Genetic Prediction

BY ERIC TURKHEIMER

The fundamental reason the genetics of behavior has remained so controversial for so long is that the layer of theory between data and their interpretation is thicker and more opaque than in more established areas of science. It is a matter of record that identical twins resemble each other, behaviorally as well as physically; that they are relatively more similar than fraternal twins is not seriously questioned either. The meaning of these facts, however, remains deeply divisive, and the disagreement is renewed each time the discovery is remade in a slightly different domain of human activity. In the same way, the finding that variations in tiny snippets of DNA have small but detectable relations to variation in behavior surprises no one, at least no one who was paying attention to the twin studies. How such snippets of DNA are related to differences in behavior—known as the gene-to-behavior pathway—is the great theoretical problem of modern behavioral genetics.

Technology is the incontrovertible mark of successful science. Theory is fine, and theory backed with data is better, but building bridges that don't fall down is the real thing and leaves no room for argument. A Doonesbury cartoon once depicted a doctor speaking to a patient diagnosed with tuberculosis; the patient professes to be a creationist. Well, the doctor explains, you have a choice: you can stick to your principles and have the old antibiotic that doesn't work anymore, or be a "Sunday creationist" and opt for the new one that was developed after the tubercle bacillus evolved into its modern drug-resistant form.[1] One could easily suspect that many common doubts about the validity of behavioral genetics are of the "Sunday environmentalist" variety. Genetic effects on behavior have the potential to challenge some closely held intuitions about free will, the importance of child rearing, and the indeterminacy of human choice; literal and uncritical acceptance of behavioral genetics has led in some awful directions in recent historical time.[2] It is better, one might conclude, to play it safe and stick with free will and environmentalism, twin and adoption studies be damned.

In defense of the skeptics, however, it must be admitted that human behavioral genetics has not produced very much in the way of useful technology—the equivalents of bridges or vaccines that might give the Sunday environmentalist reason to pause. The revolution in medicine that was anticipated on the eve of the Human Genome Project has been slower to arrive than anyone expected, and it is hard to point to anything at all in the realm of behavior, such as in clinical psychiatry.[3]

Fortunately, it is not possible to conduct breeding experiments in humans, a fact that goes a long way toward explaining why the social sciences in general are methodologically problematic. Given that intentional human breeding is a horrific prospect, what kind of technology might we want (or fear) out of human behavioral genetics? One possibility is a technology that could predict important behavioral characteristics of humans based on their genomes alone. A moment's thought suggests significant benefits and risks that might be associated with such a possibility, but for the moment, just consider how *convincing* it would be if on the day of a baby's birth we could make meaningful predictions about whether he or she would become a concert pianist or an alcoholic. This article will consider where we are right now as regards that possibility, using human height and intelligence as the primary examples. For data about familial correlations for intelligence, one need look no further than Thomas Bouchard and Matt McGue's classic summary;[4]

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for height correlations, we will rely on Peter Visscher, Brian McEvoy, and Jian Yang.[5] (Like the others in this special report, when I refer to "intelligence," I mean what behavioral geneticists and psychometricians mean by "general intelligence" or "general cognitive ability"; for more on *g*, see Amy Shelton and Jonathan Plucker's contribution to this special report.[6])

Two important topics will not be covered here. There is an extensive literature on the quantitative genetics of prediction, much of it by Naomi Wray and colleagues, that is too technical to be included.[7] In addition, I will not pause to think through the considerable ethical problems that would attach to effective genetic prediction if it were to be possible. In particular, any speculation about the eventual feasibility of prediction technology should not be taken as implying that it would be a good idea. Such scientific genies can be difficult to keep in the bottle, however.

Prediction from Phenotype

The most obvious example of something resembling genetic prediction is prediction based on observation of an identical twin, with the non-negligible caveats that it isn't entirely genetic and it isn't prediction. Most identical (that is, monozygotic, or MZ) twins share both a genome and a rearing environment, so any similarity between them is a mix of genetic and family-environmental factors. And twins, being born at the same time, are perhaps the best application of the dictum (often but not conclusively attributed to Nils Bohr) that prediction is very difficult, especially when it's about the future. Use of the word "prediction" to refer to a merely statistical procedure like regression analysis is of course commonplace in the social sciences. Identical twins are correlated nearly perfectly for height, and at .85 for IQ. Identical twins reared apart provide a more purely genetic platform for "prediction," to the extent that their rearing environments are truly independent. And in fact, identical twins reared apart are nevertheless nearly perfectly correlated for height and almost as highly correlated for IQ as twins reared together (.67). The height correlation for identical twins reared apart remains over .9.[8]

One can overcome this difficulty by studying siblings who are not twins, but doing so introduces other problems. Older siblings are real and often useful predictors of outcomes in younger siblings, but since siblings share on average only 50 percent of their DNA and are usually raised in the same home, the problems of distinguishing genetic and environmental prediction are even more acute than they are for identical twins. The correlation for height in same-sex sibling pairs raised together is about .45;[9] for IQ it is .4.

Individual parents and biological children are genetically like siblings in that they share 50 percent of their DNA; the genetic correlation between pairs of parents and their biological children depends on the degree of similarity between the parents, known as assortative mating. For parents, the idea of prediction is even more apropos, as any parent will wonder about the extent to which a child may come to resemble him or her, for good or ill. For some clearly genetic syndromes based on what are called genes of large effect, about which I will say more below, parent-child relations are the basis for genetic counseling; but for outcomes like height and intelligence, for which genetic pathways are more complex, the usual confounding of genetics and family environment obtains. Parent-child correlations for height and IQ are similar to those for siblings: around .3 for height and .4 for IQ.

Both theoretically and practically, adoptive families provide the most interesting problems in genetic prediction we have encountered so far. Adoptive families have two parts: adoptive parents and children to whom they are not biologically related, and biological parents and adopted-away children whom they did not raise. The prediction results are striking, real, and practical: biological parents are better predictors of practically all outcomes in adopted children than adoptive parents. For height, it is obvious: who would expect anything other than adopted children whose height is better predicted by the height of their biological parents? We take it for granted, but that is a real example of genetic prediction. On the day a child is born, we can make a pretty good prediction of his or her eventual height. All we need to know is the height of his or her biological parents.

The results for intelligence are less dramatic. The IQs of adoptive children are correlated around .2 with the IQs of both their biological parents and their adoptive parents. There are, of course, complications: there may be prenatal effects of biological parents even when children are adopted at birth; children are not placed in adoptive homes at random; adoptive homes are usually selected for environmental quality; the adoptive correlation with IQ is higher when children are young than it is after adolescence. But is anyone willing to discount the correlation between the heights of biological parents and their adopted-away children for

reasons like these? And because adoption is a choice, genetic prediction for adoptees has real consequences. Although an adoptive parent could certainly make a principled decision to ignore knowledge of genetic risks in a potential adoptee, such knowledge exists.

Prediction from DNA

Everything that has been discussed so far has been based on what a geneticist would call phenotypic prediction. The word "phenotype" refers to an observed characteristic of an organism, like height or intelligence, as opposed to the genetic and environmental processes that underlie it. This is probably not what most people have in mind when they think of genetic prediction. Scientists—and, more and more, the general public—now have access to the actual DNA sequences of individuals, or at least to approximations of the sequences. We can now ask whether it is possible to predict outcomes in children from their DNA. If it were possible, this would allow us to predict the outcome of an individual while knowing nothing of that person's background, family, or circumstances. This possibility, with all of its fantastic and disturbing consequences, is the topic of the remainder of this essay.

It is common to think of the era of DNA-based prediction as beginning with the completion of the Human Genome Project, but simpler methods have been available for longer than that. Some disorders of height and intelligence are caused by genes of large effect that are either spontaneous mutations or mutations in autosomal genes that are transmitted in families according to Mendelian laws. Down's syndrome, for example, is caused by a random abnormality in cell division, producing an extra copy of chromosome 21, which causes, among other things, decrements in intelligence; genetic testing for Down's is in a straightforward way a form of genetic prediction of intelligence. Huntington's disease, associated with intellectual difficulties (among other symptoms) later in life rather than in childhood, is caused by an autosomal dominant gene mutation. An individual with the mutated gene has a 100 percent chance of developing the disorder; children of a parent with the mutation have a 50 percent chance of inheriting it and a 100 percent chance of illness if they do. Genetic testing for Huntington's disease, now readily available, is therefore also a form of genetic prediction.

There are several points to make about prediction from genes of large effect on height and intelligence. The effects of such genes on intelligence are universally negative: there is no gene for genius, as we will see in detail below. The genes are also relatively rare, which is a good thing given the previous point. Their rarity has an important consequence for the mathematics of prediction. The abnormality that causes Down's syndrome has a large effect on intelligence, equal to around thirty IQ points or two standard deviations. But if one were to ask how much of the population variance in intelligence is explained by Down's syndrome, the answer is almost none of it, because so few people are affected. Down's syndrome is a good predictor of intelligence among individuals who manifest it, but concentrating on it would be of little use in a society-wide effort to predict cognitive ability. Finally, genetic testing for Mendelian genes of large effect works within families as well as between them, and indeed this is how they are usually used. It has been known for a long time that children of individuals with the Huntington's mutation have a 50 percent chance of developing the disorder: what modern genetic testing adds is the ability to determine which of the offspring of an affected parent will develop it.

Efforts to predict human characteristics that vary widely in the general population must be based on similarly common variation in DNA. The first method to be widely available, called linkage analysis, relied on within-family variation in the form of differences among pairs of siblings and their parents. The DNA sequence can be searched for "linkage" between a segment of DNA and an outcome of interest. Because sequences of DNA at proximate locations on the chromosome are usually transmitted together, within-family correspondence between a genetic marker and an outcome suggests that the marker may be close to a relevant gene. Linkage analysis has limited statistical power and is thus best suited to detection of genes of large effect; it played a key role in the discovery that there are not any genes of large effect for behavior in the normal range—nor, for that matter, for height.

A second common method for conducting genetic prediction from DNA is called a candidate-gene association study. Association studies examine variation among individuals in different families, and they couldn't be simpler. One measures variation in a gene or a portion of a gene and sees if it is correlated with an outcome of interest. Because association studies do not require family members, they have more statistical power than linkage studies, but their outcome is essentially the same: because there are no genes of large effect for complex human characteristics, the effect of any individual unit of DNA is almost vanishingly small, making meaningful prediction impossible. In addition, because of the multitudes of genes that are available for testing, the process is beset by Type I errors ("finding" an effect that isn't really there) as well as Type II errors (failing to find an effect that is there). The resulting inferential problems are legion: virtually every association study conducted before 2010 relied on sample sizes that were far too small, and most if not all of the proposed associations with candidate genes were not replicable.

The methodological difficulties of basing genetic prediction efforts on the actions of individual genes, com-

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bined with the discovery of new genomic technologies, led to a sea change in scientific strategy. It is now possible, for a relatively small amount of money, to conduct tests for more than a million genetic associations on a single chip. These tests are based not on genes but on individual units of DNA called single nucleotide polymorphisms, or SNPs; the research method is called a genome-wide association study. The GWAS method is not usually thought of as a basis for genetic prediction but, rather, as a method for searching the genome for associations (the reader is referred elsewhere for descriptions of the method and its results from that point of view[10]). Simply put, it confirmed what linkage and association studies had already hinted at: that there are no genes of large effect for complex human phenotypes, certainly not for either height or intelligence. Any effort at prediction from the genome, therefore, would have to be based on the effects of multiple units of DNA.

There are several ways to go about aggregating these effects. The first is to use some criterion to select a set of SNPs with the largest association with the outcome and sum them: this is called a polygenic score. Another class of methods uses a very active area of statistical investigation called machine learning to find more complex ways to combine bits of genetic information to predict an outcome. One can think of such methods as teaching a computer to predict human height from the genome. A third class of methods, the best-known instance of which is called genome complex-trait analysis, is more like a twin or family study than a DNA-based prediction algorithm.[11] In GCTA, one starts with a collection of genetically unrelated individuals (except that at the end of the day we are all genetically related), and SNP chips are used to compute the amount of genetic background shared by each pair of people. This number is on the order of a couple percentage points. The pair-wise degree of genetic similarity is then compared to similarity in phenotype. As a prediction algorithm, GCTA posits that a participant's height or IQ will be most like that of people with the most similar arrays of SNPs.

In some very interesting ways, the results for height and intelligence have begun to diverge in this new era of genomic prediction. Of course, height can always be somewhat better predicted than intelligence. It is measured more reliably, if nothing else. Identical twins are almost perfectly correlated for height, but under ordinary circumstances they are almost as correlated for intelligence. Certainly if everyone had an identical twin, we could use the first twin's IQ to "predict" the second twin's IQ in a statistically useful way.

Although it still has a long way to go, genomic prediction of height is making real progress. More and more SNPs are being discovered at very stringent levels of statistical significance. Polygenic scores combining individual SNPs can predict height at about half the rate that one twin's height can predict the other's; GCTA does even a little better.[12] The same cannot be said for intelligence. A few SNPs have achieved statistical significance in one study or another, but none are well established. Polygenic scores predict no more than a few percentage points of the variation in intelligence, and GCTA does only slightly better.[13]

The crucial question is whether the divergence of height and intelligence is simply a temporary difference in the rate of the long-term inevitable progress of science or represents a qualitative difference in their genetic architecture. There are surely *some* differences. Height, as we have noted, can be measured more reliably than intelligence. In the absence of hunger or disease, there are no environmental methods to decrease height. With no environmental main effects for height, there are few opportunities for gene-environment correlation or interaction: tall children are not placed in special environments to enhance their size. Height, to put it plainly, is outside the domain of human intention and action. Intelligence is behavior.

The question of the difference between height and intelligence is important because it is another way of posing a problem that is more general: is there a ceiling on genetic prediction? Given that identical twins are correlated .9 for height and given that we are within a very few years of having inexpensive access to the complete genomic sequence of anyone who chooses to share it, is it simply a matter of time, sample size, and scientific progress before we can predict people's adult height in utero at r = .9?[14] And if so, will it just take more time, even bigger samples, and greater scientific progress before we can make the same prediction, with only slightly less accuracy, for intelligence? Much depends on the answer.

First, we should note that, in an important sense, there is less than meets the eye to the accuracy of current tech-

nology for genomic prediction. It is natural to calibrate accuracy of prediction in terms of what could be achieved with a sample of genomic sequences selected blind and at random from the population. That is fair enough as a theoretical or statistical exercise, but it is difficult to imagine a situation in the real world in which prediction took place in such an isolated context. What we really imagine is this: two tall parents-to-be, he six foot eight and she six foot one, basketball players, dreaming of a tall child whom they can groom to become a star. They are expecting a girl, and at three months have the fetus genotyped. The doctor smiles as he enters the consulting room and says, "I have good news: your daughter is going to be six foot two."

There are many less pleasant stories we could tell about this possibility, and we should not make light of the thorny, indeed frightening, ethical problems of a world in which this were possible for height (never mind intelligence), but that discussion is for another article. For now, what concerns us is that in any real-world scenario, prediction of human characteristics will take place in the presence of knowledge of the parental phenotype. We already know that tall parents have tall children, and we are ready to believe that the reasons for this are broadly genetic. What we need to know is whether genomic data can improve on the prediction we can make from parental phenotype alone or, put another way, whether prediction will work within families as well as between them, allowing parents to predict differences among their own children (because within-family prediction of siblings effectively holds parental phenotype constant). This is a much more difficult standard than general prediction in the population.

There are few good examples of this kind of prediction in the literature, and nothing of which I am aware for height or intelligence. Jessica Salvatore and colleagues recently published a very provocative report combining parental phenotype and a polygenic SNP score in the prediction of externalizing behavior in adolescents and young adults.[15] A polygenic score derived on the parents accounted for between 5 and 6 percent of the variation in the externalizing behavior of the children, even after parental phenotype was controlled statistically. That is not a huge effect, certainly not large enough to support practical prediction, but it is very interesting scientifically and may well be a marker for what the future holds.

Predictions about Prediction

Can behavioral differences be predicted from genotype? If one is willing to count prediction from an identical twin or other biological relative as "genetic" (fairly reasonable, for example, in separated twins or adoptees) and as "prediction" (usually not so much), then the answer is yes. Practical instances of genetic prediction of this kind occur under the broad rubric of genetic counseling. Biological children of two alcoholic parents would be well advised to be especially careful with their drinking; younger siblings of children on the autism spectrum are at increased risk for the disorder; prospective adoptive parents, if they choose to do so, can learn about risks and strengths of potential adoptees by inquiring about the biological parents; clients at sperm banks are routinely provided with information about the donors. Whether one would want to use this sort of information as the basis for family decisions about height or intelligence is another question, one that leads back to ethical issues that will not be addressed here.

Prediction from DNA is a much more complex and potentially much more important problem. If it were possible to draw up an adult physical or behavioral profile based on DNA obtained from a fetus or embryo, the resulting information would be demonstrably genetic and predictive. Moreover it would be available to everyone, not just the rare few with an identical twin or those with an absent biological parent. I will repeat one more time that even if it were possible, it might or might not be a good idea. In fact it would almost certainly be both, which is why the prospect is simultaneously exciting and alarming.

For the time being, we can all breathe easier, however, because right now it is not possible, and there are some good reasons to wonder if it ever will be. The divergence of height and intelligence is important here. We can today make DNA-based predictions of human height that would pass muster in a social science journal, accounting for perhaps 20 percent of the variability in height. That level of prediction is borderline in terms of real-world utility, but it doesn't matter: we can already predict height that well, in fact, better, by simply observing that tall parents have tall children. To the best of my knowledge, the marginal utility of prediction from DNA over prediction from parental height has never been reported, but it seems safe to say that it would be very small, too small to be of practical use to anyone.

Not even this much is true for intelligence. The effect sizes for polygenic scores for intelligence are on the order of a single percentage point at best, below the level that would be considered acceptable in a social science journal, statistical significance notwithstanding, and considerably lower than could be obtained with an ordinary sociological indicator like family income. A good phenotypic predictor like an identical twin is even better. I would contend that were it not for both the technological gloss offered by the genomic technology underlying SNP-based prediction and the lingering refusal of skeptics to accept twin correlations as genetic, no one would be much interested in polygenic scores to predict intelligence.

It might be argued that even very small genetic correlations could be useful at the margins, as a way of predicting

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high ability if not ability differences in general. One could perhaps ignore routine signals from the genome, taking action only when a result is obtained in the upper percentiles. But there is little reason to think such a procedure would be successful. Extraordinary as modern genomics may be, it is not immune to the ineluctable rules of regression and prediction. A correlation of r = .1 is what it is, and the standard error of a prediction based on a correlation of .1 is equal to the square root of 99 percent (that is, $[1-.1]^2$) of the variance of IQ, even if one ignores any uncertainty arising from sampling variation in the study from which the r = .1 was estimated. Weak predictors are weak predictors, and a gene that accounts for 1 percent of the variation in an outcome has no more practical potential than a similarly weak signal from a questionnaire.

It is crucial to consider why identical twins work so well as predictors of IQ, while polygenic scores lag badly behind. This is a version of what has come to be called the "missing heritability problem": all complex behaviors are related in identical twins, for reasons that can be broadly if vaguely characterized as genetic. Yet individual units of DNA explain little of this relationship, and although for some traits like height, composites of DNA account for more, even for those there is a long way to go. How can this be? Identical twins prove the feasibility of using the genomic sequence to generate a prediction about intelligence. Why can't this activity be reproduced in the geneticist's laboratory and the statistician's computer? Searches for answers to the missing heritability problem, unsurprisingly, usually focus on technical solutions, but the real answer is both obvious and intractable. In fact, it is staring us in the face.

Here is how to make useful predictions of IQ. Soon after conception, retrieve the embryo, clone it, and freeze one of the clones. Implant the other, let it come to term and be raised as a normal child, and obtain an IQ score in adulthood. Fifty years later, implant the preserved identical twin, again raise it as normally as possible, and obtain a score on the same IQ test. Repeat for a hundred artificial twin pairs. Glossing over a few complications (the later-born twins will probably be smarter, thanks to the Flynn effect![16]), the pairs of twins will be correlated in the neighborhood of r = .8 for IQ. No problem.

Not possible, you say? Perhaps not, but the thought experiment shows us something important. How can we "compute" over a genome to come up with a predicted IQ score? We can raise a child from it, that's how. Anything short of that is a model, either statistical or biological. The thought experiment demonstrates that the genetic prediction problem, and by extension the missing heritability problem, are coextensive with no less than developmental biology—psychology for present purposes—in general. Generating a prediction from a genome is a matter of figuring out how the individual elements combine with each other, with the environment, and with time to develop an organism.

This is why intelligence—the best-established and most reliably measured of human behavioral individual differences—is already turning out to be so much more difficult than height. The missing heritability gap between what can be predicted with an identical twin and what is possible with a genetic sequence is an index of the nonlinear developmental complexity inherent in a trait. It is often presumed that making progress in genetic explanation is simply a matter of increasing sample size. For height, it has turned out that thousands of participants are necessary to reach the (stringent but arbitrary) standard for genome-wide significance; for schizophrenia, tens of thousands are necessary; for educational attainment, hundreds of thousands. This process has become a matter of finding smaller and smaller needles in bigger and bigger haystacks, but there are no mathematical or empirical guarantees about limits that the sum of all those needles may approach. There are a lot of possibilities: the perfect correlation of 1.0, the MZ twin correlation, the parent-child correlation, the GCTA correlation. There is considerable variation among phenotypes in how rapidly such standards are being approached. It appears, for example, that the GCTA heritabilities of some demonstrably heritable phenotypes are close to zero.[17] Important theoretical and statistical work on these questions remains to be done.

In the meantime, I suspect that the missing heritability gap will continue to exist for everything polygenic, and it may well be permanent for complex human behavioral traits, for two reasons. The first is that, at such high levels of complexity, mathematical problems of indeterminacy intervene between predictors and outcomes. Weather forecasters, for example, do not anticipate a time when we can predict the daily details of a hurricane season twenty years

out, for reasons that have little to do with empirical meteorological science. Nonlinear interactions among multiple genes or between genes and environments can produce unpredictability in outcomes even in completely deterministic processes.[18] The second reason is that the tools that would be most useful in breaking down the complexity of development—random assignment to experimental condition and subsequent dissection of sacrificed individuals—are unavailable to human researchers and will forever remain so, once again for reasons having nothing to do with science. The possibility of genetic prediction of behavior fascinates because it leads to the edge of the possible in scientific psychology.

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2. J. Tabery, "Why Is Studying the Genetics of Intelligence So Controversial?," *The Genetics of Intelligence: Ethics and the Conduct of Trustworthy Research*, special report, *Hastings Center Report* 45, no. 5 (2015): S9-S14.

3. In contrast, the genetics of behavior in lower animals has produced a successful technology that is convincingly probative: selective breeding. Much of the foundational work on behavioral genetics involved temperament in dogs, and breeding for behavior in domestic animals had been conducted systematically if nonscientifically since time immemorial. As a sometime skeptic myself, I have respect for a broad spectrum of doubters of human behavioral genetics, even when I disagree with them, but contending that behavioral differences between Labradors and beagles have nothing to do with their genes—which, tellingly, no one bothers to do—would be science denialism of the creationist sort.

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11. Visscher, Yang, and Goddard, "A Commentary on 'Common SNPs Explain a Large Proportion of the Heritability for Human Height.'"

12. A. R. Wood, "Defining the Role of Common Variation in the Genomic and Biological Architecture of Adult Human Height," *Nature Genetics* 46, no. 11 (2014): 1173-86.

13. M. Trzaskowski, "DNA Evidence for Strong Genetic Stability and Increasing Heritability of Intelligence from Age 7 to 12," *Molecular Psychiatry* 19, no. 3 (2014): 380-84.

14. The variable "r" is the correlation coefficient, which indicates the strength of the correlation between two variables. A perfect correlation would yield an r of 1, and in the absence of any correlation, r would equal 0. In this case, r indicates a strong correlation between the height one predicts during gestation on the basis of genotype alone and the height the person actually reaches as an adult.

15. J. E. Salvatore, "Polygenic Risk for Externalizing Disorders Gene-by-Development and Gene-by-Environment Effects in Adolescents and Young Adults," *Clinical Psychological Science* 3 (2014): 1-13.

16. R. E. Nisbett, "Intelligence: New Findings and Theoretical Developments," *American Psychologist* 67, no. 2 (2012): 130-59.

17. M. Trzaskowski, P. S. Dale, and R. Plomin, "No Genetic Influence for Childhood Behavior Problems from DNA Analysis," *Journal of the American Academy of Child & Adolescent Psychiatry* 52, no. 10 (2013): 1048-56.

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