Neither nature nor nurture: Using extended pedigree data to elucidate the origins of indirect genetic effects on offspring educational outcomes.

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Abstract

Background: More highly educated parents tend to raise children who go on to complete more education themselves. Strong evidence for environmental transmission arises from the fact that offspring outcomes correlate to parental genotypes even when controlling for the offspring genotype. The process that gives rise to an environmentally mediated correlation between parental genotype and offspring education (“indirect genetic effects”) remains poorly understood. A key question is whether intergenerational transmission reflects within-family processes, such as parenting behaviors (i.e. “Genetic nurture”), or social inheritance that could reflect either genetic ancestry or social stratification (i.e. “Dynastic effects”).

Methods: We analyzed data from N = 25,215 genotyped parent-offspring trios participating in the Norwegian Mother, Father, and Child Cohort Study (MoBa), where many of the participants in the parental generation are siblings (N = 3,500 sibling pairs; children’s uncles/aunts). We correlate genetic differences *within* the parental family, conditional on offspring genetics, to offspring’s educational outcomes (test scores; Grades 5-9). The strategy isolates indirect genetic effects that play out in the nuclear family from indirect genetic effects that arise through social or ancestral genetic stratification. We additionally partition genetic variants associated with educational attainment (EA) into those associated with cognitive versus non-cognitive skills.

Results: We find that children’s genetics, measured using polygenic indices (PGIs) for cognitive and non-cognitive components of EA, is associated with their educational performance. Parents’ genetics are also associated with their children’s educational performance, over and above the child’s own genetics. However, we find no evidence that parents’ PGI are specifically related to offspring academic achievement over and above the average PGI of the siblings in the parental generation.

Conclusions: Our result suggests that the effects of the environmental processes captured by genome-wide association studies of EA and characterized as “nurture” are explained less by parents’ specific behaviors and more by dynastic stratification in environments relevant to success in school.

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Introduction

Surprisingly, some of the clearest evidence that education is transmitted between generations via the inheritance of *environmental* advantage has come from genetically-informed research. Adoption¹, twin², molecular genetic³, and genome wide association studies (GWAS)⁴⁻⁶ designs all show that the intergenerational transmission of educational attainment occurs via both genetic and environmental mechanisms (**Box 1**). Studies of adoptees show that children resemble their adopted (social) parents in education despite not being genetically related to them⁷. Studies of twins reveal educational similarities within monozygotic and dizygotic pairs that are in line with a role for both the genome and the environment⁸. Recently, molecular genetics studies have also established environmental mechanisms of intergenerational transmission of educational attainment⁹. Specifically, molecular-genetic studies of parent-offspring trios, of adopted parent-child dyads, and of biological siblings all show that people's educational attainment (EA) is associated with the genes they did *not* inherit -- an association that can only operate via the environment.¹⁰⁻¹³

The new wave of molecular genetic studies measure genetic influences on educational attainment using polygenic indices (PGI). The PGI method uses results from genome-wide association studies (GWAS) to score research participants' genomes to summarize the combined influence of hundreds of thousands of variants on a target trait or behavior. PGIs based on GWAS of educational attainment can predict as much as 10% of variance in EA in population-based samples, similar to the predictive power of parental education. However, although a PGI is measured from the offspring's DNA, its effects do not only capture genetic influence. Studies of gene-environment correlation reveal that children's EA PGIs are correlated with environments they inherit from their parents, including the social and economic circumstances of their families and neighborhoods.¹³⁻¹⁵

In family-based PGI studies, researchers can separate out the effects of parents' transmitted from non-transmitted genotypes (i.e. genetic variants carried by parents that are not passed on to children). These studies find that children's EA is influenced by PGIs based on both the transmitted and non-transmitted genotype. The effects of the non-transmitted genetics reflect a process of inheritance mediated by the environment. These environmentally-mediated or "indirect" genetic effects arise due to unmodeled gene-environment correlations, and introduces bias in GWAS and PGI analyses of educational attainment¹⁶. The indirect genetic effect also

offers a means to study how parental traits affect childhood outcomes, while accounting for the direct genetic effect on offspring outcomes¹⁷.

The indirect genetic effects of PGI on education have been replicated using various designs. Cheesman et al.¹⁸ showed that PGIs predict EA significantly better in a population raised by their biological parents than in a population of adoptees. The stronger relation between PGI and education in those reared by biological parents is attributable to the environmentally-mediated effects of heritable parental behavior and/or economic position, which are correlated to a child's PGI in biological children but not adopted children¹⁸. Similarly, Domingue and Fletcher¹⁹ showed a significant prediction of education in adopted offspring by the adoptive parents' PGI. This cannot be explained by direct genetic transmission and must be environmentally mediated. Selzam et al.^{12,20} study siblings to show that the effect of the PGI on EA within sibling pairs is lower than between sibling pairs, suggesting the presence of an indirect effect. Much of this indirect genetic effect disappeared after conditioning on observed SES.^{12,20} Isungset et al. use trio data in Norwegian families and find a small to moderate indirect genetic effect.^{21,22} There are hints the indirect effect may be more modest in childhood (educational achievement or test performance) than in adulthood (educational attainment in years or degree completion).^{9,22} Finally, GWASs that explicitly estimate the effect of SNPs on EA within siblings,⁴ or account for the geographic region of birth²³ estimate a substantially lower heritability for EA, again suggesting the presence of indirect genetic effect.

While there is consistent evidence for the presence of an indirect genetic effect, the mechanisms that produce the effect remain unclear. Among the most evocative descriptions of the indirect genetic effect are: "Nature of nurture" and "Dynastic effects"^{10,24}. The former invokes the notion of nurturing behavior within the family, while the latter invokes the notion of intergenerational transmission of wealth or status enabling a sought-after educational career. Beyond various informal interpretations of the effect, researchers have identified various mechanisms that could account for the presence of an indirect effect: assortative mating,^{25–27} subtle population stratification^{28,29}, sibling on sibling indirect effects³⁰ could all induce an indirect genetic effect⁹.

Here, we aim to refine understanding of the mechanisms underlying the indirect genetic effect on educational outcomes, using data from a birth cohort in which both children and their parents are genotyped, and there are over 3.000 sibling relationships in the parental generation (i.e., the

children's uncles and aunts). An indirect genetic effect is estimated by testing whether the parental genotype is associated with the offspring phenotype, above and beyond the offspring's own genes, a relationship that must be environmentally mediated. An extended pedigree design that includes sibling relationships in the parental generation allows us to further decompose the parental genotype into two components: (1) the average PGI of the siblings in the parental generation (between family indirect effects), and (2) the deviation of the parental genotype from the parental-sibling-pair average (within family indirect effects). Including parental-sibling-pair average into the model controls for effects of the grandparental genotype, as well as for all aspects of the environment that are shared by the extended family (the parent and their sibling). This design further includes perfect control for subtle population stratification, as the parent and their sibling are very closely matched for ancestry. If the parents' PGI is associated with their offspring's phenotype, even after controlling for the parental-sibling-pair average PGI, this suggests that the indirect genetic effect operates via "nurture" plays out in the context of the nuclear family environment, such as parenting or investment behaviors. If, however, the parental-sibling-pair average PGI is associated with offspring outcomes, above and beyond the parents' PGI deviation, this suggests that the indirect genetic effect is tapping multigenerational stratification in environments. The indirect genetic effect could represent both nuclear and extended-family effects.

One additional critical question is what specific skills of parents (or of the extended family) relate to childhood school performance. Most previous work tests for indirect genetic effects of the PGI for EA. Here we rely on recent work³¹ that disentangles, albeit imperfectly, processes that affect EA through cognitive and non-cognitive mechanisms. Examples of non-cognitive skills include grit, self-control and conscientiousness (#add your favorite refs). For cognitive and non-cognitive genetic contributions to EA we can construct separate PGIs.

In this study we compute two PGIs, based on well powered GWASs for cognitive (N = 257,700) and non-cognitive (N= 510,795) contributions to educational attainment³¹, and test for an indirect genetic effect of parental PGI on child standardized test scores. We repeat these analyses while leveraging data on siblings in the parental generation to introduce a family fixed effect at the level of the parents. This enables us to disentangle within-extended family (controlled for social and genetic stratifications) from between-extended-family indirect genetic effects. This analysis parses whether parents' own genetics are (environmentally) related to offspring academic achievement, as would be predicted by theories of environmental transmission that emphasize

“nurture”, or whether parents’ genetics are tapping a multigenerational, dynastic process of environmental advantage.

Box 1. Evidence from Genetically Informed Studies for Environmental Transmission of Educational Outcomes

Design	Key Comparison
Twins	Are fraternal twins more similar in their EA than can be accounted for by their genetic relatedness?
Twins + offspring	Are children of (e.g. female) monozygotic twins more similar in their EA to their mother than to their aunt?
Adoptees	Do adopted offspring resemble their adopted parents in their EA?
Adoptees + siblings	Do offspring adopted into more environmentally advantaged homes have higher EA than their siblings who were not adopted away?
Adoptees + PGIs	Do adopted parents’ PGIs predict adopted children’s EA? Is the association between one’s own PGI and one’s own EA stronger if raised by biological parents than by adopted parents?
Parent-offspring trios + PGIs	Is the portion of the parental genotype that is not inherited by the offspring (untransmitted PGI) associated with offspring EA?
Siblings + PGIs	Is the PGI-EA association attenuated after controlling for a family-specific effect or family SES?

Methods

Subjects

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health²¹. Participants were recruited from all over Norway from 1999-2008. Women consented to participation in 41% of the pregnancies. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. The current study is based on version 12 of the quality-assured data files released for research

in January 2019. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act. The current study was considered by The Regional Committees for Medical and Health Research Ethics.

In our version of the data, 25,215 nuclear families have genotype information on complete trios (mother, father, and child) where both parents were born in Norway. The Norwegian system of personal ID numbers facilitates linking of data from MoBa to educational outcomes, basic demographic information and links between parents and their siblings. In the analytic sample, there are 2,980 nuclear families where one parent has a sibling in the data set, the child and both parents are all genotyped, the child has taken at least one standardized test.

Measures

Educational outcomes are children's results on national standardized test scores ("Nasjonale prøver") in reading (i.e., reading comprehension in Norwegian, for almost all their first language), math, and English. Reading and Math were administered in 5th, 8th and 9th grades and English in 5th and 8th grades. All MoBa children have data on 5th grade tests, while the youngest cohorts do not yet have data on 8th and 9th grade tests. The test scores were obtained from Norwegian administrative registries. The scores were standardized within the test and year to control for test version and secular changes.

Polygenic scores for cognitive and non-cognitive skills were computed for all individuals in the PRSice software using all available SNPs (i.e. a p -threshold of 1.0). GWAS summary statistics were obtained from a GWAS-by-subtraction splitting cognitive and non-cognitive SNP effects on educational attainment³¹.

Statistical analysis

Indirect effects

We fit four models. The first two models can establish the presence of an indirect effect in the sample of all genotyped parent-offspring trios:

$$Edu_i = \beta_{PGI} PGI_{child\ i} + \dots + e_i \quad (\text{model 1})$$

$$Edu_i = \beta_{dir} PGI_{child\ i} + \beta_{fath} PGI_{father\ i} + \beta_{moth} PGI_{mother\ i} + \dots + e_i \quad (\text{model 2})$$

In a third model, we select parents for whom one or more siblings are among the other parents. We then compute the following predictors:

$$PGI_{\mu} = \frac{\sum_{m=1}^m PGI_m}{m}$$

Where PGI_{μ} is the mean PGI for the sibship of size m , we then compute for each of the individual parents in the sibship their personal deviation from the sibling mean:

$$PGI_{\Delta} = PGI_m - PGI_{\mu}$$

Where PGI_{Δ} is the *within-sibship* polygenic score for a parent. We then predict the educational test performance (Edu) of the children using the following model:

$$Edu_i = \beta_{dir} PGI_{child\ i} + \beta_{within} PGI_{\Delta} + \beta_{between} PGI_{\mu} + \beta_{other} PGI_{other\ parent} \dots + e_i$$

(model 3)

As often only a single parent in each spouse pair has a sibling in the data, we introduce a PGI “other” for the parent without a sibling in the data. Children where neither parent is in a known sibship are omitted. The chosen parameterisation (which resembles previous work²⁰) results in identical between-family and within-family effects in the absence of population stratification and/or the absence of a multi-generational effect on childhood educational test scores³². In the presence of either, we expect the between parental-sibling-pair effect to be larger than the within parental-sibling-pair effect.

The fourth model is a mixed-effects repeated measures model where the eight educational outcomes (across grades and subjects) are combined into a single regression. A random intercept for participants is added (u_i), trading increased precision for specificity in the outcome.

$$Edu_{ij} = \beta_{dir} PGI_{child\ i} + \beta_{within} PGI_{\Delta} + \beta_{between} PGI_{\mu} + \beta_{other} PGI_{other\ parent} \dots + u_i + e_{ij}$$

(model 4)

Here the educational test score j , nested in child i , is regressed on the aforementioned child and parent specific PGI, and a random intercept u_i . In all regression models, the omitted covariates (...) are child’s sex, child’s birth year, child’s 10 first principal components (to account for population stratification), and genotyping-batch fixed effects (to account for batch to batch variation in genotype processing and measurement).

Assortative mating

One possible bias that persists in the within-family analysis of the indirect effect is assortative mating with respect to educational attainment or SES. Active mate selection would induce similarity between parents and introduce an indirect effect that persists even within families. There are various hypothetical processes that yield similarities between spouses, for example that educational institutions are arenas for partner search. A test to distinguish active mate selection from mere social homogamy (similarities due to living in close spatial and social proximity to our partners) is to correlate the PGI, or the phenotype EA, within a parental couple, and test whether this correlation exceeds the correlation between a sibling-in-law.

We test the null hypothesis (social homogamy):

$$\text{cor}(\text{spouse1}, \text{spouse2}) = \text{cor}(\text{spouse1}, \text{sib spouse2})$$

We then specify as an alternative hypothesis (active mate selection):

$$\text{cor}(\text{spouse1}, \text{spouse2}) > \text{cor}(\text{spouse1}, \text{sib spouse2})$$

The test we propose can be used to distinguish active mate selection from homogamy, but the correlation between in-laws itself cannot be viewed as a quantification of social homogamy. For obvious reasons, siblings are alike on their PGI and EA than to others in the population. They are therefore expected to be more similar to their in-laws than to others in the population, regardless of whether assortment is the outcome of active mate selection or social homogamy.

Results

Results of model 1 confirm that both the Cognitive and Non-cognitive PGI are associated with children's test performance (estimates and 95% confidence intervals labeled in Figure 1 in blue). The effect of the cognitive PGI is larger For all subjects and all grades. Consistent with previous studies, the second model (Figure 1 in orange) estimated a small but significant effect of the parental PGI on all outcomes. The effects of paternal and maternal PGI are similar across all childhood outcomes. While the cognitive PGI has a larger direct effect than the non-cognitive PGI, the indirect effect of the cognitive and non-cognitive PGI is similar for all eight outcomes. We also tested differences between boys and girls, and there was little to no systematic variation across sexes.

Standardised test scores predicted by cognitive and non-cognitive PGIs in two generations

Figure 1: Regression results for English, Math and Reading (top to bottom) tested in grade 5, 8 and 9 (left to right). Each panel contains in blue the estimate from model 1, which contains only the child PGI. Each panel contains in orange the estimates from model 2, which contains 6 PGIs: namely 3 cognitive PGIs (dots: the child's, the father's and the mother's) and 3 non-cognitive PGIs (triangles: the child's, the father's, and the mother's). All models include the covariates PC1-10, batch ID, sex, and cohort.

In model three, we exploit the presence of siblings in the parental generation in MoBa to control

for fixed family effects. Figure 2 shows estimates for all eight outcomes from models estimated on the sibling sample. For many but not all outcomes, the indirect between parental-sibling-pair PGI is significantly related to the child outcome (grey), but in no instance is the indirect within parental-sibling-pair PGI related to the child outcome (green). For reference, estimates from the model which omit all but the child PGI are included in blue.

Standardised test scores predicted by cognitive and non-cognitive PGIs in 'three' generations

Figure 2. Regression results for English, Math and Reading (top to bottom) tested in grade 5, 8 and 9 (left to right). Each panel contains (omitting technical covariates) the estimates from model 3: in

blue for cognitive and noncognitive PGIs for the child, in orange the parent without a sibling in the data, in gray the (between) sibship average, and in green the within-sibship deviation.

In a final, fourth, model, we increase our statistical power by pooling test scores over three grades and three subjects and estimate a mixed model with a person-specific random effect. The results for this model are shown in Figure 3, and are consistent with the pattern shown in Figure 2. In predicting children's pooled test scores, we observe a substantial effect of the child's cognitive PGI ($\beta = 0.203$, $se = 0.021$) and a modest effect of the child's non-cognitive PGI ($\beta = 0.080$, $se = 0.022$). The between parental-sibling-pair PGIs were significant for the cognitive PGI ($\beta = 0.075$, $se = 0.021$) but not for the non-cognitive PGI ($\beta = 0.035$, $se = 0.020$). Crucially, neither the effect of the within parental-sibling-pair cognitive ($\beta = -0.002$, $se = 0.031$) nor non-cognitive ($\beta = 0.031$, $se = 0.033$) PGI were significant.

Standardised test scores predicted by cognitive and non-cognitive PGIs in 'three' generations

Figure 3. Regression results for a model for all tests combined, with a child-specific random effect. Regression coefficients in blue for cognitive and noncognitive PGIs for the child, in orange the parent without a sibling in the data, in gray the between-sibships average, and in green the within-sibship deviation.

Spouses correlated weakly on their cognitive and non-cognitive PGIs (all rho's < 0.06, Supplemental table D). These correlations were not significantly higher than the correlations between siblings-in-law. On their observed educational attainment, spouses correlated

moderately ($\rho = 0.412$, $p < 0.0001$), while siblings-in-law correlated substantially less ($\rho = 0.272$, $p < 0.0001$).

Discussion

The discovery of specific genetic variants associated with educational attainment has given researchers a new tool for investigating the intergenerational transmission of education. In particular, the observation of indirect genetic effects, whereby the parental genotype is associated with offspring outcomes beyond the child genotype, compellingly illustrates the role of the environment in intergenerational transmission. In order to elucidate the environmental processes driving the indirect genetic effect, we used a unique extended pedigree dataset with genotyped relatives from multiple generations. In contrast to the processes implied by the phrase “genetic nurture,” our results are inconsistent with the conclusion that the indirect genetic effect is driven by environmental mechanisms happening within the nuclear family, such as parental behaviors or investments. Parents’ own genes were not specifically related to their offspring’s test scores; rather, the genes shared by a parental sibling pair, which are a proxy for the grandparental genotype and for the environmental factors shared by an extended family, were what was associated with offspring test scores, above and beyond the child’s own genes.

The indirect genetic effects we observe in this study for childhood educational achievement are lower than those observed for adulthood educational attainment.¹² Our findings are consistent with previous analysis of exam or test performance in MoBa²² and a Dutch³³ but not a UK cohort²⁰. Interpreting differences in the contribution of indirect effects estimated based on PGI between outcomes is complicated by certain “known unknowns”: the GWAS that supplies the effect size estimates for the PGI contains an unknown mix of direct and indirect effect signals. Given the PGI are an unknown mix of indirect and direct effects, the expected direct and indirect estimates depend on the true correlation between the direct and indirect effects and the relative size of the total direct and indirect genetic contributions^{34,35}.

Our results are consistent with subtle socioeconomic and ancestral stratification co-occurring within homogeneous populations^{28,29}, as well as with the characterisation of the observed indirect effect as a “dynastic effect”⁴ where the parental PGI is correlated to offspring socioeconomic position early in life (likely closely matched with the offspring’s uncles and aunts’

SES) and gives rise to the indirect effect on offspring's test scores. The results are further consistent with large grandparental effects. However, the presence of strong grandparental effects in the absence of parental effects is considered unlikely^{36,37}. Reflection on the mediators and mechanisms that give rise to the indirect genetic effects remains speculative. We can conclude that for childhood test scores, in the context of Norwegian social policies, the mechanisms that give rise to indirect genetic effects appear to play out outside the nuclear family.

In order to assess the role of active assortative mating over passive social homogamy, we correlated parents' PGIs, which is a result of active choice, and compared them to correlations of one parent and her partner's sibling, which would be to a lesser degree affected by choice. Both for cognitive and non-cognitive skills PGIs, correlations are significantly different from zero. For both cog and non-cog PGI the correlations between partners are higher than between sibling-in-laws, but not significantly so. The phenotypic correlation between the educational attainment of spouses is (far) higher than the correlation between siblings-in-law, suggesting a form of active mate selection. The result seems inconsistent with a model where assortment merely reflects selection on parental/family SES or intergenerational wealth. Assortative mating is a candidate explanation for the observed indirect genetic effect of parental PGI on childhood outcomes above the childhood PGI. This is because, under assortative mating, the PGI of a parent's untransmitted alleles (indirect effect) is not independent but correlated with the PGI of the other parent's transmitted alleles (direct effect), and so the indirect effect correlates with the effect of the alleles that the child inherited, even in the absence of environmental effects.

Substantial standard errors of the key estimate of interest (the within-family indirect genetic effect) limit how certain we can be of our conclusions. Replicating our results in a larger sample (likely a future freeze of MoBa or the HUNT study³⁸), especially the within parental-sibling-pair effect, should be a primary concern. Replication should be closely followed by generalization to outcomes related to educational attainment, such as college enrolment or completion, or years of education, as those are understood to be more strongly influenced by the familial and socioeconomic environment shared between family members than are childhood test scores³³. Any further generalization should concern generalization beyond Norway, which has relatively low income inequality, a high quality tuition-free public education system, and a generous welfare state system. It would further be desirable to triangulate our result across alternate

designs that rely on, for example, adoption in the parental generation or observed grandparental genotypes.

A definitive future PGI study of the nature of the indirect genetic effect, that accounts for the aforementioned, could be designed as follows: As a basis for the PGI for education or cognition it would rely on a GWAS within siblings. This would ensure the PGI itself is a reflection of direct genetic effects alone. It would have to be larger in sample size to shrink standard errors and to compensate for the power loss incurred when computing PGI based on (far smaller) within-sibling or family GWAS. Ideally, the study would consider a larger cross section of outcomes (both attainment and test performance) and it would be performed across multiple countries, generations and educational environments to ensure the effects generalize. While these conditions cannot be met using current PGI and data, they could be in the foreseeable future.

It's important to emphasize that our results in no way imply parenting, a nurturing family environment, or, for example, advocating for a child in the educational environment, do not affect school performance. Our results merely shed light on the mechanism behind the widely observed indirect effect of parental education related PGI on offspring education outcomes^{10,12,18–20}. Any effects of parenting which are not related to the parental cognitive or non-cognitive skill PGI are not detected in studies of the indirect genetic effect. By narrowly focusing on parental PGI for cognitive and non-cognitive traits, we omit various important parental influences. Parental life events like divorce³⁹ and maternal job loss⁴⁰ relate to lower educational outcomes in children, effects which the current PGI would likely not detect. Finally, any parental influences on a child that arise from childhood experiences shared between parents and their siblings, and are correlated to the PGI of the grandparents, would result in a significant between-sibling PGI effect we observe. So while our analysis can speak to the widely studied effect of parental cognitive and noncognitive PGI on childhood education, and is well designed to avoid genetic confounding, it by no means represents a comprehensive evaluation of parental influences on educational outcomes.

There are various strategies conceivable to leverage genetic data to study parenting without relying on education-related PGI. An immediately obvious follow-up would be to repeat the current analysis at the level of individual variants by performing a GWAS of parental effects on childhood outcomes, while using the parental sibling structure to control for confounding (i.e., a

within-sibling GWAS). The primary constraint on future analyses are the type of data needed (either genotyped family members in 3 generations, or genotyped family members in 2 generations with known sibling relations) and the sample size requirements, which will likely exceed those for ordinary GWASs on unrelated individuals. Finally, better social science genetics requires a tighter integration between social scientific (register) data and genetic data. For now, (end strong with the conclusion from the abstract or a variant thereof).

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