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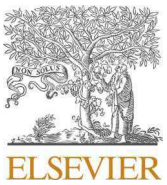

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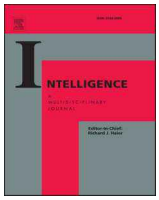

Using DNA to predict intelligence

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ABSTRACT

The DNA revolution made it possible to use DNA to predict intelligence. We argue that this advance will transform intelligence research and society. Our paper has three objectives. First, we review how the DNA revolution has transformed the ability to predict individual differences in intelligence. Thousands of DNA variants have been identified that – aggregated into genome-wide polygenic scores (GPS) – account for more than 10% of the variance in phenotypic intelligence. The intelligence GPS is now one of the most powerful predictors in the behavioral sciences. Second, we consider the impact of GPS on intelligence research. The intelligence GPS can be added as a genetic predictor of intelligence to any study without the need to assess phenotypic intelligence. This feature will help export intelligence to many new areas of science. Also , the intelligence GPS will help to address complex questions in intelligence research, in particular how the gene-environment interplay affects the development of individual differences in intelligence. Third, we consider the societal impact of the intelligence GPS, focusing on DNA testing at birth, DNA testing before birth (e.g., embryo selection), and DNA testing before conception (e.g., DNA dating). The intelligence GPS represents a major scientific advance, and, like all scientific advances, it can be used for bad as well as good. We stress the need to maximize the considerable benefits and minimize the risks of our new ability to use DNA to predict intelligence.

1. Introduction

Thirty years ago, most scientists had become convinced of the influence of genetics on the origins of individual differences in intelligence, which was a dramatic shift from the environmentalism that had prevailed in the previous generation. Twin and adoption studies around the world converged on the conclusion that about half of the variance in intelligence test scores could be ascribed to inherited DNA differences (Knopik, Neiderhiser, DeFries, & Plomin, 2017; Polderman et al., 2015).

The next step was to identify the DNA variants that are responsible for the heritability of intelligence. The DNA revolution, which began with the sequencing of the human genome in 2003, offered a systematic strategy for identifying inherited DNA differences across the genome that drive the heritability of intelligence, an approach known as genome-wide association (GWA) analysis. GWA studies confirmed a foundational assumption of quantitative genetic theory: the heritability of complex traits like intelligence is caused by many genetic variants of small effect (Fisher, 1918). In fact, GWA research revealed that the biggest effect sizes were even smaller than anyone anticipated, with individual DNA variants accounting for at most 0.05% of the variance (Plomin & von Stumm, 2018). This meant that thousands of inherited DNA differences are responsible for the heritability of complex traits like intelligence, and that huge sample sizes would be needed to scoop up these tiny effects.

What good are DNA variant associations that have such minuscule effects? The answer is 'not much' for molecular biologists wanting to study pathways from genes to brain to behavior because there is a welter of convoluted, interwoven trails. But quantitative geneticists realized that the thousands of DNA variant associations could be aggregated to create genome-wide polygenic scores (GPS). GPS capture an individual's genetic propensity for a given phenotype and thus they can be used to predict individual differences in complex traits including intelligence.

In 2017, a GWA meta-analysis with a sample size of 78,000 yielded a GPS that predicted 3% of the variance in intelligence (Sniekers et al., 2017), and in 2018 a GPS derived from a GWA sample of 280,000 accounted for 4% of the variance (Savage et al., 2018). In contrast, up to 7% of the variance in intelligence could be predicted (Allegrini et al., 2019) by a GPS derived from a GWA analysis for years spent in education, a single self-reported item (Lee et al., 2018). Years of education can be considered a proxy for intelligence because it correlates with

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intelligence phenotypically (0.50) and genetically (0.65) (Rietveld et al., 2014). The GPS for years of education predicts almost twice as much variance in intelligence, because the GWA meta-analytic sample size for years of education was 1.1 million, four times larger than the latest GWA meta-analysis for intelligence. This enormous GWA sample for years of education was possible because most genetically sensitive studies routinely assess years of education as a demographic marker, but very few measured intelligence.

The ability to predict intelligence from DNA can be boosted by aggregating the effects of several GPS (Krapohl et al., 2018). For example, using the GPS for years of education and the GPS for intelligence together predicted more than 10% of the variance in intelligence (Allegrini et al., 2019). This multi-GPS approach can be extended further to include GPS for other traits that are genetically related to intelligence, such as income (Hill et al., 2019) and white matter tracts (Zhao et al., 2019), as well as to apply novel analytical approaches like genomic structural equation modelling (de la Fuente, Davies, Grotzinger, Tucker-Drob, & Deary, 2021).

Predicting more than 10% of the variance in intelligence is an effect large enough to be 'perceptible to the naked eye of a reasonably sensitive observer' (Cohen, 1988, p. 80). To critics who argue that GPS are not useful for individual prediction, it should be noted that the behavioral sciences rarely observe effects that account for more than 10% of the variance. For example, the intelligence GPS is comparable in effect size to the prediction of children's intelligence in the early school years from their parents' socioeconomic status (von Stumm & Plomin, 2015), which determines whether a child qualifies to receive free school meals or not. Another example is that, in the UK, ratings of school quality only predict 4% of the variance in tested educational achievement, and this effect reduces down to 1% after accounting for prior school performance and family background (von Stumm et al., 2020a). Yet, Britain spends annually over £40 million to obtain school quality ratings, which are a key factor in parents' choice of the 'best' school for their children.

Ten percent of the variance is equivalent to a correlation of 0.32; a corresponding oval-shaped scatterplot between the intelligence GPS and intelligence test scores reflects the probabilistic nature of GPS-based predictions and their limits for forecasting individual-level outcomes (Plomin & von Stumm, 2018; von Stumm et al., 2020b). Even so, powerful predictions can be made at the extremes. For example, the lowest and highest GPS deciles have mean IQs of 92 and 108, respectively, based on normal distributions with a mean IQ of 100 and a standard deviation of 15.

There is room to improve the GPS prediction further: 10% is only one-fifth of the heritability of 50% for intelligence. This difference between 10% and 50% is the 'missing heritability' gap, an issue that confronts all DNA research in the life sciences (Manolio et al., 2009), not just intelligence (Plomin & von Stumm, 2018). The missing heritability gap will be narrowed with larger GWA samples and with whole-genome sequencing (Wainschtein et al., 2019), as well as by using alternative study designs that afford greater statistical power, such as sampling individuals with extremely high intelligence scores (Zabaneh et al., 2018). Another issue is that GWA samples have largely been drawn from populations of European ancestry (e.g., US, UK, Iceland; Mills & Rahal, 2019). GPS derived from these samples tend to be less predictive in other ancestral populations; efforts to conduct GWA analyses in other populations are underway, with the greatest progress made so far in southeast Asia and China (Peterson et al., 2019).

This recent history of the DNA revolution is described elsewhere in greater general detail (Plomin, 2019) and specifically in relation to intelligence (Plomin & von Stumm, 2018). The purpose of the present article is to look to the future use of DNA to predict intelligence in science and in society.

2. Impact on science

The intelligence GPS enables any study that obtained DNA to add a genetic predictor of intelligence without having to assess phenotypic intelligence. Although GWA analyses require huge numbers of participants, GPS derived from GWA results can add a genetic dimension to any research study, even with modest sample sizes. 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 ($p = .05$, one-tailed).

Once a sample is genotyped, the intelligence GPS – just like any other GPS for a given phenotype – can be derived from these data. For this reason, we predict that a major impact of the DNA revolution will be to introduce intelligence to new areas of science, not only to fields like neuroscience where its relevance is obvious (Deary, Cox, & Hill, 2021; Haier, 2017), but also to far-flung areas of biology and medicine as well as economics and sociology. As expected from the pervasive effects of intelligence on education (Malanchini, Rimfeld, Allegrini, Ritchie, & Plomin, 2020), occupation (Schmidt & Hunter, 2004) and mental and physical health (Deary, Harris, & Hill, 2019), the intelligence GPS is correlated with a wide range of traits across the life sciences. For example, in the UK Biobank study, genetic correlations were estimated between hundreds of traits, including intelligence (Palmer, 2019). This resource revealed that intelligence is correlated phenotypically and genetically with heritable traits as diverse as sun exposure (−0.64 genetic correlation), watching television (−0.44), using computers (0.51), being in a noisy workplace (−0.67), heart rhythm (i.e. exercise electrocardiogram; 0.40), astigmatism (0.62), and age at first live birth (0.52).

GPS are unique predictors of intelligence for two reasons. First, the GPS for intelligence is a predictor of learning ability and disability at the level of the individual that is available in early life. Other predictors from early in life such as parental intelligence and family SES are not specific to an individual – the same prediction would pertain to any child in the family. Second, inherited DNA differences do not change from the moment of conception. For this reason, GPS can be just as predictive of adult intelligence in infancy as they are in adulthood, which makes them especially valuable early in life before intelligence can be assessed. The unchanging nature of inherited DNA variation also means that correlations between GPS and traits have a unique causal status. Other correlations do not allow inferring a direction of causality; for example, a correlation between measures of brain function and intelligence could emerge because brain function gives rise to intelligence, or because intelligence drives brain function. By contrast, correlations between intelligence and GPS can only be interpreted in one direction causally: there can be no backward causation in the sense that the brain, behavior or the environment cannot change inherited DNA variation.

The intelligence GPS will advance research on traditional quantitative genetic issues because, for the first time, genetic effects can be assessed directly using DNA rather than indirectly through twin and adoption study designs. These issues include the developmental course of the intelligence GPS (e.g., its earliest neurocognitive correlates), multivariate links (e.g., its network of associations with medical disorders), and the genotype-environment interplay (e.g., how the intelligence GPS interacts with interventions). The intelligence GPS also affords opportunities to ask novel questions in genetics that could not be addressed in twin and adoption study designs, such as the effect of selective and non-selective schooling on school performance (Smith-Woolley et al., 2018), intergenerational educational mobility (Ayorech, Plomin, & von Stumm, 2019), and secular trends in society (Rimfeld et al., 2018).

Because GPS are perfectly normally distributed, they underline the point that qualitative disorders are, from a genetic perspective, quantitative dimensions (Plomin, Haworth, & Davis, 2009). In other words, there are no etiologically distinct disorders, just normally distributed dimensions. Unlike most genomic research that focuses on diagnostic dichotomies (i.e., cases and controls), intelligence is generally recognized as a normally distributed trait dimension. That said, the intelligence GPS can enhance research on both very high and very low intelligence as the tails of the normal distribution, rather than as distinct

diagnoses such as 'gifted' or 'intellectually disabled' (Plomin, Shakeshaft, McMillan, & Trzaskowski, 2014). The intelligence GPS will be especially useful in distinguishing the very low end of the normal genetic distribution from intellectual disability that is caused by rare, often de novo, mutations with large effects (Reichenberg et al., 2016; Vissers, Gilissen, & Veltman, 2016).

3. Impact on society

Direct-to-consumer companies have until recently offered only single-gene results and ancestry data, but now they are beginning to provide polygenic scores. Typically, the customer downloads their 20-megabyte file with half a million of their DNA variants from a genotyping company like 23andMe and then uploads the file to another company that creates reports based on polygenic scores. We caution that these polygenic scores are often poorly constructed and as a result, they are impossible to interpret in meaningful ways. However, one not-for-profit company, *Impute.me*, has begun to compute hundreds of state-of-the-art GPS, including intelligence, for its users (Folkersen et al., 2019).

In 1997, a prescient science fiction film called *Gattaca* prophesied a dystopian world where DNA is used to select embryos, to test babies at birth, and to determine identity, education, insurance, occupation and even dating prospects. *Gattaca* has become a catchword for a future in which DNA seals a child's fate at birth. The DNA revolution may make the science of this science fiction film a reality, but the dystopian future predicted by *Gattaca* is not inevitable. The question is not whether the DNA revolution will affect society but how, when, and to what extent (Metzl, 2019; Rochman, 2017). We consider here three important areas of impact: DNA testing at birth, DNA testing before birth, and DNA testing before conception.

3.1. DNA testing at birth

For decades, DNA testing at birth has been compulsory in most countries to screen for single-gene mutations like phenylketonuria (PKU), which, if untreated, causes severe intellectual disability. But now, at the same cost as genotyping a few single-gene mutations, it is possible to genotype hundreds of thousands of inherited DNA differences that predict mental and physical health – and intelligence – from birth. Francis Collins, the head of the US National Institutes of Health and leader of the Human Genome Project, predicted: "I am almost certain that complete genome sequencing will become part of newborn screening in the next few years. .. It is likely that within a few decades people will look back on our current circumstance with a sense of disbelief that we screened for so few conditions" (Collins, 2010, p. 50).

More than a dozen direct-to-consumer DNA companies exist, mostly in Singapore and China, that market DNA testing internationally to parents who want to predict their child's intelligence as well as other traits (Standaert, 2019). In addition to parents paying to genotype their children, the current five-year plan of the Chinese government is to sequence at least 50% of the 15 million babies born each year in the country (Metzl, 2019). Concerns about data privacy are especially relevant here because the Chinese government reserves the right to access DNA data not just in the context of public health provision but also for national security or public interest (Ha, 2019).

One unrecognized benefit for parents in testing their children's DNA is to study the wide range of GPS differences within families – that is, differences between siblings and between parents and their children. First-degree relatives are 50% similar genetically but that also means they are 50% different genetically. In terms of standardized IQ test scores with 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 and between siblings is 13 IQ points (Plomin & DeFries, 1980; von Stumm & Plomin, 2018). In particular, the intelligence GPS might help parents who have two or more children understand why one of their children does better at school than the others.

Parents' attitudes toward genetic testing of children are overall positive, at least for health conditions (Lim et al., 2017). The intelligence GPS might be high on the list of what parents want to know about their children because intelligence is the best predictor of their offspring's educational and occupational outcomes, and it is also associated with a broad range of health outcomes (Deary et al., 2021). Notwithstanding, DNA testing at birth raises many issues, including – but not limited to – the problem of expectancy effects. Expectancy effects occur when a person's behavior becomes influenced by a belief or expectation, even if they are inaccurate or unsubstantiated (i.e. self-fulfilling prophecy). For example, older adults who knew they were carriers of the apolipoprotein E (APOE) ε4+ risk allele for Alzheimer's disease rated their memory function as lower and performed worse in a memory test than older adults who did not know their carrier status (Lineweaver, Bondi, Galasko, & Salmon, 2014). Conversely, older adults who knew they were carriers of the ε4− allele (i.e. reduced risk for Alzheimer's) judged their memory more positively than did ε4− carriers who did not know their status, but these groups did not differ in memory test performance (Lineweaver et al., 2014). Although only small effect sizes were observed, it is plausible that DNA-based predictions of intelligence can lead to significant expectancy beliefs. It is urgent that studies are conducted to test this hypothesis, especially as DNA-based trait predictions are becoming increasingly available and individual-level prediction from GPS currently includes a considerable number of false positives and false negatives (Plomin & von Stumm, 2018).

3.2. DNA testing before birth: Embryo selection

In vitro fertilization has been used since 1978. Eggs from the mother are harvested and impregnated with sperm to create embryos, typically about a dozen. Couples who are matched carriers of a deleterious recessive gene can expect 25% of the embryos to have inherited a double dose and, thus, to go on to have the disorder. After excluding those embryos, a decision must then be made as to which of the remaining ones to implant. Embryos can be winnowed further to exclude those with other single-gene mutations and chromosomal abnormalities like Down syndrome, which is currently the most common cause of intellectual disability. Still, several embryos are likely to remain, and polygenic scores could help with the decision about which to implant.

Taking a big step toward *Gattaca*, a company called *Genomic Prediction* began offering preimplantation genetic testing in 2019 that includes GPS for medical and mental problems, as well as for physical traits like height and weight (Regalado, 2019a). At present, the company only reveals intelligence GPS below the fifth percentile, not for the rest of the distribution.

As a result of having relatively few viable embryos available to implant from the standard in vitro fertilization protocol, the average gain from embryo selection can be estimated to be 5 IQ points with an intelligence GPS that accounts for 10% of the variance (Karavani et al., 2019). More relevant than the average gain is the average difference between embryos with the lowest and highest intelligence GPS, which has been estimated to be 12 IQ points with a batch of a dozen embryos (Shulman & Bostrom, 2014), although the lowest and highest intelligence GPS only weakly indexes the actual IQ difference.

It is unlikely that many parents will choose to undergo in vitro fertilization solely to select an embryo with a high GPS for intelligence. The process is unpleasant, requiring women to receive hormonal injections for at least ten days and an operation to harvest eggs, and it only results in a successful pregnancy about half of the time. DNA testing of embryos is also expensive, about $1500 per embryo in addition to the cost of in vitro fertilization, which stands at about $15,000. However, if a couple has opted to undergo in vitro fertilization for whatever reason, it will be necessary to make a decision about which embryo to implant –

or to decide not to choose. Left with several embryos without single-gene mutations, chromosomal anomalies, or high GPS risk for physical and mental disorders, it may be tempting for parents to consider the intelligence GPS.

3.3. DNA testing before conception: DNA dating

Not only are parents genotyping their children's DNA before and after birth, but people are now also using DNA testing to identify their potential mates. DNA matchmaking companies that bring together DNA testing and online dating include DNA Romance, GenePartner, and Instant Chemistry. These companies focus on candidate genes that are presumed to relate to sexual attraction and fertility, relationships, and personality. At present, these companies do not create GPS, although it is technically possible. We anticipate that DNA matchmaking will incorporate the intelligence GPS because it is more predictive (10%) than personality GPS (2%) and because assortative mating for intelligence is at least twice as strong as that for personality (Vandenberg, 1972).

Although the DNA dating industry seems frivolous, it may be the single most important societal application of the DNA revolution in relation to intelligence. DNA matchmaking can potentially reduce the genetic transmission of thousands of single-gene recessive disorders that induce intellectual disability. About 80% of children born with a single-gene recessive condition have no family history of the condition, with their parents discovering that they are matched carriers for a single-gene recessive disorder only after their child presents with symptoms (Rochman, 2017). Although these disorders are rare, a couple has about a 5% chance of being matched carriers for at least one pathogenic recessive mutation (Regalado, 2019b). Screening couples could greatly reduce the occurrence of single-gene recessive disorders, which have been estimated to cost one trillion dollars a year, and which are responsible for a large share of the heavy burden of intellectual disability (Regalado, 2019b).

4. Wider societal implications

GPS offer the opportunity to move away from treating problems after they occur to preventing them before they manifest. Prediction is key for prevention: Women with a GPS for breast-cancer in the top centile have a four-fold greater risk of developing breast cancer after the age of 50 compared to women whose GPS fall between the 40th and 60th percentile (i.e., middle quintile; Mavaddat et al., 2019). Knowing their genetic propensity for breast cancer enables women to make informed medical decisions about their healthcare, such as undergoing frequent mammographic examinations or, in extreme cases, preventive surgery (Jolie, 2013).

Although intelligence might be thought to be off-limits to this preventive perspective, the intelligence GPS could, for example, help to identify infants at risk for later learning difficulties, so that they receive the learning support they need early on. This notion is similar to Binet and Simon's rationale for developing the first intelligence test: To identify children who were likely to struggle with compulsory schooling, so they could be allocated additional tutoring and academic supervision (von Stumm, 2019). Likewise, the intelligence GPS could help to identify children whose disadvantaged family background may have suppressed the actualization of their high intelligence GPS (von Stumm et al., 2020a).

At the crossroads

The intelligence GPS represents a major scientific advance, and, like all scientific advances, it can be used for bad as well as good. In this review, we have highlighted the potential for good of the intelligence GPS for science and society as an antidote to the doom and gloom that often permeates discussions about the DNA revolution. That said, there are some notable concerns that accompany the advent of DNA-based prediction for intelligence, which can be broadly mapped into three categories.

First, the companies that offer predictions based on genomic information directly to consumers currently operate in a poorly regulated market space. The origin and validity of their DNA-based predictions are often indeterminable, the further use and storage of their customers' DNA for research and other purposes is unclear and unprotected, and customers typically receive feedback that is allegedly based on their genomic information without much explanation, guidance and support. We call on lawmakers to remedy this issue by developing regulatory frameworks that specify the operational standards, quality controls, and protection of consumers' rights and well-being for genomic prediction services.

Second, using GPS to reflect individuals' genetic propensities requires clear warnings about the probabilistic nature of DNA-based predictions and the limitations of their effect sizes. These constraints must be understood by individuals and societal institutions alike, especially as we are fast-tracking into a world where DNA-based predictions for individual differences are becoming increasingly available.

Finally, the intelligence GPS could offer opportunities for positive intervention, but it also bears the risk of being perverted to serve discriminatory ideologies, policies, and practices that promote the exclusion and rejection of individuals because of their inherited DNA differences. The concerns surrounding DNA-based discrimination are particularly pertinent in the context of distributing limited public resources, such as education and healthcare. We hope that the fears of the potential misuse of genomic science will not stifle the discussions that are most urgently needed today in science and society, to ensure that we maximize the benefits and minimize the risks of our new ability to use DNA to predict intelligence.

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