For example, if a trait SNP had a minor allele frequency of 0.08 in European populations, it was assigned to the (0.05, 0.1] bin. I did the same for all (un-associated) SNPs in the .vcf files, then paired each trait SNP with a random SNP from the .vcf file in the equivalent bin. These allele-frequency-paired random SNPs formed our set of “control SNPs”, which I used to infer the F_{ST} distribution of a random set of SNPs with the same allele frequencies as the trait SNPs, and against which I could compare the F_{ST} distribution of the trait SNPs.

5.2.4 F_{ST} and ranking traits by signed Kolmogorov-Smirnov D statistic

I then calculated F_{ST} for each of the trait SNPs and their matched control SNPs using the Weir and Cockerham method,⁶² as implemented in the R package *pegas*.⁶³ To rank all traits based on the directional difference in F_{ST} distributions between trait and control SNPs, I ran three Kolmogorov-Smirnov (KS) tests for each trait t with $x_t = F_{ST,traitSNPs}$ and $y_t = F_{ST,controlSNPs}$:

1. two-sided (D_t) ;
2. one-sided “greater” (D_t^+) ; and
3. one-sided “less” (D_t^-).

I note that $D_t = \max(D_t^+, D_t^-)$, where D_t^+ is the greatest vertical distance attained by the eCDF of x_t over the eCDF of y_t , and D_t^- is the greatest vertical distance attained by the eCDF of y_t over the

⁶²B. S. Weir and C. Clark Cockerham, “Estimating F-Statistics for the Analysis of Population Structure,” *Evolution* 38, no. 6 (1984): 1358–70, <https://doi.org/10.2307/2408641>.

⁶³Emmanuel Paradis, “Pegas: An R Package for Population Genetics with an Integrated–Modular Approach,” *Bioinformatics* 26, no. 3 (February 1, 2010): 419–20, <https://doi.org/10.1093/bioinformatics/btp696>.

eCDF of x_t .⁶⁴ Accordingly, we used a comparison of D_t^+ and D_t^- to formulate a signed D statistic (D_t^S), based on the logic that trait SNPs with a lower overall F_{ST} than control SNPs tend to have a higher D under the “greater” test than the “less” test, and vice versa.

Therefore, D_t^S :

$$\begin{aligned} D_t^- > D_t^+ : & -D_t \\ D_t^- = D_t^+ : & 0 \\ D_t^- < D_t^+ : & D_t \end{aligned}$$

In **Figure 5.2** I present the F_{ST} distributions of trait SNPs for an illustrative subset of 28 human traits, ranked by D_t^S when compared with their matched control SNPs. **Figure 5.2A** shows the densities of SNPs as a function of F_{ST} , and **Figure 5.2B and C** show their empirical Cumulative Distribution Functions (eCDFs). **Figure 5.2B** includes the eCDFs of control SNPs in grey. eCDF figures for all 587 traits that passed our filters (Methods) are provided in 5.3.

5.3 Implications

The low F_{ST} that we see for trait-associated alleles across various polygenic traits show that their allele frequencies do not substantially differ between populations. This means that, generally speaking, the genetic architecture of polygenic traits is shared across global populations.

This leads to the conclusion that the poor transferability of PGS across populations is not primarily driven by differences in trait-associated allele frequencies, but must rather be caused by differences in LD structure and environment.

⁶⁴W. J. Conover, *Practical Nonparametric Statistics* (John Wiley & Sons, 1999), https://books.google.com?id=n_39DwAAQBAJ; J. Durbin, *Distribution Theory for Tests Based on Sample Distribution Function* (SIAM, 1973), <https://books.google.com?id=zAryCrTIIUYC>.

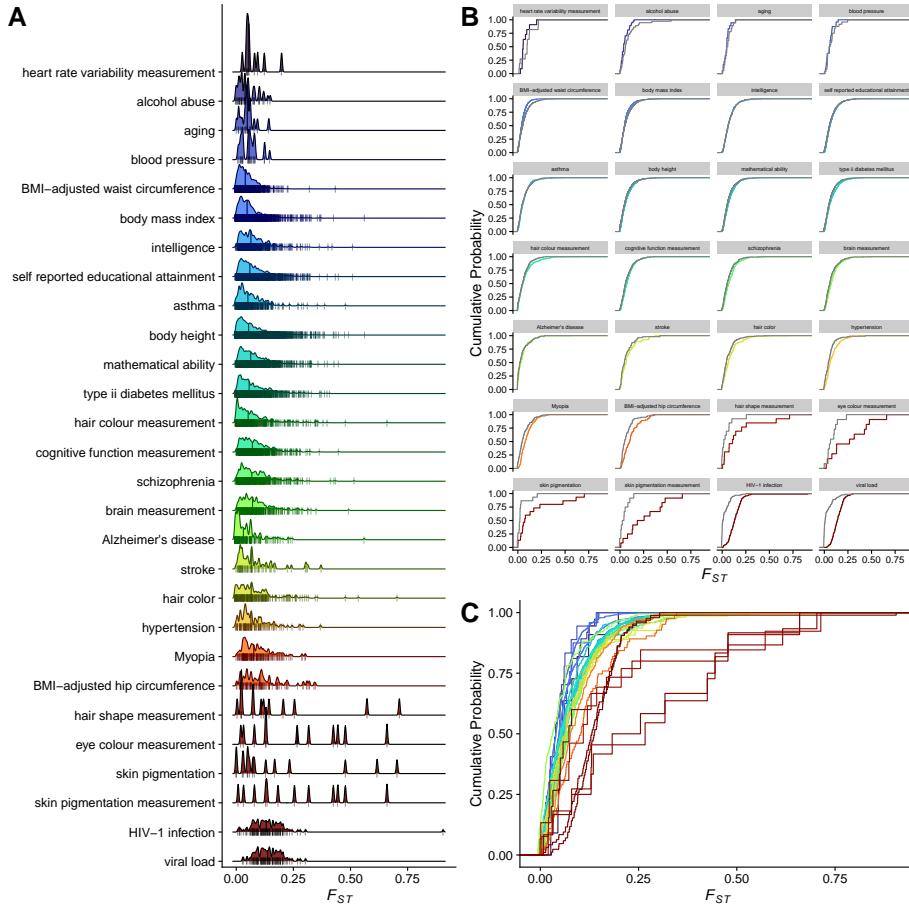


Figure 5.2: Distributions of F_{ST} across 28 illustrative human traits, ranked by signed-D (Kolmogorov-Smirnov test) comparing trait and control SNPs. A. F_{ST} density ridge plots with SNP markers. B. Empirical Cumulative Distribution Functions (eCDFs) of F_{ST} for trait-associated (colour) and random control (grey) SNPs, faceted by trait. C. Consolidated eCDFs of trait-associated SNPs from (B). eCDFs for all traits are included in Supplementary Figure 1.

5.3.1 F_{ST} has no connection with mean population values

The loci of educational attainment have similar F_{ST} distributions to those of most polygenic traits.

As F_{ST} does not take into account the effect size or direction of the effect of the trait-associated allele, for highly-polygenic traits like the ones shown here, F_{ST} is almost entirely decoupled from the mean additive genetic value (or polygenic risk score) between populations.⁶⁵

Height and BMI, which are under strong differential selection, look the same as other polygenic traits, which illustrates the limitations of this analysis [CITE]

5.3.2 The importance of environment, and its complex interactions with genetics

Genes interact with themselves (GxG, or “epistasis”),⁶⁶ the genes of one’s parents (“genetic nurture”, Augustine Kong et al.⁶⁷) or social companions (“social genetic effects”)⁶⁸ and Chapters 3 and 4, and the wider non-genetic environment (GxE).

⁶⁵Jeremy J. Berg and Graham Coop, “A Population Genetic Signal of Polygenic Adaptation,” *PLOS Genetics* 10, no. 8 (August 7, 2014): e1004412, <https://doi.org/10.1371/journal.pgen.1004412>.

⁶⁶Pierre-Alexis Gros, Herv'e Le Nagard, and Olivier Tenaillon, “The Evolution of Epistasis and Its Links With Genetic Robustness, Complexity and Drift in a Phenotypic Model of Adaptation,” *Genetics* 182, no. 1 (May 1, 2009): 277–93, <https://doi.org/10.1534/genetics.108.099127>.

⁶⁷“The Nature of Nurture: Effects of Parental Genotypes,” *Science* 359, no. 6374 (January 26, 2018): 424–28, <https://doi.org/10.1126/science.aan6877>.

⁶⁸Benjamin W. Domingue et al., “The Social Genome of Friends and Schoolmates in the National Longitudinal Study of Adolescent to Adult Health,” *Proceedings of the National Academy of Sciences* 115, no. 4 (January 23, 2018): 702–7, <https://doi.org/10.1073/pnas.1711803115>; Amelie Baud et al., “Genetic Variation in the Social Environment Contributes to Health and Disease,” *PLOS Genetics* 13, no. 1 (January 25, 2017): e1006498, <https://doi.org/10.1371/journal.pgen.1006498>.

5.3.3 A push for diversity in genetic studies

The obvious solution to this issue of non-transferability of PGS scores to diverse populations is to increase the representation of those populations in GWAS and PGS studies, as has been often proposed elsewhere.⁶⁹

⁶⁹Martin, Gignoux, et al., “Human Demographic History Impacts Genetic Risk Prediction Across Diverse Populations”; Alicia R Martin et al., “The Critical Needs and Challenges for Genetic Architecture Studies in Africa,” *Current Opinion in Genetics & Development*, Genetics of Human Origins, 53 (December 1, 2018): 113–20, <https://doi.org/10.1016/j.gde.2018.08.005>; Stephanie A. Bien et al., “The Future of Genomic Studies Must Be Globally Representative: Perspectives from PAGE,” *Annual Review of Genomics and Human Genetics* 20, no. 1 (August 31, 2019): 181–200, <https://doi.org/10.1146/annurev-genom-091416-035517>; Martin, Kanai, et al., “Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities”; Giorgio Sirugo, Scott M. Williams, and Sarah A. Tishkoff, “The Missing Diversity in Human Genetic Studies,” *Cell* 177, no. 1 (March 21, 2019): 26–31, <https://doi.org/10.1016/j.cell.2019.02.048>; Genevieve L. Wojcik et al., “Genetic Analyses of Diverse Populations Improves Discovery for Complex Traits,” *Nature* 570, no. 7762, 7762 (June 2019): 514–18, <https://doi.org/10.1038/s41586-019-1810-4>.

Appendix

eCDF of all polygenic traits in the GWAS Catalog ranked by D_t^S

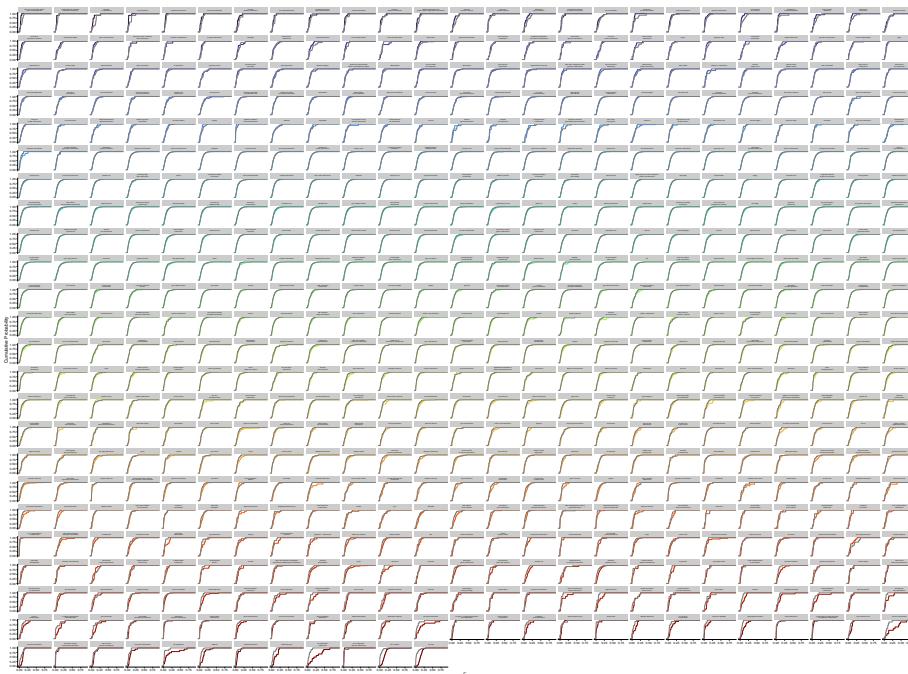


Figure 5.8: 587 traits from the GWAS Catalog that passed our filters for polygenic traits, ranked by D_t^S .

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