The new genetics of intelligence

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Abstract | Intelligence — the ability to learn, reason and solve problems — is at the forefront of behavioural genetic research. Intelligence is highly heritable and predicts important educational, occupational and health outcomes better than any other trait. Recent genome-wide association studies have successfully identified inherited genome sequence differences that account for 20% of the 50% heritability of intelligence. These findings open new avenues for research into the causes and consequences of intelligence using genome-wide polygenic scores that aggregate the effects of thousands of genetic variants.

Twin studies
Studies comparing the resemblance of identical and fraternal twins to estimate genetic and environmental components of variance.

Variance
An index of how spread out scores are in a study population, which is calculated as the average of the squared deviations from the mean.

Genome-wide association studies
(GWAS). Studies that aim to identify loci throughout the genome associated with an observed trait or disorder.

Heritability
The proportion of observed differences among individuals that can be attributed to inherited differences in genome sequence.

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Life is an intelligence test. During the school years, differences in intelligence are largely the reason why some children master the curriculum more readily than other children. Differences in school performance predominantly inform prospects for further education, which in turn lead to social and economic opportunities such as those related to occupation and income. In the world of work, intelligence matters beyond educational attainment because it involves the ability to adapt to novel challenges and tasks that describe the different levels of complexity of occupations. Intelligence also spills over into many aspects of everyday life, such as the selection of romantic partners and choices about health care[1]. This is why intelligence — often called general cognitive ability[2] — predicts educational outcomes[3], occupational outcomes[4,5] and health outcomes[6] better than any other trait. It is also the most stable psychological trait, with a Pearson correlation coefficient of 0.54 from 11 to 90 years of age[7]. BOX 1 describes what intelligence is and how it is assessed.

During the past century, genetic research on intelligence was in the eye of the storm of the nature–nurture debate in the social sciences[8,9]. In the 1970s and 1980s, intelligence research and its advocates were vilified[10–12]. The controversy was helpful in that it raised the quality and quantity threshold for the acceptance of genetic research on intelligence. As a result, bigger and better family studies, twin studies and adoption studies have amassed a mountain of evidence that consistently showed substantial genetic influence on individual differences in intelligence[13]. Meta-analyses of this evidence indicate that inherited differences in DNA sequence account for about half of the variance in measures of intelligence[14].

These studies and applications in neuroscience[15] were already pushing intelligence research towards rehabilitation when it was thrust to the forefront of the DNA revolution 4 years ago by genome-wide association studies (GWAS) focused on a very different variable — years of education. In this Review, we discuss early attempts to find the inherited genetic differences that account for the substantial heritability of intelligence, and a twist of fate involving GWAS on years of education, before discussing the results of recent large GWAS on intelligence. The second half of this Review focuses on genome-wide polygenic scores (GPSs) for intelligence that aggregate the effects of thousands of DNA variants associated with intelligence across the genome (see BOX 2 for how GPSs are constructed). We illustrate how GPSs for intelligence will transform research on the causes and consequences of individual differences in intelligence before ending with a discussion of societal and ethical implications. We do not discuss other important research related to intelligence, such as evolutionary research[16,17] and neuroscience research[15], in order to focus on the role of GPSs in the new genetics of intelligence.

Finding the heritability of intelligence

Similar to results for many other complex traits, early results for intelligence were disappointing for more than 100 candidate gene studies[18] and for seven GWAS[19–25]. From the 1990s until 2017, no replicable associations were found. GPSs from these early GWAS, which we refer to collectively as 'IQ1', predicted only 1% of the variance of intelligence in independent samples. It became clear that the problem was power: the largest effect sizes of associations between individual single-nucleotide polymorphisms (SNPs) and intelligence were extremely small, accounting for less than 0.05% of the variance of intelligence. The average effect size of the tens of thousands of SNPs needed to explain the 50% heritability of intelligence is of course much lower. If the average effect size is 0.005%, 10,000 such SNP associations would be needed to explain the 50% heritability of intelligence. To achieve sufficient power for detecting such small effect sizes (that is, power of 80%, $P = 0.05$, one-tailed), sample

Genome-wide polygenic scores
(GPSs). Genetic indices of a trait for each individual that are the sum across the genome of thousands of single-nucleotide polymorphisms (SNPs) of the individual's increasing alleles associated with the trait, usually weighted by the effect size of each SNP's association with the trait in genome-wide association studies.

Candidate gene studies
Studies that focus on genes for which the function suggests that they are associated with a trait, in contrast to genome-wide association studies.

sizes greater than 250,000 are required. Early IQ GWAS had sample sizes from 18,000 to 54,000, which seemed large at the time but were not sufficiently powered to detect such small effects.

Breakthrough for years of education. A breakthrough for intelligence research came from the unlikely variable of the number of years spent in full-time education, often referred to as educational attainment. Because 'years of education' is obtained as a demographic marker in nearly every GWAS, it was possible to accumulate sample sizes with the necessary power to detect very small effect sizes[26]. Its relevance to intelligence is that years of education is highly correlated phenotypically (0.50) and genetically (0.65) with intelligence[27].

In 2013, a meta-analytic GWAS analysis of years of education yielded three genome-wide significant SNP associations in a sample of 125,000 individuals from 54 cohorts[28]. These associations could be replicated in independent samples[29]. The largest effect size associated with an individual SNP accounted for a meagre 0.02% of the variation, equivalent to about 2 months of education. Although individual SNPs of such minuscule effect size are fairly useless for prediction, a GPS based on all SNPs regardless of the strength of their association with years of education predicted 2% of the variance in years of education in independent samples[28,29]. We refer to this GPS as 'EA1' (where EA stands for educational attainment).

Spurred on by this success, in 2016, a second meta-analytic GWAS analysis with a sample size of 294,000 identified 74 significant loci[30]. This analysis produced a GPS, EA2, that predicted 3% of the variance in years of education on average in

Box 1 | **What is intelligence?**

Intelligence can be broadly defined as the ability to learn, reason and solve problems[74]. It is a latent trait that cannot be directly observed but is inferred from a battery of diverse cognitive test scores, as in widely used 'intelligence tests' that yield a so-called IQ score, in which IQ is an acronym for an outdated concept of an 'intelligence quotient'. Psychometric tests of cognitive abilities differ widely in form and content. For example, some psychometric tests assess verbal ability and others, nonverbal ability; some give strict time limits, and some are untimed (see figure for examples). Notwithstanding these differences, cognitive test scores are positively intercorrelated[75], suggesting that any differences in test scores that occur within an individual are smaller than test score differences that exist between individuals. In other words, a person who scores high on one type of cognitive test relative to other people will also do comparatively well on other cognitive tests. This phenomenon is known as the positive manifold, or simply 'g', the general factor of intelligence, which emerges from the test scores' covariance and was discovered by Spearman in 1904 (REF. 76), about the same time that Mendel's laws of inheritance were rediscovered. The g-factor exemplifies the generalist nature of intelligence as a complex trait that penetrates many behavioural and psychological outcomes, including educational attainment, occupational status, health and longevity[77,78].

Individual differences in intelligence are fairly stable across the lifespan, especially from teenage years onwards, with correlations of 0.6 and above[32,79]. However, intelligence is also subject to change, both within and between individuals. For example, scores from timed cognitive tests tend to peak in young adulthood and decline thereafter[80]. More importantly, intelligence has been shown to be malleable, especially in children, through major systematic interventions, such as education[81], dietary supplementation[82] or adopting children away from impoverished home environments[83]. That said, identifying ways to effectively improve intelligence remains a key challenge for intelligence research, with many interventions failing to produce reliable and long-term positive effects[82,84,85].

Missing letter

Which one letter completes these words?

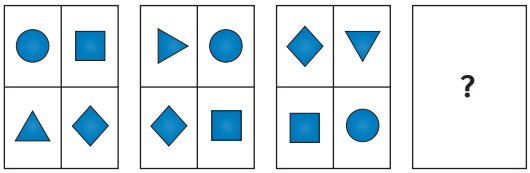
CA*
*US
RU*Y
*OTH

Complete the sentence

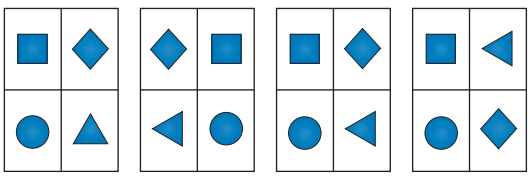
Which two words complete the sentence?

Fingers are to **nails/fish/gloves/hands**
as toes are to **tip/feet/flip-flops/running**.

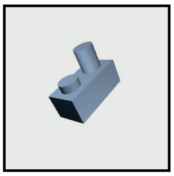
Complete the sequence



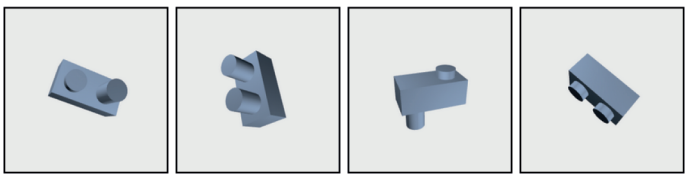
Which picture completes the pattern above?



Match the shape



Which of the four options is the same object shown above?



independent samples[30]. Surprisingly, GPSs for years of education predicted more variance in intelligence than they predicted for the GWAS target trait of years of education[27]. For example, the EA2 GPS predicts 3% of the variance in years of education but it predicts 4% of the variance in intelligence[30]. A third GWAS currently in progress includes more than 1 million participants, making it the largest GWAS for any trait to date. Preliminary results from this GWAS have identified more than 1,000 significant associations and a GPS, EA3, that predicts more than 10% of the variance in years of education in independent samples[31] (P. D. Koellinger, personal communication). Hence, the EA3 GPS is expected to predict more than 10% of the variance in intelligence. The effect size of the EA3 GPS for predicting intelligence is likely to rival that of family socio-economic status, which is indexed by parents' years of education. Across studies, the correlation value for parents' education with children's intelligence is 0.30, implying that it accounts for 9% of the variance in children's intelligence[32]. However, this association is confounded by genetics because children inherit the DNA differences that predict their intelligence from their parents. Furthermore, parental phenotypes, such as education, estimate only an average association for offspring, whereas GPSs predict intelligence for each individual.

Box 2 | **Creating genome-wide polygenic scores**

Thousands of single-nucleotide polymorphisms (SNPs) are needed to account for the heritability of intelligence and other complex traits because the effect sizes of SNP associations are so small. Aggregating thousands of these minuscule effects in a genome-wide polygenic score (GPS) is the crux of the new genetics of intelligence. There are at least a dozen labels to denote GPSs. Most involve the word 'risk', such as polygenic risk scores. We prefer the term 'genome-wide polygenic score' because 'risk' does not apply to quantitative traits, such as intelligence, that have positive as well as negative poles[86]. The 'genome-wide' addition to 'polygenic score' distinguishes GPSs from polygenic scores that aggregate candidate genes or just the top hits from genome-wide association studies (GWAS). Finally, another reason for using the acronym GPS is that we cannot resist the metaphor of the other 'GPS', global positioning system. We see IQ GPSs as a system to triangulate on the genetics of intelligence from all domains of the life sciences.

An intelligence test score is a composite of several tests, often with each test weighted by its contribution to general intelligence. In the same way, a GPS is a composite of SNP associations, weighted by their correlation with the trait. The table shows how a GPS could be constructed for one individual for ten SNPs. GWAS results are used to determine which of the two alleles for a SNP is positively associated with the trait, called the 'increasing allele'. For each SNP, a genotypic score is created by adding the number of increasing alleles. A GPS sums the number of increasing alleles across SNPs, which is why this is called an additive model. In this example, the individual's GPS is 9. Because there are 10 SNPs, the possible range of the GPS is from 0 to 20.

A more predictive GPS can be constructed by weighting each genotypic score by the effect size of the SNP (β for quantitative traits, odds ratio for qualitative traits) as gleaned from GWAS results (see table). For instance, for SNP 1, the correlation with the trait is five times greater than for SNP 10. Multiplying the genotypic score by the correlation gives a weighted genotypic score (see table, last column). Summing these weighted genotypic scores gives this individual a GPS of 0.023 for intelligence. Other ways to improve the predictive power of GPSs include taking into account expected SNP effect sizes, the genetic architecture of the trait and specifically modelling linkage disequilibrium[87]. Programmes including LDpred[88] and PRSice[89] provide pipelines for the construction of GPSs.

How many SNPs should be included in a GPS? The goal is to maximize predictive power in samples independent from the GWAS samples. The use of only genome-wide significant hits does not predict nearly as well as the use of tens of thousands of SNPs. LDpred uses all SNPs, imputed as well as measured, although most SNPs are given near-zero weights.

Once a GPS for intelligence is created for each individual in a sample, it can be used like any other variable in analyses. For example, it can be used to investigate the extent to which this genetic index of intelligence mediates or moderates effects on variables of primary interest to the researcher.

SNP	Increasing allele	Allele 1	Allele 2	Genotypic score	Correlation with trait	Weighted genotypic score
SNP 1	T	A	T	1	0.005	0.005
SNP 2	C	G	G	0	0.004	0.000
SNP 3	A	A	A	2	0.003	0.006
SNP 4	G	C	G	1	0.003	0.003
SNP 5	G	C	C	0	0.003	0.000
SNP 6	T	A	T	1	0.002	0.002
SNP 7	C	C	G	1	0.002	0.002
SNP 8	A	A	A	2	0.002	0.004
SNP 9	A	T	T	0	0.001	0.000
SNP 10	C	C	G	1	0.001	0.001
Polygenic score				**9**		**0.023**

Effect sizes
Proportions of variance of traits in the study population accounted for by a particular factor such as a genome-wide polygenic score.

Single-nucleotide polymorphisms
(SNPs). Single base pair differences in inherited DNA sequence between individuals.

Large-scale genome-wide association studies of intelligence. In 2017, the largest GWAS meta-analysis of intelligence, which included 'only' 78,000 individuals, yielded 18 genome-wide significant regions[33]. A GPS (IQ2) derived from these GWAS results finally broke the 1% barrier of previous GWAS of intelligence by predicting 3% of the variance of intelligence in independent samples. However, IQ2 still has less predictive power than the 4% of the variance explained by the EA2 GPS.

A follow-up GWAS meta-analysis reached a sample size of 280,000 with the inclusion of cognitive data from the UK Biobank. This GWAS analysis increased the number of identified genome-wide significant regions from 18 to 206 (REF. 34). A GPS derived from these GWAS analyses, IQ3, predicts about 4% of the variance of intelligence in independent samples[34]. Other meta-analytic GWAS using the UK Biobank data, which were released in June 2017 and are publicly available, yield similar results[35].

These IQ and EA GPS results are summarized in FIG. 1. It might seem disappointing that the increase of the intelligence GWAS sample sizes from 78,000 to 280,000 boosted the predictive power of the IQ GPS only from 3% to 4%. However, this result is parallel to GWAS results for years of education: after increasing sample sizes from 125,000 to 294,000, the variance in years of education predicted by the EA GPS grew only from 2% to 3%. Note that the predictive power of the EA GPS jumped to more than 10% of the variance in preliminary analyses of the latest meta-analytic GWAS (EA3) with a sample size of more than 1 million[31] (P. D. Koellinger, personal communication). We can expect a similar jump in the predictive power of the IQ GPS when the sample size for GWAS meta-analyses of intelligence exceeds 1 million. However, it is more difficult to obtain very large sample sizes for intelligence, which has to be tested, than for years of education, which can be assessed with a single self-reported item.

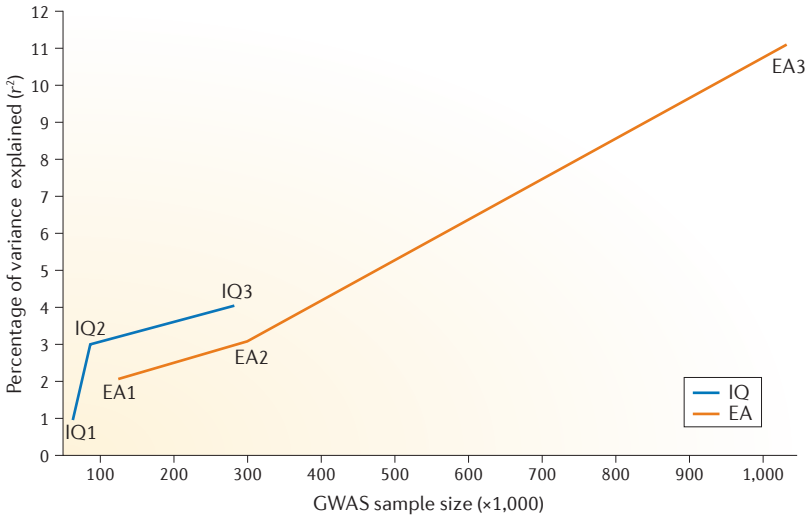


Figure 1 | **Variance explained by IQ GPSs and by EA GPSs in their target traits as a function of GWAS sample size.** Genome-wide polygenic score (GPS) prediction of intelligence (IQ) and educational attainment (EA) increased linearly with sample size. The predictive power of GPSs derived from genome-wide association studies (GWAS) of intelligence has increased in the past 2 years from 1% to 4%. The latest EA GPS, EA3, predicts more than 10% of the variance in intelligence (P. D. Koellinger, personal communication) — more than twice as much as the latest IQ3 GPS. Extrapolating from the results of EA3 with a sample size of more than 1 million, we predict that more than 10% of the variance in intelligence will be predicted from IQ GPSs derived from a GWAS of intelligence with a sample size of 1 million. IQ1 (REF. 22): $n = 54{,}000$, $r^2 = 0.01$. IQ2 (REF. 33): $n = 78{,}000$, $r^2 = 0.03$. IQ3 (REF. 34): $n = 280{,}000$, $r^2 = 0.04$. EA1 (REF. 28): $n = 125{,}000$, $r^2 = 0.02$. EA2 (REF. 30): $n = 294{,}000$, $r^2 = 0.03$. EA3 (REF. 31): $n = 1{,}100{,}000$, $r^2 > 0.10$.

Missing heritability. It is possible to use multiple GPSs to boost the power to predict intelligence by aggregating GPSs in a way analogous to aggregating SNPs to produce GPSs (BOX 3). Including the EA2 GPS, IQ2 GPS and other GPSs in this multivariate way can already predict up to 7% of the variance in intelligence[36,37]. Multivariate GPS analyses that incorporate multiple GPSs in addition to the EA2 GPS and IQ2 GPS will explain substantially more than 10% of the variance in intelligence, which is more than 20% of the 50% heritability of intelligence.

Nonetheless, 10% is a long way from the heritability estimate of 50% obtained from twin studies of intelligence[14]. This gap is known as 'missing heritability', which is a key genetic issue for all complex traits in the life sciences[38] (BOX 4). The current limit for the variance that can be predicted by GPSs is SNP heritability, which estimates the extent to which phenotypic variance for a trait can be explained by SNPs across the genome without identifying specific SNP associations. For intelligence, SNP heritability is about 25%[34,39]. It is safe to assume that GPSs for intelligence using current SNP chips can approach the SNP heritability limit of 25% by amassing ever-larger GWAS samples and by using multitrait GWAS that include traits related to intelligence, such as years of education. However, breaking through this ceiling of 25% SNP heritability to the 50% heritability estimated from twin studies — assuming that twin studies yield accurate estimates of the total variance explained by inherited DNA differences — will require different technologies, such as whole-genome sequencing data that include rare variants, not just the common SNPs used on current SNP chips.

GPSs in intelligence research

A bottom-up approach to intelligence focused on specific genes will be difficult for three reasons. First, genetic effects are extremely pleiotropic. Second, many hits are in intergenic regions, which means that there are no 'genes' to trace through the brain to behaviour. Third, the biggest hits have minuscule effects — less than 0.05% of the variance — which means that hundreds of thousands of SNP associations are needed to account for the 50% heritability estimated by twin studies. A systems biology approach to molecular studies of the brain is needed that is compatible with this extreme pleiotropy and polygenicity[40].

By contrast, the top-down approach of GPSs that aggregate thousands of these tiny effects is already transforming research on intelligence[41]. Unlike quantitative genetic studies that require special samples, such as twins, or GWAS that require very large samples in

Box 3 | **The use of multiple genome-wide polygenic scores to predict a trait**

Aggregating thousands of single-nucleotide polymorphism (SNP) associations in genome-wide polygenic scores (GPSs) has been key to predicting individual differences in complex traits such as intelligence. In an analogous manner, it is possible to aggregate many GPSs to exploit their joint predictive power. For example, multiple GPSs were used to predict intelligence in a sample of 6,710 unrelated 12-year-old children[36]. This approach is a multiple regression prediction model that accommodates multiple correlated predictors while preventing overfitting on the basis of training in one sample and testing in another sample in a repeated cross-validation design. This approach predicted 4.8% of the variance in intelligence. Although the EA2 GPS alone accounted for most of the variance, other GPSs added significantly to the prediction of intelligence, especially GPSs derived from genome-wide association studies (GWAS) of high-IQ individuals[57], childhood IQ[19] and household income[90]. More than 7% of the variance in intelligence was predicted[37] through the use of another approach called multitrait analysis of GWAS (MTAG)[91], which performs a meta-analysis from summary statistics for a few correlated GPSs and produces new summary statistics that can be used to create a multivariate GPS.

The success of GWAS comes from their atheoretical approach that analyses all SNPs in the genome rather than selecting candidate genes. In the same way, an atheoretical approach can be used in analyses of multiple GPSs by incorporating as many GPSs as possible rather than selecting a few candidate GPSs. For example, the first study of this sort, mentioned above[36], included a total of 81 GPSs from well-powered GWAS of cognitive, medical and anthropometric traits available in LD Hub[92] that together predicted 4.8% of the variance in intelligence. Although EA2, IQ and income GPSs drove most of the predictive power of this multiple-GPS analysis, significant independent contributions to the prediction of intelligence were also found for major depressive disorder GPSs and autism spectrum disorder GPSs. These latter associations were in the direction expected on the basis of the negative genetic correlation between intelligence and depression and the surprising positive genetic correlation between intelligence and autism (see *Multivariate genetic research*).

the hundreds of thousands, GPSs can be used to add a genetic dimension to any research with modest sample size. For example, a GPS for intelligence that predicts 10% of the variance needs a sample size of only 60 to detect its effect with 80% power ($P = 0.05$, one-tailed).

GPSs are unique predictors in the behavioural sciences. They are an exception to the rule that correlations do not imply causation in the sense that there can be no backward causation when GPSs are correlated with traits. That is, nothing in our brains, behaviour or environment changes inherited differences in our DNA sequence. A related advantage of GPSs as predictors is that they are exceptionally stable throughout the lifespan because they index inherited differences in our DNA sequence. Although mutations accrue in the salivary and blood cells used to collect DNA, these mutations would not be expected to systematically change the thousands of inherited SNPs that contribute to a GPS.

In other words, GPSs derived from GWAS of any trait at any age would be expected to have a correlation near 1.0 when GPSs are constructed from DNA obtained at birth and in adulthood for the same individual, although we are not aware of any empirical evidence relevant to this prediction. If GPSs for individuals do not change during the lifespan, a GPS derived from GWAS of intelligence in adulthood will predict adult intelligence just as well from DNA obtained at conception or birth as from DNA obtained in adulthood. By contrast, intelligence tests at birth cannot predict intelligence at age 18 years. At 2 years of age, infant intelligence tests predict less than 5% of the variance of intelligence in late adolescence[32,42].

GPSs are unbiased in the sense that they are not subject to training, faking or anxiety. They are also inexpensive, costing less than US$100 per person. This expense would not be incurred specifically to predict intelligence; the same SNP chip genotype information used in GWAS can be used to create GPSs for hundreds of disorders and traits, one of which is intelligence.

GPSs for intelligence will open new avenues for research into the causes and consequences of intelligence. Three examples are developmental change and continuity, multivariate links between traits and gene–environment (GE) interplay. A critical requirement for capitalizing on these opportunities is to make the ingredients for GPSs publicly available — that is, GWAS summary-level statistics (BOX 5).

Developmental research. One of the most interesting developmental findings about intelligence is that its heritability as estimated in twin studies increases dramatically from infancy (20%) to childhood (40%) to adulthood (60%), whereas age-to-age genetic correlations are consistently high[43,44]. What could account for this increasing heritability despite unchanging age-to-age genetic correlations? Twin studies suggest that genetic effects are amplified through GE correlation as time goes by[45]. That is, the same large set of DNA variants affects intelligence from childhood to adulthood, resulting in high age-to-age genetic correlations, but these DNA variants increasingly have an impact on intelligence as individuals select environments correlated with their genetic propensities, leading to greater heritability of intelligence.

Developmental hypotheses about high age-to-age genetic correlations and increasing heritability can be tested more rigorously and can be extended through the use of GPSs. Does the variance explained by GPSs for intelligence increase from childhood to adolescence to adulthood? Are the correlations between GPSs at these ages consistently high?

High age-to-age genetic correlations for intelligence imply that GWAS of adults should predict intelligence in childhood. The EA2 GPS[30], currently the best genetic predictor of intelligence until the EA3 GPS becomes available, was derived from a GWAS meta-analysis of years of education in adults who had completed their education. Nonetheless, the EA2 GPS predicts 2% of the variance in intelligence at age 7 years, 3% at age 12 years and 4% at age 16 years in a longitudinal study[46].

Multivariate genetic research. Multivariate genetic research focuses on the genetic covariance between traits rather than the variance of each trait. A specific multivariate question for intelligence research is why EA GPSs predict twice as much variance in intelligence as do GPSs for intelligence itself. This question raises interesting methodological and conceptual issues (BOX 6).

Multivariate genetic research is especially important for intelligence because genetic effects in the cognitive domain have been shown in twin studies to be general. That is, genetic effects correlate highly across most

Box 4 | **Twin, single-nucleotide polymorphism and genome-wide polygenic score heritabilities**

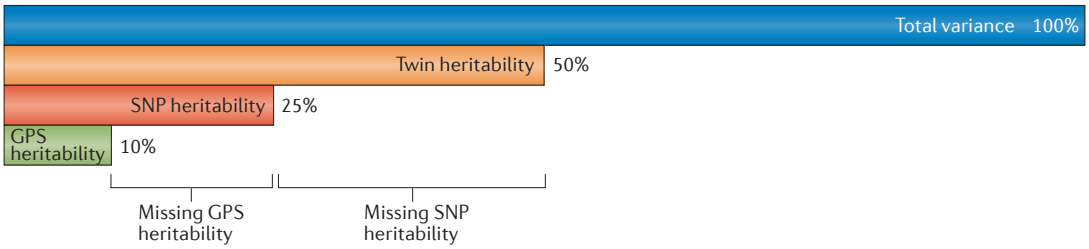
Heritability is the proportion of observed (phenotypic) differences among individuals that can be attributed to genetic differences in a particular population. Broad heritability involves all additive and nonadditive sources of genetic variance, whereas narrow heritability is limited to additive genetic variance. Additive genetic variance refers to the independent effects of alleles or loci that 'add up'. Nonadditive genetic variance involves effects of alleles or loci that interact.

Twin heritability compares the resemblance of identical and fraternal twins to estimate genetic and environmental components of variance. For intelligence, twin estimates of broad heritability are 50% on average[14]. Adoption studies of first-degree relatives yield similar estimates of narrow heritability of intelligence, suggesting that most genetic influence on intelligence is additive.

Single-nucleotide polymorphism (SNP) heritability is estimated directly from SNP differences between individuals. It does not specify which SNPs are associated with a trait. Instead, it uses chance genomic similarities across hundreds of thousands of SNPs genotyped on an SNP chip for thousands of unrelated individuals to estimate the extent to which genomic covariance accounts for phenotypic covariance in these individuals. For intelligence, SNP heritability is about 25%[22,34,39].

Genome-wide polygenic score (GPS) heritability is the proportion of variance that can be predicted by the GPS. For intelligence, GPS heritability is currently about 10%[31] (P. D. Koellinger, personal communication).

These three types of heritability denote two types of 'missing heritability', as shown in the figure. SNP heritability is the ceiling for genome-wide association study (GWAS) and for GPS heritability because all three rely on the additive effects of SNPs genotyped on SNP chips[93]. The missing heritability gap between GPS heritability (10%) and SNP heritability (25%) can be narrowed by increasing GWAS sample size. Narrowing the missing heritability gap between SNP heritability (25%) and twin heritability (50%) will require different technologies that consider, for example, rare variants, gene–gene interactions and gene–environment interactions.



cognitive abilities, such as verbal and spatial abilities, as well as most educational skills, such as reading and mathematics[47]. A recent multivariate finding is that the EA2 GPS predicts 5% of the variance in comprehension and efficiency of reading[48]. This is by far the most powerful GPS predictor of reading ability because there have as yet been no large GWAS of reading with replicable results[49]. EA GPSs are also likely to predict other educational skills, such as mathematics, and other cognitive abilities, such as spatial ability.

EA GPSs are correlated genetically with a wider range of variables than any other GPS[50]. This pervasive genetic influence of EA GPSs extends to a negative genetic correlation with schizophrenia and positive genetic correlations with height[51], with myopia[52] and, surprisingly, with autism[53]. Linkage disequilibrium (LD) score regression analysis[54], which uses summary GWAS statistics rather than GPSs for individuals, finds a similar pattern of results for intelligence using the IQ2 GWAS: the negative genetic correlation with schizophrenia (−0.20) and the positive genetic correlations with height (0.10) and autism (0.21)[33]. The same LD score regression analysis[33] found that intelligence significantly correlated genetically with many other traits, including Alzheimer disease (−0.36), smoking cessation (−0.32), intracranial volume (0.29), head circumference in infancy (0.28), depressive symptoms (−0.27), attention-deficit–hyperactivity disorder (−0.27), having ever smoked (−0.23), longevity (0.22) and, of course, years of education (0.70).

Despite this evidence for ability-general genetic effects, genetic correlations across cognitive abilities and educational skills are not 1.0, which implies that there are ability-specific SNP associations. An important direction for research is to identify ability-specific GPSs derived from large GWAS analyses focused on specific cognitive abilities independent of general intelligence. Preliminary analyses of this sort would be possible using existing GWAS of intelligence because most of these studies assessed multiple measures of specific cognitive abilities, which were combined to index intelligence. These data could be reanalysed in meta-analytic GWAS that focus on specific abilities included in multiple studies. However, what is needed are large GWAS focused on well-measured specific cognitive abilities, such as verbal, spatial and memory abilities and specific cognitive skills taught in schools, for example reading, mathematics and language. The pay-off from these studies will be GPSs that predict specific abilities independent of general intelligence. These ability-specific GPSs could be used to create profiles of genetic strengths and weaknesses for individuals who could be targets for personalized prediction, prevention and intervention.

In addition to investigating links between different traits, multivariate genetic research can examine genetic links between dimensional and diagnostic measures of the 'same' domain. For example, the EA2 GPS predicts reading disability just as much as reading ability, from slow readers to speed readers[48]. Because GPSs are always

Linkage disequilibrium (LD) score regression analysis
Analysis that, for each single-nucleotide polymorphism in a genome-wide association study (GWAS), regresses χ^2 statistics from GWAS summary statistics against LD scores.

Box 5 | **Make genome-wide association study summary-level statistics publicly available**

It is essential for continued rapid scientific advances using genome-wide polygenic scores (GPSs) that summary-level statistics from genome-wide association studies (GWAS) be made publicly available for all single-nucleotide polymorphisms (SNPs) following publication. The reason why public access to summary statistics is important is that the construction of GPSs requires an effect size indicator and *P* value for each SNP in the GWAS. GWAS summary-level statistics are also necessary for other analyses, most notably linkage disequilibrium (LD) score regression, which is used to estimate genetic correlations among traits[54].

Until 2017, GWAS summary-level data were stored in different databases using different formats, which made it difficult to use the data to investigate traits across studies. This problem has been solved with LD Hub, a centralized database and web interface that provides an automated pipeline for entering and using GWAS summary-level data[92].

However, only about 10% of published GWAS results are publicly available on LD Hub. Some GWAS consortia are exemplars for making GWAS summary-level data available immediately upon publication, or even before publication, such as the Psychiatric Genomics Consortium[94]. In intelligence research, a paragon is the Social Science Genetic Association Consortium[27], which is responsible for five of the six GWAS for which summary statistics are publicly available in the intelligence section of LD Hub, although three of the five GWAS were for years of education rather than for intelligence itself.

By contrast, some authors apply conditions for the use of the summary statistics from their published GWAS paper. Others refuse to share these statistics altogether. A worrying trend is that several commercial organizations do not allow summary GWAS statistics from their samples to be used in open-access summary-level statistics for all SNPs when their samples are included in meta-analytic GWAS. Concerns about privacy have been put forth as an explanation, but these fears should be allayed as it is not possible to reconstruct individual-level data from summary-level GWAS statistics in large heterogenous samples[95].

Such asymmetrical data-sharing policies between industry and academia will hold back research in the field. If a group does not want its summary-level GWAS statistics to be freely available for a published meta-analytic GWAS, its data should not be used in 'publication', true to its Latin origin *publicare*, which means 'to make public'.

normally distributed, they will show that there are no aetiologically distinct common disorders, only continuous dimensions[55]. This is also true for very low and for very high intelligence[46]. Even extremely high intelligence is only quantitatively, not qualitatively, different genetically from the normal distribution[56,57]. The exception is severe intellectual disability, which is genetically distinct from the rest of the distribution of intelligence[58] and affected by rare, often *de novo* mutations with large effects[59].

Research on gene–environment interplay. The high heritability of intelligence should not obscure the fact that heritability is considerably less than 100%. Research using genetically sensitive designs has led to one of the most important findings about environmental influence on intelligence. Intelligence has always been known to run in families, but it was assumed that this family resemblance was due to nurture, called 'shared family environmental influence'. That is, siblings were thought to be similar in intelligence because they grew up in the same family and attended the same schools. Twin and adoption studies consistently support this assumption, but only until adolescence. After adolescence, the effect of shared family environmental influence on intelligence is negligible, which means that family environments have little effect on individual differences in the long run[45,60]. Family resemblance for intelligence is due to nature rather than nurture, although it should be emphasized that we are referring to the normal range of environmental influence, not the extremes such as neglect or abuse. However, little is known about the specific environmental factors that make children growing up in the same family different[14].

The importance of both genetics and environment for cognitive development is a recommendation for investigating the interplay between them. GPSs for intelligence will greatly facilitate this research because they offer, for the first time, the possibility of directly assessing genetic propensities of individuals to investigate their interplay with aspects of the environment. GE interplay refers to two different concepts — GE interaction and GE correlation.

GE interaction denotes a conditional relationship in which the effects of genes on intelligence depend on the environment. For example, some twin research suggests that the heritability of intelligence is lower in low-socio-economic-status family environments and higher in high-socio-economic-status family environments[61]. This hypothesis predicts that GPSs for intelligence will correlate less with intelligence in environments of low socio-economic status than in those of high socio-economic status. The first test of this hypothesis using the EA2 GPS found no evidence for such an interaction[46]. That is, the EA2 GPS were correlated with intelligence in low-socio-economic-status just as much as in high-socio-economic-status family environments. GPSs provide a particularly powerful approach to test for GE interaction compared with twin studies[62].

In contrast to GE interaction, GE correlation refers to the correlation between genetic propensities and experiences. GE correlation is the reason why most environmental measures used in the behavioural sciences show genetic influence in twin studies[63]. Associations between environmental measures and behavioural traits such as intelligence are also mediated in part by genetic differences. Research using GPSs is beginning to confirm these twin study findings about the 'nature of nurture' by showing, for

example, that EA GPSs correlate with social mobility[64] and capture covariation between environmental exposures and children's behaviour problems and educational achievement[65]. GE correlation provides a general model for how genotypes become phenotypes — how children select, modify and create environments correlated with their genetic propensities. GPSs will greatly advance research on GE correlation by providing an individual-specific index of the 'G' of GE interplay. GPSs will also make it possible to assess environmental influences on intelligence while controlling for genetic influences.

Implications for society

The most exciting aspect of GPSs is their potential for addressing novel, socially important questions, which we will illustrate with three recent examples from our own research. First, children in public and private schools differ in their EA2 GPSs because private schools select pupils on the basis of genetic differences in intelligence[66]. Second, intergenerational educational mobility reflects EA2 GPS differences[67]. Finally, the EA2 GPS predicts twice as much variance in educational attainment and occupational status in the post-Soviet era as in the Soviet era in Estonia, a finding compatible with the hypothesis that heritability is an index of equality of opportunity and meritocracy[68].

Understanding ourselves. IQ GPSs will be used to predict individuals' genetic propensity to learn, reason and solve problems, not only in research but also in society, as direct-to-consumer genomic services provide GPS information that goes beyond single-gene and ancestry information. We predict that IQ GPSs will become routinely available from direct-to-consumer companies along with hundreds of other medical and psychological GPSs that can be extracted from genome-wide genotyping on SNP chips. The use of GPSs to predict individuals' genetic propensities requires clear warnings about the probabilistic nature of these predictions and the limitations of their effect sizes (BOX 7).

Although simple curiosity will drive consumers' interests, GPSs for intelligence are more than idle fortune telling. Because intelligence is one of the best predictors of educational and occupational outcomes, IQ GPSs will be used for prediction from early in life before intelligence or educational achievement can be assessed. In the school years, IQ GPSs could be used to assess discrepancies between GPSs and educational achievement (that is, GPS-based overachievement and underachievement). The reliability, stability and lack of bias of GPSs make them ideal for prediction, which is essential for the prevention of problems before they occur. A 'precision education' based on GPSs could be used to customize education, analogous to 'precision medicine'.

A novel, socially important direction for research using IQ GPSs is to understand differences within families. First-degree relatives are on average only 50% genetically similar, which means they are on average 50% genetically different. A major impact of GPSs will be to recognize and respect these large genetic differences within families.

For scores on an intelligence test standardized to have a mean of 100 and a standard deviation of 15, the average difference between pairs of individuals who are selected randomly from the general population is 17 IQ points. The average difference between parents and offspring

Box 6 | **Educational attainment genome-wide polygenic scores and intelligence**

Educational attainment (EA) genomic-wide polygenic scores (GPSs) predict intelligence because the genetic correlation between years of education and intelligence is greater than 0.50 in twin studies[96] and linkage disequilibrium score regression studies[97]. The genetic correlation of 0.50 also sets a limit on the extent to which EA GPSs can predict intelligence.

However, why do EA GPSs predict intelligence to a greater extent than they predict educational attainment itself? That is, the EA2 GPS predicts 3% of the variance in years of education[30], but it predicts 4% of the variance in intelligence[46]. Moreover, EA GPSs predict intelligence much better than IQ GPSs predict intelligence themselves. The IQ3 GPS from the most recent genome-wide association study (GWAS) of intelligence predicts 4% of the variance of intelligence[34], but the EA3 GPS predicts more than 10% of the variance in intelligence[31] (P. D. Koellinger, personal communication).

There are two likely reasons why EA GPSs currently predict intelligence to a greater extent than EA GPSs predict years of education itself. First, intelligence is more heritable (60% in adults) than years of education (40%), as shown in twin studies[98]. Second, years of education is a coarse measure, primarily indicating whether an individual completed university. Years of education is largely bimodal, with a peak at the end of secondary school and another peak for individuals who attended university. By contrast, intelligence is a more refined measure than years of education that captures the commonalities among diverse tests of cognitive abilities and is normally distributed. That is, educational achievement is not just a proxy for intelligence. It is also predicted by personality traits, such as conscientiousness and well-being, and having fewer mental health problems, such as depression. Together, these nonability traits account for as much of the heritability of educational achievement as intelligence[99]. The educational attainment GWAS incorporates SNPs associated with any of these traits, not just with intelligence[14].

Of note, the current GWAS sample sizes for educational attainment are three times larger than for intelligence. The GPS effect sizes for intelligence are similar to those for EA GPSs for comparable effect sizes (that is, IQ2 as compared to EA1 and IQ3 as compared to EA2; see FIG. 1). For this reason, we predict that an IQ GPS derived from a GWAS of intelligence with a sample size of 1 million, such as EA3, will predict at least as much variance in intelligence as does the current EA3 GPS. In other words, intelligence is not actually predicted to a greater extent by EA GPSs than by intelligence GPSs when the powers of the discovery GWAS are similar.

and between siblings is 13 IQ points[69]. IQ GPSs might help parents understand why their children differ in school achievement. Because GPSs are probabilistic, a low-IQ GPS does not mean that a child is destined to go no further in education than secondary school. However, it does mean that the child is more likely to find academic learning more difficult and less rewarding than a sibling with a high-IQ GPS.

Ethical implications. Genomic research and studies of intelligence face four principal ethical concerns: the notion of biological determinism; the potential for discrimination and stigmatization; the question of ownership of information; and the emotional impact of knowledge of one's personal genomics and intelligence. These and other ethical issues are explored in detail by the Ethical, Legal and Social Implications (ELSI) Research

Box 7 | **The use of genome-wide polygenic scores to predict outcomes in individuals**

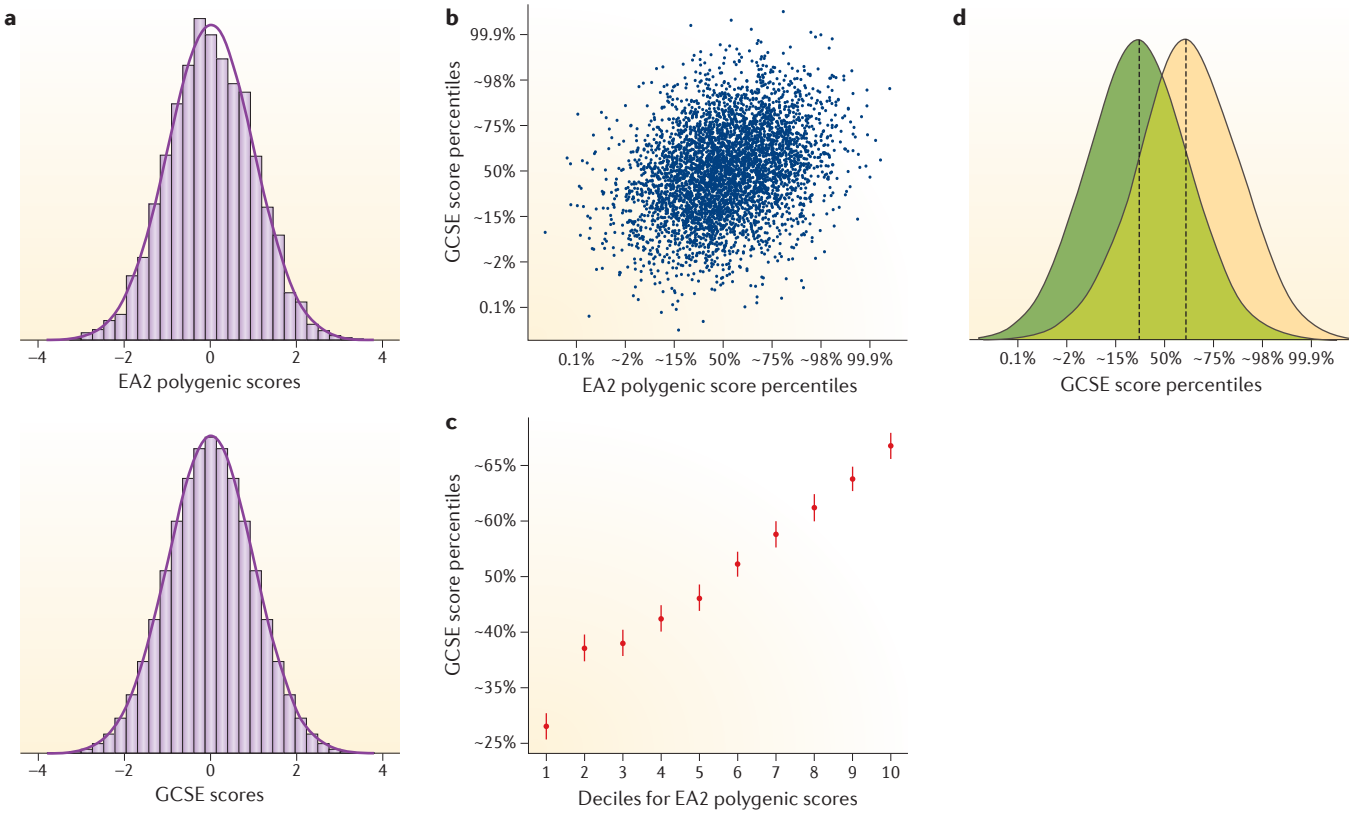
Genome-wide polygenic scores (GPSs) must be used with caution when predicting outcomes in individuals. We illustrate the probabilistic nature of GPS predictions using data on EA2 GPSs and school achievement from the Twins Early Development Study[100]. School achievement was assessed by scores from a UK-wide examination, the General Certificate of Secondary Education (GCSE), administered at the end of compulsory education at age 16 years. GCSE scores were age-regressed and gender-regressed, and EA2 GPSs were constructed as described elsewhere[46]. We used the EA2 GPS prediction of GCSE scores as an example because the effect size of this association is currently the strongest in the behavioural sciences, accounting for 9% of the variance[46]. It will soon be possible to explain a similar amount of variance in intelligence, and with that, GPSs will become available to predict intelligence for individuals.

The starting point for prediction is the distribution of individual differences (see the figure, part **a** top). The EA2 GPS is normally distributed, as GPSs always are, as is the measure of school achievement (see the figure, part **a** bottom). GPS prediction of individual differences is based on its covariance with the target trait (school achievement in this example). The scatterplot between EA2 GPSs and GCSE scores (see the figure, part **b**) indicates the difficulty of predicting individual outcomes when the correlation is modest (0.30 in this example). Squaring this correlation indicates that the EA2 GPS predicts 9% of the variance in GCSE scores. Although higher EA2 GPSs can be seen to predict higher GCSE scores on average, there is great variability between individuals. For example, the individual with the second-highest EA2 GPS has a GCSE score only slightly above the average. Conversely, an individual with the eighth-lowest EA2 GPS has a GCSE score above the 75th percentile.

Despite this variability, powerful predictions can be made at the extremes. For example, when the sample was divided into ten equal-sized groups (deciles) on the basis of their EA2 GPS, a strong relationship between average EA2 GPS and average GCSE scores emerged that was most evident at the extremes (see the figure, part **c**). Specifically, the average school achievement of individuals in the lowest EA2 GPS decile is at the 28th percentile. For the highest EA2 GPS decile, the average school achievement is at the 68th percentile.

Nonetheless, individuals within the lowest and highest EA2 GPS deciles vary widely in school achievement (see the figure, part **d**). The overlap in the two distributions is 61%. These issues of variability in prediction are the same for any predictor that accounts for 9% of the variance in the target trait. As bigger and better GPSs emerge, the predictive power will increase.

In summary, GPSs are useful for individual prediction as long as the probabilistic nature of the prediction is kept in mind.



Programme, which is an integral part of the Human Genome Project[70]. In addition, recent books discuss ethical as well as scientific issues about personal genomics, specifically in relation to education[71] and occupation[72]. Many of these ethical discussions focus on single-gene disorders, for example, Huntington disease, which has 100% penetrance. By contrast, GPSs are 'less dangerous' because they are intrinsically probabilistic, not hard-wired and deterministic like single-gene disorders. It is important to recall here that although all complex traits are heritable, none is 100% heritable. A similar logic can be applied to IQ scores: although they have great predictive validity for key life outcomes[1–6], IQ is not deterministic but probabilistic. In short, an individual is always more than the sum of their genes or their IQ scores.

Issues of discrimination and stigmatization have accompanied research into genetics and intelligence from the beginning, typically because findings from both fields of study were applied to justify policies that served sociopolitical ideologies. For example, IQ testing was infamously used to differentiate European immigrants to the United States of America who arrived at Ellis Island in the early 1900s, as well as to guide eugenic ideas about sterilization in Britain and the United States of America throughout the 20th century[11]. It is important to acknowledge the risk of discrimination that occurs on the back of scientific findings about individual differences. However, it is equally important to realize that research does not lead directly to any policy recommendations. We must be careful not to blame the scientists or entire disciplines when their findings are used wrongly[9].

Who 'owns' our genetic information? And who should decide who can access it? The question of ownership of personal data has become pivotal but also increasingly complex in our current age of information. At the same time, understanding and managing the emotional impact that stems from knowledge of our genomics and intelligence have emerged as new societal responsibilities. It is beyond the scope of this paper to elucidate these issues in the depth that they deserve, but we expect that the discussions of ethical issues that surround personal genomics will consolidate the DNA revolution.

Conclusions

Genetic association studies have confirmed a century of quantitative genetic research showing that inherited DNA differences are responsible for substantial individual differences in intelligence test scores. A reachable objective shared with all complex traits in the life sciences is to close the gap between the 10% variance in intelligence scores explained by GPSs and the SNP heritability of intelligence of about 25%. A more daunting challenge is to break through the ceiling of 25% SNP heritability to reach the 50% heritability estimated by twin studies.

Until 2016, GPSs could predict only 1% of the variance in intelligence. Progress has been rapid since then, reaching our current ability to predict 10% of the variance in intelligence from DNA alone. GPSs will soon be available that can predict more than 10% of the variance in intelligence (that is, more than 20% of the 50% heritability of intelligence estimated from twin studies) and more than 40% of the 25% SNP heritability of intelligence. This is an important milestone for the new genetics of intelligence because effect sizes of this magnitude are large enough to be "perceptible to the naked eye of a reasonably sensitive observer" (REF. 73). With these advances in the past few years, intelligence steps out of the shadows and takes the lead in genomic research.

In addition to investigating traditional issues about development, multivariate links among traits and GE interplay, IQ GPSs will open new avenues for research into the causes and consequences of intelligence. The new genetics of IQ GPSs will bring the omnipotent variable of intelligence to all areas of the life sciences without the need to assess intelligence.

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