Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Genetics & Development

Leveraging GWAS for complex traits to detect signatures of natural selection in humans

Jing Guo[1], Jian Yang[1,2] and Peter M Visscher[1,2]

Natural selection can shape the genetic architecture of complex traits. In human populations, signals of positive selection at genetic loci have been detected through a variety of genome-wide scanning approaches without the knowledge of how genes affect traits or fitness. In the past decade, genome-wide association studies (GWAS) have provided unprecedented insights into the genetic basis of quantitative variation in complex traits. Summary statistics generated from these GWAS have been shown to be an extraordinary data source that can be utilized to detect and quantify natural selection in the genetic architecture of complex traits. In this review, we focus on recent discoveries about selection on genetic variants associated with human complex traits based on GWAS-facilitated methods.

Addresses
[1] Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland 4072, Australia
[2] Queensland Brain Institute, The University of Queensland, Brisbane, Queensland 4072, Australia

Corresponding author: Visscher, Peter M (peter.visscher@uq.edu.au)

Current Opinion in Genetics & Development 2018, **53**:9–14

This review comes from a themed issue on **Genetics of human origins**

Edited by **Brenna M Henn** and **Lluis Quintana-Murci**

For a complete overview see the Issue and the Editorial

Available online 16th June 2018

https://doi.org/10.1016/j.gde.2018.05.012

Introduction

Quantitative genetics aims to understand trait variation within and between populations, including how genetic variation arises, is maintained and changes over generations. Genetic architecture of any complex trait can be defined as the number of loci affecting the trait and the joint distribution of allele frequency and effect size at the trait-associated loci [1•]. The genetic architecture of a complex trait could be shaped by natural selection, since observations about the segregation of loci that are associated with a trait in the current population is a consequence of evolutionary forces in the past. For example, trait-associated variants that reduce fitness will be constrained in frequency and, conversely, variants that confer increased adaptation will tend to increase in frequency [2•].

In the past decade, the experimental design of genome-wide association studies (GWAS) has provided unprecedented insights into the genetic basis of complex trait variation in humans [3]. In addition to individual-level data (genome-wide genotypes and one or multiple phenotypes measured on the same individuals), there are now GWAS summary statistics available on hundreds of complex traits, each consisting of estimated effect sizes and sampling variance at millions of SNP variants. This extraordinary data source can be leveraged to detect signatures of natural selection in the genetic architecture of complex traits.

Here we review recent discoveries about selection on genetic variants associated with complex traits using GWAS data. We first briefly overview the essence of classical and their recently extended versions of genome-wide scanning approaches for locus-specific signatures of positive selection (natural selection favouring beneficial mutations) and then focus on summarizing GWAS-facilitated methods and their applications to identify signals of natural selection on alleles associated with complex traits.

Genome-wide scanning approaches for locus-specific signatures of selection

There are multiple empirical methods to detect evidence of selection without the knowledge of how individual loci or genes are associated with traits or fitness.

Signals of positive selection have been detected at more than 4000 gene loci through a variety of approaches such as the genome-wide scans using molecular polymorphism data within and between populations and comparative methods using sequence divergence between human and other primates and between modern and archaic humans (e.g. Neanderthals and Denisovans) [4]. Positive selection increases the frequency of the focal variant and reduces genetic variation at its linked neighbouring loci. Genome-wide scanning approaches detect such variation patterns and test against expectation under neutrality (refer to [4,5] for a comprehensive review of methods and [2•] for exemplars of local adaptation in humans). Most methods of this kind utilize changes in allele frequency or linkage disequilibrium (LD) (Table 1). A strong selective sweep can push variants under selection to fixation, giving rise to increased homozygosity at nearby neutral loci due to LD.

Table 1

Methods to detect selection signals at individual locus and loci associated with human complex traits

	Genome-wide scans for locus-specific selection without trait information	GWAS-facilitated analysis for selection at trait-associated loci
Allele frequency-based	A surplus of rare alleles [56]	Singleton density score to infer allele frequency shifts associated with complex traits [55••]
	Distorted spectrum towards derived alleles [57]	Variation of allele frequencies among populations at trait-associated loci [22]
	Extreme differentiation between populations measuring by locus-specific F_{ST} [58]	Differentiation of genetic predictors (allele frequencies weighted by genetic effects) between populations [26]
	Correlation of differences in allele frequency to non-genetic factors (e.g. discrete population index, gradients of population ancestry, age groups and ecological conditions) [9,11,14,15]	Relationship between allele frequency and genetic effect [38••,41]
LD-based	Homozygosity of haplotypes [6]	Variation of LD scores among populations at trait-associated loci [23]
	LD decay of homozygous SNPs [59]	
	Identity-by-decent (IBD) analyses [60]	Levels of LD versus per-SNP heritability within population [39••]

The LD-based approaches essentially assess the excess of homozygosity around a locus to test whether the locus has been under selection. Such methods (e.g. integrated haplotype score (iHS) [[2•]]) have been shown to be more powerful than allele-frequency-based approaches in detecting signals of incomplete selective sweep, where the variants under selection are still segregating in the population.

Different alleles can be favoured in different populations due to varied environmental conditions, resulting in differentiation of allele frequency between populations (measured as Wright's fixation index (F_{ST}) [7]) [8]. Such differentiation can be implemented in the framework of regression to detect association with different environmental factors [9,10], age groups [11,12] and populations [13–15] (Table 1). For example, Yang *et al.* detected genome-wide signals of high-altitude adaptation in Tibetans by testing the difference in allele frequency of each SNP between Tibetan and Han Chinese populations, whilst conditioning on the background genetic differentiation between these populations by fitting a mixed linear model [15].

In GWAS, principal component analysis (PCA) on SNP data is routinely used to detect, quantify and adjust for population structure [16]. PCA can also be used to detect evidence of selection, by testing the association of individual loci with a principal component (PC). If specific genomic loci explain a disproportionate amount of variation in PCs then this is evidence for selection because under drift population differences are randomly spread among many loci. PC-based selection statistics are conceptually very close to the estimates of SNP-specific F_{ST} [17], but can provide meaningful genome-wide statistical inference and are more suitable when populations are admixed or when pre-specification of populations is not available [13,14,18].

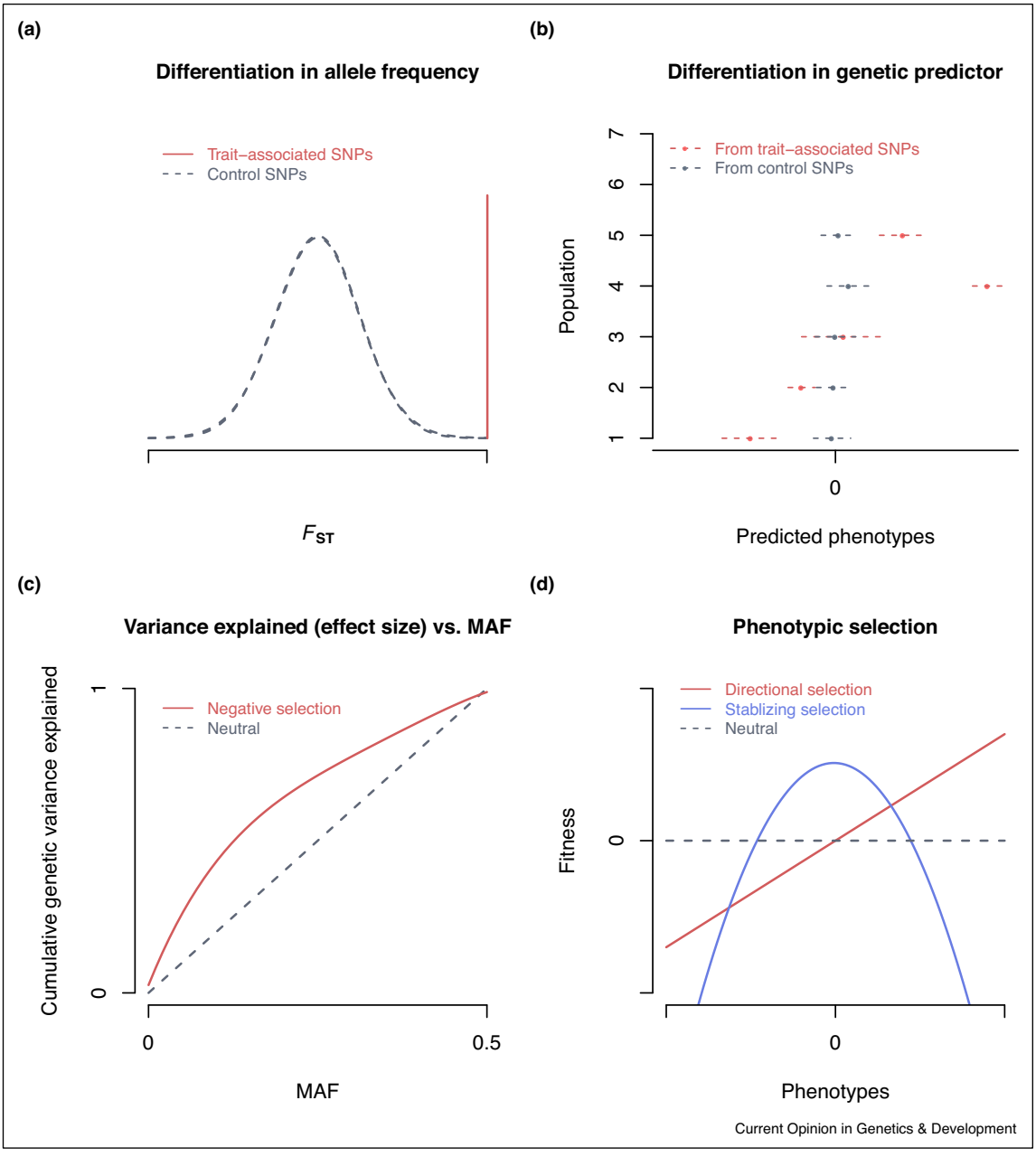
GWAS-based approaches for signatures of selection at trait-associated loci

It has been shown in GWAS that most human complex traits, including common diseases, are highly polygenic, that is, the genetic variation of a complex trait in a population is caused by a large number of genetic variants [3]. This means that the effect of an individual locus on the trait is, on average, small, which implies that the signatures of selection at trait-associated loci are also likely to be small. Therefore, methods that interrogate the genome for signatures of selection without the use of trait information are not powerful when selection and adaptation is polygenic [19]. GWAS data can be leveraged in a number of ways to detect and quantify selection, first, by contrasting differences in population frequencies of trait-associated variants to frequencies of the same number of variants chosen at random (with similar minor allele frequency (MAF) and LD features as the associated variants), second, by quantifying the variation in predicted genetic values between and within populations, and third, by quantifying the relationship between effect sizes and allele frequencies across loci. In this section, we discuss these methods to detect signatures of selection facilitated by GWAS data (Table 1).

Differentiation in allele frequency at trait-associated loci

There is substantial difference in phenotypic mean among human populations for many complex traits, for example height [20] and prevalence of common disease such as schizophrenia [21]. Such phenotypic differences have led researchers to investigate whether this is associated with genetic differentiation in allele frequency at trait-associated loci and whether the genetic differentiation is driven by natural selection. The first attempt traces back to Lohmueller *et al.* [22] at the early stage of GWAS, where the mean F_{ST} value of a set of 39 GWAS-identified SNPs associated with ~20 traits did not appear to show stronger differentiation than that of random SNPs in the

Figure 1



Detection and quantification of natural selection using GWAS data. The four schematic plots correspond to GWAS-based approaches to quantify differentiation in **(a)** allele frequencies and **(b)** genetic predictors, **(c)** to model the relationship between MAF and effect sizes of SNPs and **(d)** to estimate the strength of selection on phenotypes via fitness.

genome. A more recent study [23] detected signatures of natural selection at SNPs associated with three complex traits: height, schizophrenia and waist-hip-ratio adjusted to body-mass-index (Figure 1a). This study gained power from using summary-level data from published GWAS with very large sample sizes (n = up to ~405 000). The direction of genetic differentiation (at least partly driven by natural selection) varied across traits and populations. For example, the trait-increasing loci were enriched in Europeans for height but East Asians were enriched for alleles that were associated with increased waist-to-hip ratio. Such a systematic shift was first reported for height between Northern and Southern Europeans [24].

Differentiation in genetic predictors across populations and over time

We have mentioned above that systematic frequency shifts at many loci under polygenic selection will lead

to a difference in mean genetic values between populations. These can in principle be detected using genetic predictors. Genetic predictors of a trait (sometimes termed polygenic scores or polygenic risk scores) are the sum of alleles weighted by their corresponding genetic effects estimated in GWAS [25]. Berg *et al.* made use of genetic predictors to detect local adaptation by testing if the genetic predictors for a given trait are overdispersed among populations against that expected under a neutral model [26]. Racimo *et al.* recently presented a novel method to detect which population is subject to natural selection and when the selection processes occurred [27]. However, caution is required when interpreting the detected signals given first, the existing debate of the portability of GWAS results (e.g. effect sizes of genetic variants) generated in European ancestry populations to non-European populations andsecond, a potential between-population difference in LD between GWAS tag variants and true causal variants [28–30]. Robinson *et al.* found selection signals based on the predicted height across fourteen European countries by focusing on trait-associated loci selected via meta-analysis in a European-ancestry sample but re-estimating the genetic effects in a within-family study design to avoid the confounding in estimated SNP effects due to population stratification [31] (Figure 1b).

Genetic predictors can also be used to investigate a shift in the mean genetic value for a trait in a population over time. Kong *et al.* applied a genetic predictor of educational attainment (a proxy for intelligence and other behavioural traits) to data spanning a 100-year period in Iceland and observed a decrease in the average value of the predictor, consistent with a reported negative genetic covariance between reproductive fitness and educational attainment [32].

Relationship between allele frequency and effect size

Mutations with large effects on traits might have been maintained at low frequencies due to their disadvantageous effects on fitness, by negative selection (selective removal of deleterious alleles) [33]. Such an inverse relationship between allele frequencies and effect sizes has been used to detect signatures of selection [34–36]. Speed and colleagues proposed to fit a parameter to model the association between effect size and allele frequency directly in the context of estimation genetic variation from individual-level GWAS data [37]. Zeng *et al.* recently used a Bayesian mixed linear model to estimate the relationship between MAF and effect size, the degree of polygenicity and SNP-based heritability simultaneously from GWAS data [38••] (Figure 1c). They found widespread signatures of negative selection across 23 traits including reproduction related traits such as age at menopause and waist-hip-ratio, anthropometric traits such as height and behaviour traits such as education attainment years, in line with previous reports [39••,40]. These findings appear to contradict the signals of local positive selection detected for height as discussed above. However, the authors proposed that when the genetic variants of a trait are undergoing stronger negative selection than positive selection, a population as a whole evolves towards adaptation whilst stabilizing selection keeps deleterious alleles at low frequencies. Whereas Zeng *et al.* estimated the relationship between effect size and allele frequency from GWAS data directly and interpreted the estimated parameter in terms of selection, a different approach is to model the selection process explicitly by assuming an evolutionary model [34,41]. Simons and colleagues modelled the genetic architecture of a trait assuming stabilizing selection and pleiotropy, and estimated selection coefficients of $\sim$0.001 at loci associated with height and BMI from GWAS summary statistics [41].

Detection of phenotypic selection in contemporary populations

GWAS data in the current population can be used to detect signals of natural selection in the past that have caused population frequency differences at trait-associated alleles, mean genetic differences between populations and an association between effect size and allele frequency. GWAS data can also be leveraged to quantify phenotypic selection in contemporary populations, by using a proxy trait for fitness. The most commonly used proxy trait of fitness is lifetime reproductive success (LRS; the number of children ever born for females or children fathered for males), reflecting the genetic contribution of an individual to the next generation [42]. Barban *et al.* leveraged GWAS in European samples to identify genetic loci influencing the traits age at first birth and/or number of children ever born, reproductive behavioural traits strongly related to fitness. They detected 12 independent SNP-based loci and one locus harbours SNPs with signals of positive selection detected by iHS [43]. On the phenotypic level, how strongly selection acts can be inferred from a linear regression of fitness (e.g. relative LRS, individual LRS divided by the population mean) on trait values (also known as selection gradient) [44] (Figure 1d). Accordingly, the effects of selection on the genetic level can be inferred by estimating the correlation coefficients between rLRS and genetic predictors built from external GWAS summary data [32,45••] or by estimating the genetic correlation between rLRS and a trait of interest (e.g. height), using a mixed linear model analysis of individual-level genotype data [46] or LD score regression analysis of summary data [47]. Previous studies found consistent evidence of directional selection on anthropometric traits (e.g. increased body-mass-index (BMI) and decreased height) at both the phenotypic and genetic level. In contrast, only partial agreement was found for phenotypically more complex traits, e.g. reproduction. For example, the correlation between age at menopause and rLRS is positive at a phenotypic level but appears to be negative at the genetic level [47]. The latter is inconsistent with a previous finding that selection tends to

increase reproductive lifespan (earlier age at first birth and later age at menopause) (see [48] and Discussion in [47]).

Future directions

We have reviewed how GWAS data and methods can be leveraged to detect and quantify selection for human complex traits. A few points of caveats and potential interests for future studies are worth to point out. First, widespread polygenicity [3,49] and pleiotropy [50,51] are the two primary characteristics of the genetic architecture of complex traits. Therefore, GWAS-based results of polygenic tests of selection need careful interpretation [30]. For example, the differentiation signals of allele frequency at trait-associated loci do not necessarily mean the traits themselves have been directly targeted by selection but probably through the genetic variants that have pleiotropic effects on fitness [52]. Studies making use of fitness-proxy traits or multiple traits in one context [53] are expected to illustrate this more directly. Second, whole-genome sequencing data will provide more accurate measures of selection for the genetic variants with low frequencies. Johnson and Voight recently used an extended version of the iHS method to detect positive selection signals within and shared between 20 populations using whole genome sequence (WGS) data from the 1000 Genomes Project [54]. Field *et al.* used WGS data leveraged by GWAS results to infer very recent (past ~80 to 120 generations) changes in allele frequencies at trait loci, consistent with polygenic sweeps for height and other traits [55••].

In the future, there will be deeper coverage of genetic data (from SNP arrays to sequence data), results from ever-larger GWAS for more traits and across multiple populations. Such data will offer opportunities to better understand genetic differences in trait values between and within populations and should lead to the estimation of locus-specific selection coefficients.

Conflict of interest statement

Nothing declared.

Acknowledgements

This research was supported by the Australian National Health and Medical Research Council (1078037 and 1113400) and the Sylvia & Charles Viertel Charitable Foundation.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. • Timpson NJ, Greenwood CMT, Soranzo N, Lawson DJ, Richards JB: **Genetic architecture: the shape of the genetic contribution to human traits and disease**. *Nat Rev Genet* 2018, **19**:110-124.
A recent and comprehensive review of genetic architecture of human traits including the influence of selection.

2. • Fan S, Hansen ME, Lo Y, Tishkoff SA: **Going global by adapting local: a review of recent human adaptation**. *Science* 2016, **354**:54-59.
A comprehensive review of human genetic adaptation across various environmental conditions such as diet, latitude and pathogen exposure.

3. Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MIMI, Brown MA, Yang J, Visscher PM, Brown MA, McCarthy MIMI *et al.*: **10 years of GWAS discovery: biology, function, and translation**. *Am J Hum Genet* 2017, **101**:5-22.

4. Fu W, Akey JM: **Selection and adaptation in the human genome**. *Annu Rev Genomics Hum Genet* 2013, **14**:467-489.

5. Vitti JJ, Grossman SR, Sabeti PC: **Detecting natural selection in genomic data**. *Annu Rev Genet* 2013, **47**:97-120.

6. Voight BF, Kudaravalli S, Wen X, Pritchard JK: **A map of recent positive selection in the human genome**. *PLoS Biol* 2006, **4**:e72.

7. Wright S: **The genetical structure of populations**. *Ann Eugen* 1951, **15**:323-354.

8. Lewontin R, Krakauer J: **Distribution of gene frequency as a test of the theory of the selective neutrality of polymorphisms**. *Genetics* 1973, **74**:175-195.

9. Novembre J, Di Rienzo A: **Spatial patterns of variation due to natural selection in humans**. *Nat Rev Genet* 2009, **10**:745-755.

10. Coop G, Witonsky D, Di Rienzo A, Pritchard JK: **Using environmental correlations to identify loci underlying local adaptation**. *Genetics* 2010, **185**:1411-1423.

11. Mostafavi H, Berisa T, Day FR, Perry JRB, Przeworski M, Pickrell JK: **Identifying genetic variants that affect viability in large cohorts**. *PLoS Biol* 2017, **15**:e2002458.

12. Rodríguez JA, Marigorta UM, Hughes DA, Spataro N, Bosch E, Navarro A: **Antagonistic pleiotropy and mutation accumulation influence human senescence and disease**. *Nat Ecol Evol* 2017, **1**:1-5.

13. Galinsky KJ, Bhatia G, Loh PR, Georgiev S, Mukherjee S, Patterson NJ, Price AL: **Fast principal-component analysis reveals convergent evolution of ADH1B in Europe and East Asia**. *Am J Hum Genet* 2016, **98**:456-472.

14. Chen G-B, Lee SH, Zhu Z-X, Benyamin B, Robinson MR: **EigenGWAS: finding loci under selection through genome-wide association studies of eigenvectors in structured populations**. *Heredity* 2016, **117**:51-61.

15. Yang J, Jin ZB, Chen J, Huang XF, Li XM, Liang YB, Mao JY, Chen X, Zheng Z, Bakshi A *et al.*: **Genetic signatures of high-altitude adaptation in Tibetans**. *Proc Natl Acad Sci U S A* 2017, **114**:4189-4194.

16. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D: **Principal components analysis corrects for stratification in genome-wide association studies**. *Nat Genet* 2006, **38**:904-909.

17. McVean G: **A genealogical interpretation of principal components analysis**. *PLoS Genet* 2009, **5**:e1000686.

18. Duforet-Frebourg N, Luu K, Laval G, Bazin E, Blum MGB: **Detecting genomic signatures of natural selection with principal component analysis: application to the 1000 genomes data**. *Mol Biol Evol* **(33)**:2016:1082-1093.

19. Pritchard JK, Pickrell JK, Coop G: **The genetics of human adaptation: hard sweeps, soft sweeps, and polygenic adaptation**. *Curr Biol* 2010, **20**:R208-R215.

20. Stulp G, Barrett L: **Evolutionary perspectives on human height variation**. *Biol Rev Camb Philos Soc* 2016, **91**:206-234.

21. Schwartz RC, Blankenship DM: **Racial disparities in psychotic disorder diagnosis: a review of empirical literature**. *World J Psychiatry* 2014, **4**:133-140.

22. Lohmueller KE, Mauney MM, Reich D, Braverman JM: **Variants associated with common disease are not unusually differentiated in frequency across populations**. *Am J Hum Genet* 2006, **78**:130-136.

23. Guo J, Wu Y, Zhu Z, Zheng Z, Trzaskowski M, Zeng J, Robinson MR, Visscher PM, Yang J: **Global genetic differentiation of complex traits shaped by natural selection in humans**. *Nat Commun* 2018, **9**:1865.

24. Turchin MC, Chiang CWK, Palmer CD, Sankararaman S, Reich D, Hirschhorn JN: **Evidence of widespread selection on standing variation in Europe at height-associated SNPs**. *Nat Genet* 2012, **44**:1015-1019.

25. Dudbridge F: **Power and predictive accuracy of polygenic risk scores**. *PLoS Genet* 2013, **9**:e1003348.

26. Berg JJ, Coop G: **A population genetic signal of polygenic adaptation**. *PLoS Genet* 2014, **10**:e1004412.

27. Racimo F, Berg JJ, Pickrell JK: **Detecting polygenic adaptation in admixture graphs**. *Genetics* 2018, **208**:1565-1584.

28. Carlson CS, Matise TC, North KE, Haiman CA, Fesinmeyer MD, Buyske S, Schumacher FR, Peters U, Franceschini N, Ritchie MD *et al.*: **Generalization and dilution of association results from European GWAS in populations of non-European ancestry: the PAGE study**. *PLoS Biol* 2013, **11**:e1001661.

29. Martin AR, Gignoux CR, Walters RK, Wojcik GL, Neale BM, Gravel S, Daly MJ, Bustamante CD, Kenny EE: **Human demographic history impacts genetic risk prediction across diverse populations**. *Am J Hum Genet* 2017, **100**:635-649.

30. Novembre J, Barton NH: **Tread lightly interpreting polygenic tests of selection**. *Genetics* 2018, **208**:1351-1355.

31. Robinson MR, Hemani G, Medina-Gomez C, Mezzavilla M, Esko T, Shakhbazov K, Powell JE, Vinkhuyzen A, Berndt SI, Gustafsson S *et al.*: **Population genetic differentiation of height and body mass index across Europe**. *Nat Genet* 2015, **47**:1357-1362.

32. Kong A, Frigge ML, Thorleifsson G, Stefansson H, Young AI, Zink F, Jonsdottir GA, Okbay A, Sulem P, Masson G *et al.*: **Selection against variants in the genome associated with educational attainment**. *Proc Natl Acad Sci U S A* 2017, **114**: E727-E732.

33. Bodmer W, Bonilla C: **Common and rare variants in multifactorial susceptibility to common diseases**. *Nat Genet* 2008, **40**:695-701.

34. Eyre-Walker A: **Genetic architecture of a complex trait and its implications for fitness and genome-wide association studies**. *Proc Natl Acad Sci* 2010, **107**:1752-1756.

35. Mancuso N, Rohland N, Rand KA, Tandon A, Allen A, Quinque D, Mallick S, Li H, Stram A, Sheng X *et al.*: **The contribution of rare variation to prostate cancer heritability**. *Nat Genet* 2016, **48**:30-35.

36. Yang J, Bakshi A, Zhu Z, Hemani G, Vinkhuyzen AA, Lee SH, Robinson MR, Perry JR, Nolte IM, van Vliet-Ostaptchouk JV *et al.*: **Genetic variance estimation with imputed variants finds negligible missing heritability for human height and body mass index**. *Nat Genet* 2015, **47**:1114-1120.

37. Speed D, Cai N, Consortium U, Johnson MR, Nejentsev S, Balding DJ: **Reevaluation of SNP heritability in complex human traits**. *Nat Genet* 2017, **49**:986-992.

38. •• Zeng J, de Vlaming R, Wu Y, Robinson MR, Lloyd-Jones LR, Yengo L, Yap CX, Xue A, Sidorenko J, McRae AF *et al.*: **Signatures of negative selection in the genetic architecture of human complex traits**. *Nat Genet* 2018 http://dx.doi.org/10.1038/s41588-41018-40101-41584.

Application of a Bayesian mixed linear model on GWAS data to estimate the relationship between MAF and effect sizes of SNPs and detects signatures of negative selection for a number of human complex traits.

39. •• Gazal S, Finucane HK, Furlotte NA, Loh PR, Palamara PF, Liu X, Schoech A, Bulik-Sullivan B, Neale BM, Gusev A *et al.*: **Linkage disequilibrium-dependent architecture of human complex traits shows action of negative selection**. *Nat Genet* 2017, **49**:1421-1427.

This study showed that the evolutionary youngest 20% common variants explain four times more heritability than the oldest 20%, an indication of negative selection.

40. Schoech A, Jordan D, Loh P-R, Gazal S, O'Connor L, Balick DJ, Palamara PF, Finucane H, Sunyaev SR, Price AL: **Quantification of frequency-dependent genetic architectures and action of negative selection in 25 UK Biobank traits**. *bioRxiv* 2017:188086.

41. Simons YB, Bullaughey K, Hudson RR, Sella G: **A population genetic interpretation of GWAS findings for human quantitative traits**. *PLoS Biol* 2018, **16**:e2002985.

42. Stearns SC, Byars SG, Govindaraju DR, Ewbank D: **Measuring selection in contemporary human populations**. *Nat Rev Genet* 2010, **11**:611-622.

43. Barban N, Jansen R, de Vlaming R, Vaez A, Mandemakers JJ, Tropf FC, Shen X, Wilson JF, Chasman DI, Nolte IM *et al.*: **Genome-wide analysis identifies 12 loci influencing human reproductive behavior**. *Nat Genet* 2016, **48**:1462-1472.

44. Lande R, Arnold SJ: **The measurement of selection on correlated characters**. *Evolution* 1983.

45. •• Beauchamp JP: **Genetic evidence for natural selection in humans in the contemporary United States**. *Proc Natl Acad Sci U S A* 2016, **113**:7774-7779.

Application of a genetic predictor approach from GWAS data across to detect genetic covariance between complex traits and fitness in a contemporary population.

46. Tropf FC, Stulp G, Barban N, Visscher PM, Yang J, Snieder H, Mills MC: **Human fertility, molecular genetics, and natural selection in modern societies**. *PLOS ONE* 2015.

47. Sanjak JS, Sidorenko J, Robinson MR, Thornton KR, Visscher PM: **Evidence of directional and stabilizing selection in contemporary humans**. *Proc Natl Acad Sci U S A* 2018, **115**:151-156.

48. Byars SG, Ewbank D, Govindaraju DR, Stearns SC: **Natural selection in a contemporary human population**. *Proc Natl Acad Sci* 2010, **107**:1787-1792.

49. Boyle EA, Li YI, Pritchard JK: **An expanded view of complex traits: from polygenic to omnigenic**. *Cell* 2017, **169**:1177-1186.

50. Visscher PM, Yang J: **A plethora of pleiotropy across complex traits**. *Nat Genet* 2016, **48**:707-708.

51. Pickrell JK, Berisa T, Liu JZ, Segurel L, Tung JY, Hinds DA: **Detection and interpretation of shared genetic influences on 42 human traits**. *Nat Genet* 2016, **48**:709-717.

52. Johnson T, Barton N: **Theoretical models of selection and mutation on quantitative traits**. *Philos Trans R Soc Lond B Biol Sci* 2005, **360**:1411-1425.

53. Berg JJ, Zhang X, Coop G: **Polygenic adaptation has impacted multiple anthropometric traits**. *bioRxiv* 2017:1-38.

54. Johnson KE, Voight BF: **Patterns of shared signatures of recent positive selection across human populations**. *Nat Ecol Evol* 2018, **2**:713-720.

55. •• Field Y, Boyle EA, Telis N, Gao Z, Gaulton KJ, Golan D, Yengo L, Rocheleau G, Froguel P, Mark I *et al.*: **Detection of human adaptation during the past 2,000 years**. *Science (New York, NY)* 2016, **354**:760-764.

This paper provides a new method to detect allele frequency shifts at trait-associated loci in the past 2000 years driven by natural selection.

56. Tajima F: **Statistical method for testing the neutral mutation hypothesis by DNA polymorphism**. *Genetics* 1989, **123**:585-595.

57. Fay JC, Wu CI: **Hitchhiking under positive Darwinian selection**. *Genetics* 2000, **155**:1405-1413.

58. Akey JM, Zhang G, Zhang K, Jin L, Shriver MD: **Interrogating a high-density SNP map for signatures of natural selection**. *Genome Res* 2002, **12**:1805-1814.

59. Wang ET, Kodama G, Baldi P, Moyzis RK: **Global landscape of recent inferred Darwinian selection for *Homo sapiens***. *Proc Natl Acad Sci U S A* 2006, **103**:135-140.

60. Cai Z, Camp NJ, Cannon-Albright L, Thomas A: **Identification of regions of positive selection using shared genomic segment analysis**. *Eur J Hum Genet* 2011, **19**:667-671.