# Variant effects depend on polygenic background: experimental, clinical, and evolutionary implications

Madison Chapel[1], Jessica Dennis[1,2,3], Carl G. de Boer[1,4*]

[1]Bioinformatics Program, University of British Columbia, Vancouver, Canada

[2]Department of Medical Genetics, University of British Columbia, Vancouver, Canada

[3]BC Children's Hospital Research Institute, Vancouver, Canada

[4]School of Biomedical Engineering, University of British Columbia, Vancouver, Canada

*Corresponding author: carl.deboer@ubc.ca

## Abstract

Both rare and common genetic variants contribute to human disease, and emerging evidence suggests that they combine additively to influence disease liability. However, due to the non-linear relationship between disease liability and disease prevalence, risk variants have more severe phenotypic consequences in high-risk polygenic backgrounds. Consequently, selecting individuals with appropriate polygenic backgrounds may improve variant characterization experiments, as disease-relevant phenotypes may be masked or revealed in different genomic contexts. Simultaneously, selection has limited power to eliminate risk variants because they have minimal impact in low polygenic risk backgrounds, yet is more powerful with higher polygenicity because more individuals achieve genetic and phenotypic extremes. This dependence on polygenic background means that selection acting on an allele should be modeled as a distribution that differs across populations, time, environments, and individuals rather than as a single value. Overall, considering polygenic backgrounds will be critical when investigating the origins of complex traits.

## Introduction

Both rare and common variants influence human disease. Many genetic diseases are caused by highly penetrant variants that follow Mendelian inheritance patterns. These variants are typically rare, occurring at low allele frequencies throughout the population[1,2]. Disease risk can also be influenced in a polygenic manner by common genetic variants with small effect sizes throughout the genome, resulting in a spectrum of genetic risk across a population[3]. Genome-Wide Association Studies (GWAS) have become crucial for understanding how these common variants influence disease risk[4,5]. However, our conceptual understanding of how common and rare variants combine to influence disease risk and selective pressures remains incomplete. While it is common to discuss rare and common variants as though they are distinctly different categories, as we discuss below, both types of variation impact traits in a similar manner, but at different ends of the effect size spectrum.

By aggregating effect estimates from GWAS summary statistics, researchers can calculate a Polygenic Score (PGS), also called a Polygenic Risk Score (PRS), estimating an individual's genetic liability for a trait or disease based on their genotype[6,7]. For binary traits, like diagnosis of a disease, PGS are typically calculated as a weighted sum of the log odds ratio for each variant included in the score. Even with increasingly large cohort sizes, GWAS have limited power to detect effects from rare variants, and so PRSs typically capture only the influence of common genetic variation[5,8]. Similarly, rare variants are often studied in isolation, without consideration of the genetic background they arise in. Some potentially causal variants do not exhibit robust heritability patterns or occur at frequencies incompatible with causing a highly penetrant Mendelian disease[9]. Moreover, individuals with the same causal alleles may show variable expressivity of the disease phenotype[10].

These observations are consistent with a liability threshold model of disease, in which a combination of small-effect common variants, variants of intermediate effect, rare variants of large effect, and environmental factors contribute to disease liability[11,12]. Like polygenic scores, the liability threshold model assumes independent additive effects from each disease risk factor on disease liability, with some non-linear relationship relating increased liability with disease prevalence (e.g. a threshold). Under a liability threshold model of disease, the penetrance of rare variants can be modified by the genetic background: A rare variant present in a low-risk genetic background may push the risk of disease close to the threshold, but not surpass it, while the same variant in a higher-risk background would surpass the threshold and result in a high chance of developing disease. Increasingly, population genetic studies have provided support for the additivity of rare and common variant effects on disease liability.

## Penetrance and expressivity of rare variants can be modified by genetic background

Several recent studies have characterized cohorts for both rare disease variants and PGS for various genetic diseases, including breast and ovarian cancer[13,14], developmental disorders[15], Parkinson's disease[16], and others[17–20]. The combination of high PGS and rare variant results in a higher disease risk than either factor alone[14,19]. When examining the joint effect of rare and common genetic variants, several studies demonstrated that these two sources of genetic variation combine roughly additively to the log odds ratios of disease, consistent with the additivity of disease liability[13,15–18]. This additive trend was robust across multiple studies, despite differences in cohort size and approaches to PGS stratification, such as comparing across tertiles, quintiles, or percentiles.

Importantly, the additivity of genetic variation on polygenic score and disease liability does not mean that these variants have additive effects on disease prevalence (**Fig. 1; Methods**). Additivity of log odds ratios is multiplicative for odds ratios. Consequently, a variant will have the same effect on the log odds ratio of disease regardless of the genetic background it arises in but will have very different effects on the odds ratios and disease prevalence. A hypothetical large-effect variant that increases polygenic score by one unit will always increase the log odds of disease by a proportional amount. That same variant, however, will result in a minimal change in odds ratio in a low-risk background and a dramatic change in a high-risk background (**Fig. 1A,B**). These differences in odds ratios translate to different changes in disease prevalence, regardless of the background disease rate in the population (**Fig. 1C,D**). Thus, while the relationship between genetic liability and disease prevalence is non-linear, it can be captured in a linear manner through transformation to log odds ratios[21]. Since higher genetic liability will not only increase the disease prevalence, but also likely lead to earlier disease onset and severity, the same variant will alter organismal fitness in very different ways depending on the polygenic background it co-occurs with.

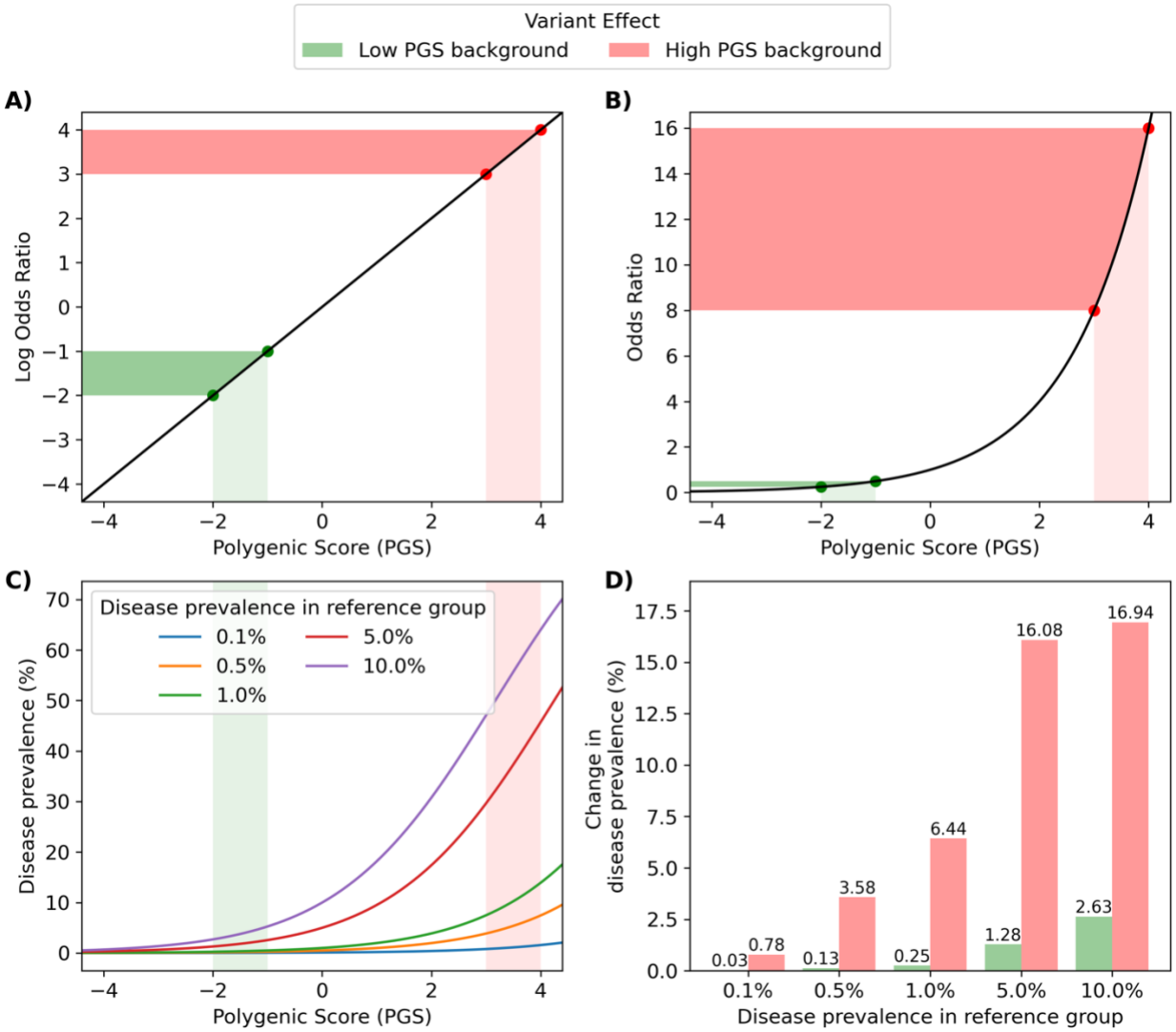


**Figure 1. Variant effects depend on polygenic background.** (**A**) Polygenic scores (PGS, x axis) are usually linearly related to log odds ratios of disease (y axis), resulting in a risk variant having the same change in log odds regardless of where on the PGS distribution the individual lies (colors). (**B**) However, because an individual's probability of getting a disease is proportional to the odds ratio (not log), similar changes to PGS (x axis) result in very different changes to odds ratios (y axis) depending on where on the PGS distribution the individual lies (colors). **(C)** The relationship between PGS (x axis) and disease prevalence (y axis) is also influenced by the background rate of disease in the population (colors), with populations already at higher risk of disease experiencing greater increases at the extreme end of the PGS distribution. **(D)** Disease prevalence (y axis) increases substantially more when risk variants are introduced to high PGS backgrounds (red bars) than low PGS backgrounds (green bars), regardless of the disease background rate (x axis).

## Research implications

Characterizing the mechanisms underlying GWAS variants using functional assays is now a major focus of human genetics research[22]. Obviously, using the correct cell type for the assay is critical to determining the true mechanisms underlying a variant's role in disease. Using an appropriate genetic background may also prove to be crucial in many circumstances as the variant's phenotypic effect could be masked by the genetic background. If a cell line used for functional characterization is derived from a low-polygenic risk background, certain variants may have no observable effect when looking at broad measures such as cellular phenotypes or even gene expression (as in shadow enhancer genes; see below). Were the same variant to be studied in a cell line derived from a higher-risk background, relevant changes in phenotype may become apparent. For instance, variation elsewhere in the genome may explain why cardiomyocytes derived from symptomatic and asymptomatic sibling carriers of the same Long QT syndrome-associated variant displayed varying responses to QT interval-modifying drugs[23,24]. Functional studies may be improved by considering the cellular model's PGSs for relevant traits, and perhaps replicating results in alternate cellular models with diverse PGSs. Ideal PGSs for functional studies will likely be towards the high end of the normal PGS range to maximize the phenotypic effects of perturbations. With the growing use of patient-derived induced pluripotent stem cells (iPSCs) as a model to research genetic disease[25], iPSC banks such as iPSCORE, which include not only phenotype data but also matched genotyping data, may prove invaluable for future research endeavors[26]. Including pre-calculated PGSs will further increase the utility of these iPSC banks by enabling researchers to quickly identify the lines most likely to reveal variant effects.

Shadow enhancers provide an intriguing example where the genetic background may sensitize mutation effects. Shadow, or distributed enhancers, are sets of enhancers that regulate a common target and drive overlapping expression patterns, seemingly with redundant functions[27]. However, this redundancy may simply reflect the genetic background of the strain being tested: should a mutation disrupt the activity of one of a pair of shadow enhancers, genetic variation elsewhere in the genome (e.g. in transcriptional regulators) could disrupt the activity of the remaining enhancer sufficiently to trigger a fitness defect. For example, deleting three of six enhancers for the *shavenbaby* gene had no effect on *D. melanogaster* development under normal conditions but caused phenotypic changes in mutants with a single copy of the *wingless* gene[28]. Similar results were shown in enhancers regulating *Pax6*[29], *Shh*[30], and several loci involved in limb development[31]. Similar circumstances could mask the effects of GWAS variants, the vast majority of which are non-coding[32], and many of which affect the expression of transcriptional regulators[33,34].

The observation that variant penetrance may be modified by polygenic background is strong incentive to prioritize patients who present with disease symptoms despite a low corresponding PGS for rare variant discovery and characterization. If an individual presents with disease but has a low PGS, it is more likely that the underlying cause is a rare variant of large effect. Multiple studies have demonstrated this in practice. Lu et al. found that patients with lower PGSs (<50th percentile) were enriched for pathogenic variants linked to breast cancer, colorectal cancer, diabetes, and osteoporosis[35]. In the context of developmental disorders, individuals with high educational attainment PGS but low fluid intelligence scores were more likely to be rare variant carriers[17]. Further, individuals whose PGS-predicted height or LDL cholesterol levels were misaligned with their phenotype were enriched for known rare large-effect variants[36].

## Clinical implications

The impact of genetic background on rare variant penetrance also has implications for interpretation and communication of genetic risk in a clinical setting. Targeted genetic testing can determine if patients are carriers of rare variants, but additional risk stratification using PGS may prioritize high-risk patients for more intensive preventative care measures or disease-screening programs, while providing peace of mind to low-risk patients. As an example, up to 50% of women who carry pathogenic *BRCA1* or *BRCA2* variants currently undergo prophylactic mastectomies[37], but as demonstrated by Fahel et al., lifetime risk for those in the lowest PGS percentile may be as low as 13% – a number comparable to the 10% average lifetime risk across the non-carrier population[13]. Conversely, variant carriers with moderate or high PGS will have substantially elevated disease risk because the odds ratios associated with the variant and the PGS multiply; in a family carrying a pathogenic *BRCA1* variant, risk stratification using a combination of rare variant status and PGS across sibling embryos revealed a 15-fold difference in odds ratios, compared to 4.5-fold or 3-fold when using solely *BRCA1* status or PGS[38], respectively. Novel tools such as RICE[39], which integrate both rare and common variant information into a single predictor, have demonstrated more accurate estimates of genetic risk than traditional PRS approaches. As more individuals seek to understand their genetic risk through both clinical and direct-to-consumer testing[40,41], genetic counselors will need to leverage all available data – including variant status, PGSs, and lifestyle information – to effectively stratify risk and guide personalized healthcare decisions.

## Genetic background modifies the strength of selection

The joint effect of rare and common genetic variation on disease risk has multi-faceted implications for how these variants behave in populations. Selection does not act directly on each allele but instead depends on the combined effects of all genetic

variation present within an individual, and how these variants interact with the environment. Selection coefficients, a measure of the relative fitness of a variant, will vary between individuals due to their different genetic backgrounds, and so may be better modeled as a distribution. Because allele frequencies differ between populations, so will the selection coefficient distributions. Even in the same population, selection coefficient distributions may not be stable over time due to shifts in allele frequencies or environmental conditions. When a population inherently has a low genetic liability of disease, a pathogenic variant – even one of large effect – may result only very rarely in disease. Selection on the pathogenic variant may be driven primarily by individuals at the high end of the risk distribution. In low-risk individuals, the variant may never result in disease and could persist in the population indefinitely.

Intriguingly, the strength of selection is increased with increasing polygenicity due to the increased variance in the genetic liability distribution. Specifically, the variance in polygenic score is proportional to the number of alleles contributing to the trait (**Fig. 2A,B**; **Methods**). In a population where more alleles contribute to a trait, more individuals will have extreme polygenic scores, and thus extreme phenotypes. Selection will act against the individuals at the high-risk end of the distribution, reducing the allele frequencies of the high-risk variants, and resulting in most phenotypic variation being explained by low-risk variants. Consequently, effect sizes of alleles in the population will be driven to be increasingly small and homogenous for traits with greater polygenicity[12,42]. Were variants to interact super-additively on genetic liability (e.g. multiplicatively), the variance would be far greater, pushing more individuals to phenotypic extremes, suggesting there may be strong evolutionary pressures to avoid such interactions.

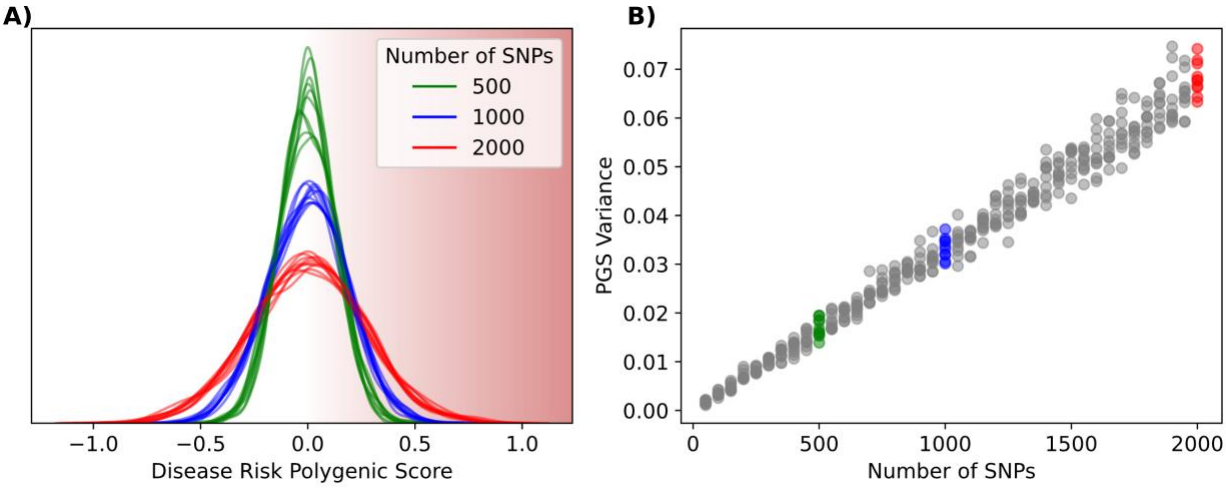


**Figure 2: Variation in disease risk increases with the number of contributing variants.** (**A**) Density of individuals (y axis) of disease risk polygenic scores (x axis) for individuals in simulated populations that are matched for population size, effect size

distributions, and allele frequencies, but differ by the number of contributing variants (colours). Individuals at extremes are more likely to get disease (red shading). (**B**) Linear relationship between the number of variants (x axis) and PGS variance (y axis).

The environment a population occupies can modify the way that selection acts on genetic variation. The environment can be thought of as an independent modifier of disease liability. If a population moves to an environment that predisposes them to disease, the liability distribution will shift, increasing the number of individuals at high risk of developing disease. More individuals in the population would be subject to selection, reducing the frequency of disease-associated variants, and leading to a population with low genetic liability. As environmental pressures relax again, the liability distribution shifts again, and the population now has a lower disease liability than at the outset (**Figure 3**). An example of this has been observed in Inuit populations. Inuit populations appear to have been under selection at the *FADS1* locus, which encodes several genes involved in fatty acid metabolism[43,44], potentially reflecting adaptation to their traditional diet high in polyunsaturated fatty acids. In European populations, variants in *FADS1*, are associated with lower blood cholesterol, suggesting a potential protective effect against cardiometabolic phenotypes[43]. However, whether the *FADS1* variants enriched in Inuit populations translate to reduced risk of heart disease, particularly in populations adopting a more Westernized diet, remains unclear[45]. Since many foods contain complex mixtures of compounds, including drug-like small molecules, some environmental risk factors may result from drug-like compounds. For example, tyrosine kinase inhibitors were more toxic to cardiomyocytes derived from Long QT syndrome patients than those derived from healthy controls[46] (which also suggests another strategy for drawing out variant phenotypes). If the environment influences disease liability, it will also modify the strength of selection and shape the population's genetics.

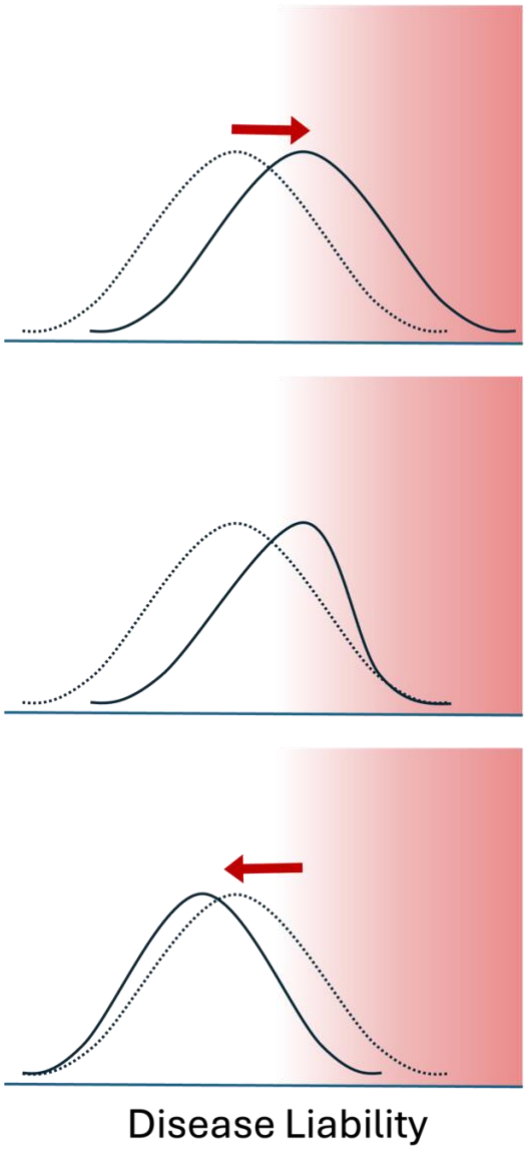


**Figure 3: The distribution of disease liability in a population changes in response to environmental factors.** A change in the environment (top panel) shifts the original distribution (dashed line) to higher disease liability (solid line), predisposing more individuals to disease (red shading). In the new environment, more individuals have a high probability of developing disease, and selection will eliminate those at highest risk (middle panel), changing the population's genetics. The environmental stressor is removed (bottom panel), resulting in a population (solid line) with lower mean disease liability than the original (dotted line).

## Conclusions

The relationship between variants and disease risk can be modified by such factors as an individual's age, environment, or sex chromosome composition, and there is a growing initiative to study and characterize these interactions[20,47,48]. The context of polygenic background is similarly important but not as widely discussed. Polygenic background can sensitize cells, individuals, or populations to variant effects, offering a mechanism for the variable penetrance that is often seen in monogenic variants

The dependence on polygenic background necessitates a shift in how we discuss and study disease-associated variants. Instead of associating each variant with a discrete effect on disease risk, each variant should instead be conceptualized as having a context-dependent distribution of effects. Incorporating genetic background when performing functional assays, estimating selection, and evaluating disease risk will drive forward our understanding of the evolutionary origins and causal mechanisms underlying complex traits.

# Methods

## Modeling variant effects and polygenic background on disease

To demonstrate how the effect of a variant changes depending on the genetic background it arises in (**Fig. 1**), a range of polygenic scores between –4 and 4 were plotted in $\log_2$ space (log odds ratio; log(OR)) and linear space (odds ratio; OR). A large-effect variant with an effect size of one PGS unit was modeled by shifting the PGS from -2 to -1 for a low-risk background, and from 3 to 4 for a high-risk background (**Fig. 1A,B**).

Disease prevalence across the range of PGS (**Fig. 1C,D**) was calculated by first determining the odds of disease in the reference group based on disease prevalence (*p*) for five different background rates of disease*:*

$$Odds = \frac{p}{1-p}$$

And then determining disease prevalence across the range of corresponding odds ratios (*OR*):

$$p_{OR} = \frac{OR \cdot odds}{1 + (OR \cdot odds)}$$

## Impact of polygenicity degree on polygenic score distributions

To model how variance in the PGS distribution increases as more variants contribute to the disease trait (**Fig. 2**), sample populations were generated for increasing numbers of SNPs, ranging from 50 to 2000 and incrementing by 50. For each of 10 replicate populations at each SNP count, SNP allele frequencies were generated from the uniform distribution *U*(0.0, 1.0), and effect sizes were generated from the normal distribution *N*(mean = 0.0, standard deviation = 0.01). 1000 individual genotypes were simulated using a binomial distribution with *n*=2 and *p* equal to the generated allele frequencies, and PGSs determined as the sum of products between effect sizes and genotypes.

# Acknowledgements

We thank S. Otto and Z. Laksman for helpful discussions. This research was supported by the Natural Sciences and Engineering Research Council of Canada (RGPIN-2020-05425), and the Canadian Institute for Health Research (PJT-180537). M.C. was supported by a UBC IGF. C.G.D. is a Michael Smith Health Research BC Scholar.

## Declaration of interests

The authors declare no competing interests.

# References


1. Pritchard, J. K. Are Rare Variants Responsible for Susceptibility to Complex Diseases? *Am. J. Hum. Genet.* **69**, 124–137 (2001).

2. Terwilliger, J. D. & Weiss, K. M. Linkage disequilibrium mapping of complex disease: fantasy or reality? *Curr. Opin. Biotechnol.* **9**, 578–594 (1998).

3. O'Connor, L. J. The distribution of common-variant effect sizes. *Nat. Genet.* **53**, 1243–1249 (2021).

4. Uffelmann, E. *et al.* Genome-wide association studies. *Nat. Rev. Methods Primer* **1**, 1–21 (2021).

5. Visscher, P. M. *et al.* 10 Years of GWAS Discovery: Biology, Function, and Translation. *Am. J. Hum. Genet.* **101**, 5–22 (2017).

6. Choi, S. W., Mak, T. S.-H. & O'Reilly, P. F. Tutorial: a guide to performing polygenic risk score analyses. *Nat. Protoc.* **15**, 2759–2772 (2020).

7. Choi, S. W. & O'Reilly, P. F. PRSice-2: Polygenic Risk Score software for biobank-scale data. *GigaScience* **8**, giz082 (2019).

8. Crouch, D. J. M. & Bodmer, W. F. Polygenic inheritance, GWAS, polygenic risk scores, and the search for functional variants. *Proc. Natl. Acad. Sci.* **117**, 18924–18933 (2020).

9. Walsh, R. *et al.* Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. *Genet. Med.* **19**, 192–203 (2017).

10. Zlotogora, J. Penetrance and expressivity in the molecular age. *Genet. Med. Off. J. Am. Coll. Med. Genet.* **5**, 347–352 (2003).

11. Walsh, R., Tadros, R. & Bezzina, C. R. When genetic burden reaches threshold. *Eur. Heart J.* **41**, 3849–3855 (2020).

12. Visscher, P. M., Yengo, L., Cox, N. J. & Wray, N. R. Discovery and implications of polygenicity of common diseases. *Science* **373**, 1468–1473 (2021).

13. Fahed, A. C. *et al.* Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. *Nat. Commun.* **11**, 3635 (2020).

14. Kuchenbaecker, K. B. *et al.* Evaluation of Polygenic Risk Scores for Breast and Ovarian Cancer Risk Prediction in BRCA1 and BRCA2 Mutation Carriers. *JNCI J. Natl. Cancer Inst.* **109**, (2017).

15. Klei, L. *et al.* How rare and common risk variation jointly affect liability for autism spectrum disorder. *Mol. Autism* **12**, 66 (2021).

16. Kmiecik, M. J. *et al.* Genetic analysis and natural history of Parkinson's disease due to the LRRK2 G2019S variant. *Brain* **147**, 1996–2008 (2024).

17. Kingdom, R., Beaumont, R. N., Wood, A. R., Weedon, M. N. & Wright, C. F. Genetic modifiers of rare variants in monogenic developmental disorder loci. *Nat. Genet.* 1–8 (2024) doi:10.1038/s41588-024-01710-0.

18. Oetjens, M. T., Kelly, M. A., Sturm, A. C., Martin, C. L. & Ledbetter, D. H. Quantifying the polygenic contribution to variable expressivity in eleven rare genetic disorders. *Nat. Commun.* **10**, 4897 (2019).

19. Vad, O. B. *et al.* Rare and Common Genetic Variation Underlying Atrial Fibrillation Risk. *JAMA Cardiol.* (2024) doi:10.1001/jamacardio.2024.1528.

20. Antaki, D. *et al.* A phenotypic spectrum of autism is attributable to the combined effects of rare variants, polygenic risk and sex. *Nat. Genet.* 10.1038/s41588-022-01064–5 (2022) doi:10.1038/s41588-022-01064-5.

21. Wray, N. R., Wijmenga, C., Sullivan, P. F., Yang, J. & Visscher, P. M. Common Disease Is More Complex Than Implied by the Core Gene Omnigenic Model. *Cell* **173**, 1573–1580 (2018).

22. Lichou, F. & Trynka, G. Functional studies of GWAS variants are gaining momentum. *Nat. Commun.* **11**, 6283 (2020).

23. Kuusela, J. *et al.* Effects of cardioactive drugs on human induced pluripotent stem cell derived long QT syndrome cardiomyocytes. *SpringerPlus* **5**, 234 (2016).

24. Roden, D. M. Drug-Induced Prolongation of the QT Interval. *N. Engl. J. Med.* **350**, 1013–1022 (2004).

25. Elitt, M. S., Barbar, L. & Tesar, P. J. Drug screening for human genetic diseases using iPSC models. *Hum. Mol. Genet.* **27**, R89–R98 (2018).

26. Panopoulos, A. D. *et al.* iPSCORE: A Resource of 222 iPSC Lines Enabling Functional Characterization of Genetic Variation across a Variety of Cell Types. *Stem Cell Rep.* **8**, 1086–1100 (2017).

27. Kvon, E. Z., Waymack, R., Elabd, M. G. & Wunderlich, Z. Enhancer redundancy in development and disease. *Nat. Rev. Genet.* **22**, 324–336 (2021).

28. Frankel, N. *et al.* Phenotypic robustness conferred by apparently redundant transcriptional enhancers. *Nature* **466**, 490–493 (2010).

29. Antosova, B. *et al.* The Gene Regulatory Network of Lens Induction Is Wired through Meis-Dependent Shadow Enhancers of Pax6. *PLOS Genet.* **12**, e1006441 (2016).

30. Sagai, T. *et al.* SHH signaling directed by two oral epithelium-specific enhancers controls tooth and oral development. *Sci. Rep.* **7**, 13004 (2017).

31. Osterwalder, M. *et al.* Enhancer redundancy provides phenotypic robustness in mammalian development. *Nature* **554**, 239–243 (2018).

32. Maurano, M. T. *et al.* Systematic Localization of Common Disease-Associated Variation in Regulatory DNA. *Science* **337**, 1190–1195 (2012).

33. Liu, X., Li, Y. I. & Pritchard, J. K. Trans Effects on Gene Expression Can Drive Omnigenic Inheritance. *Cell* **177**, 1022-1034.e6 (2019).

34. Lambert, S. A. *et al.* The Human Transcription Factors. *Cell* **172**, 650–665 (2018).

35. Lu, T. *et al.* Individuals with common diseases but with a low polygenic risk score could be prioritized for rare variant screening. *Genet. Med. Off. J. Am. Coll. Med. Genet.* **23**, 508–515 (2021).

36. Hawkes, G. *et al.* Identification and analysis of individuals who deviate from their genetically-predicted phenotype. *PLOS Genet.* **19**, e1010934 (2023).

37. Metcalfe, K. *et al.* International trends in the uptake of cancer risk reduction strategies in women with a BRCA1 or BRCA2 mutation. *Br. J. Cancer* **121**, 15–21 (2019).

38. Kumar, A. *et al.* Whole-genome risk prediction of common diseases in human preimplantation embryos. *Nat. Med.* **28**, 513–516 (2022).

39. Williams, J. *et al.* Integrating Common and Rare Variants Improves Polygenic Risk Prediction Across Diverse Populations. 2024.11.05.24316779 Preprint at https://doi.org/10.1101/2024.11.05.24316779 (2024).

40. Phillips, K. A., Deverka, P. A., Hooker, G. W. & Douglas, M. P. Genetic Test Availability And Spending: Where Are We Now? Where Are We Going? *Health Aff. (Millwood)* **37**, 710–716 (2018).

41. Chen, Z. *et al.* Trends in utilization and costs of *BRCA* testing among women aged 18–64 years in the United States, 2003–2014. *Genet. Med.* **20**, 428–434 (2018).

42. O'Connor, L. J. *et al.* Extreme Polygenicity of Complex Traits Is Explained by Negative Selection. *Am. J. Hum. Genet.* **105**, 456–476 (2019).

43. Fumagalli, M. *et al.* Greenlandic Inuit show genetic signatures of diet and climate adaptation. *Science* **349**, 1343–1347 (2015).

44. Voruganti, V. S. *et al.* Variants in CPT1A, FADS1, and FADS2 are Associated with Higher Levels of Estimated Plasma and Erythrocyte Delta-5 Desaturases in Alaskan Eskimos. *Front. Genet.* **3**, (2012).

45. Hu, X. F., Singh, K., Kenny, T.-A. & Chan, H. M. Prevalence of heart attack and stroke and associated risk factors among Inuit in Canada: A comparison with the general Canadian population. *Int. J. Hyg. Environ. Health* **222**, 319–326 (2019).

46. Zhao, Q. *et al.* Cardiotoxicity Evaluation of Tyrosine Kinase Inhibition using Human Induced Pluripotent Stem Cell-derived Healthy and Long QT Syndrome Cardiomyocytes. *Arch. Clin. Biomed. Res.* **08**, (2024).

47. Bookman, E. B. *et al.* Gene-environment interplay in common complex diseases: forging an integrative model—recommendations from an NIH workshop. *Genet. Epidemiol.* **35**, 217–225 (2011).

48. Virolainen, S. J., VonHandorf, A., Viel, K. C. M. F., Weirauch, M. T. & Kottyan, L. C. Gene–environment interactions and their impact on human health. *Genes Immun.* **24**, 1 (2022).