What About The Children?

Patrons: Sir Michael Morpurgo, Rebecca Abrams, Sir John Timpson, Dame Sarah Storey

'Raising awareness of the never-changing emotional needs of the under-threes in our ever-changing society'

Registered Address: Feldon House, Chapel Lane, Newbold on Stour, CV37 8TY.
Email: enquiries@whataboutthechildren.org.uk or research@whataboutthechildren.org.uk

RESEARCH SUMMARY

Towards a deeper understanding of nature and nurture: combining family-based quasi-experimental methods with genomic data. Tom A. McAdams, Rosa Cheesman, and Yasmin I. Ahmadzadeh (2023). *Journal of Child Psychology and Psychiatry* 64(4), 693–707. DOI: 10.1111/jcpp.13720

The 'nature versus nurture' debate is a long-standing one. The question of how much an individual's characteristics are 'pre-wired' – that is, determined from inheritance – and how much they are acquired from the environment in which that individual grew up – goes back long before the discovery of genetics, to the sixteenth century or even earlier. It is a very complex one with no simple answers. One of the main reasons why it is so difficult to disentangle nature from nurture is that most children are reared by their parents, who are of course close blood relatives. In psychiatry, for example, it has often been observed that parental mental health difficulties predict similar problems in their offspring; but those offspring will both share genetic predictors of mental ill-health and grow up in an environment that is directly affected by those same psychological difficulties. We cannot find out the effect of parental behaviour on child development without taking into account the genetic background that parents and children share.

For decades, researchers have used family-based study designs in which the interaction between genetics and environment is controlled for without necessarily knowing its extent. These are examples of what are known as 'quasi-experimental methods' because they share some aspects of 'gold standard' randomised controlled trials, but, for ethical reasons, lack any form of randomisation.

In recent years, these studies have been enhanced by the availability of genomic data. More and more individuals have full or partial genomes – that is, sequences of the DNA that makes up their genes – deposited in databases and freely available to interested researchers. Where such data is available, it can provide researchers with new tools to explore nature-nurture associations in depth through combining it with quasi-experimental family studies. In this in-depth review, Tom McAdams, Rosa Cheesman and Yasmin Ahmadzadeh from King's College London and the PROMENTA Research Centre at the University of Oslo in Norway describe how genomic data has been used with family-based quasi-experimental methods, what further insights can be gained and what problems still remain. They note that genotype-phenotype associations at the family level can be biased by a more

general genetic similarity between the groups from which people are likely to draw their partners (and thus the co-parents of their children) and by the indirect effects of parental genotype on child behaviour, known as genetic nurture. As an example of this, children of hostile parents may behave badly not because they have inherited the genetic mixture that gave rise to the hostility, but as a response to their hostile environment.

McAdams and his co-workers select three of the most popular types of family-based study – sibling comparisons, studies of adoptive families and of parent-child pairs in extended families – and describe how these have been recently used, firstly without and then including genome-wide data. Their focus is largely, but not exclusively, on mental health.

Sibling studies

Full siblings, including fraternal but not identical twins, share half their genetic material with each other and with their parents; identical twins, of course, share all their DNA. Most are also reared together in a similar if not identical environment. There is no direct relationship between genetic differences arising from the random assignation of alleles at conception and changes to the family environment over time.

One interesting example of how genomic information can provide insights into parent-child interactions that conventional sibling studies cannot is found in studies of parental feeding behaviour and child body mass index (BMI). It is known that parents react to fatter children differently during feeding. Now, studies of fraternal twins with different body shape and known genotypes have shown that these children differ also in their polygenetic risk scores for high BMI. Therefore, the fatter twins will have been genetically predisposed to put on weight; the differences in BMI cannot have been caused by differences in the way they were fed. It has also been shown that differences between siblings in IQ and education level depend more on their environment than differences in many other variables: not only height, which might be expected, but symptoms of ADHD and schizophrenia.

Genome-wide association studies (GWAS) examine genetic variants in a large group of people to see which are associated with a disease or trait. A sibling-comparison GWAS therefore needs large numbers of sibling pairs. These are still rare, but becoming less so as biobanks, which can serendipitously contain data from sibling groups are established and grow. One recent study showed some cognitive and behavioural traits to be less directly heritable between siblings than would have been expected, suggesting a strong environmental influence.

Adoption studies

Studies of children brought up by unrelated adoptive parents provide another way of disentangling genetic and environmental influences. The level and nature of these influences depend, of course, on the child's age at adoption, and with the inclusion of children conceived through gamete or embryo donation – who could perhaps be

thought of as ‘adopted at conception’ – the effects of the pre-natal environment can be disentangled from genetic ones. Before the inclusion of genetic data, adoption studies had shown that maternal depression is associated with emotional and behavioural problems in children, and *vice versa*, even when there is no genetic link between the two.

Similar studies that include DNA sequence data from adoptive parents and children have now found associations between the adoptive parents’ genetic predisposition for (for example) depression with the children’s mental health, showing that indirect genetic effects can exist in families even where there is no biological relationship. They can also suggest which traits – educational attainment, for example, rather than body mass index – depend most on the environment in which children are raised, including the genetic predispositions of the caregivers. Some caveats remain, however, as children adopted after birth will retain some genetic nurture effects through the pre- and early post-natal environment provided by their birth mothers, and more particularly in children adopted by grandparents or more distant relatives. Furthermore, it is difficult to generalise from adoptive parents to the wider society as these people share some characteristics: they are, in general, wealthier and more educated than average citizens, and psychologically stable. In contrast, children who are adopted are likely to be, or to have been, at greater risk of psychological distress. These caveats may become less important as the size of biobanks and the number of adoptive parent/child pairs with accessible DNA data both increase, enabling subtler associations between the genetic predispositions and the outcomes of adoptive – and therefore non-related – parents and children to be revealed.

Intergenerational studies

Studying parent-child relationships in extended families is useful because families include individuals with different degrees of relatedness: identical twins (100% of DNA in common), other siblings (50%), first cousins (25%) and others. Even without genetic data, these were used to estimate the degree to which specific traits in parents could predict the presence of those traits in their children. This has shown, for example, that a propensity for ADHD is much more genetically heritable than one for anxiety. It is possible to extend these studies to include family members with no direct blood relationship, such as spouses and in-laws, and therefore to distinguish between indirect and direct genetic effects.

The difficulty of finding sufficient numbers of families with the required relationships is still more significant if the study design requires extended family groups. A more practicable alternative to trawling genetic databases for extended family members is collecting and sequencing DNA by request from families already recruited into a study, and it is likely that many such volunteers – including related parent/child pairs – will be willing to take part. Data obtained from parent/child pairs has already been used to study direct and indirect genetic links with childhood anxiety and depression, and associations between the parents’ genetics and their children’s behaviour. Interestingly, they have found that in some cases that part of the parental polygenetic risk score that is not in the 50% of the DNA passed on to a child can contribute to a prediction of that child’s characteristics. This is undisputedly an indirect genetic effect. Although most studies of this type have highlighted the

importance of direct genetic effects, studies of intellectual attainment have shown an indirect link from parental genotype through parenting behaviour to child outcomes. There is much less evidence for this in other traits including ADHD risk and high body mass index. The authors suggest that there is much still to learn by including genomic information in studies of multigenerational families, particularly regarding the causes of child mental ill-health.

McAdams and his colleagues conclude their extensive review with a discussion of the many uses of these and similar techniques, what can be learned from them and how they might develop in the future. They also explore its various limitations, pointing out that all estimates of genetic effects are prone to bias. Research has shown that people are statistically more likely to choose life partners who are similar to them and who will therefore share more DNA variants than individuals taken at random. Furthermore, genomic databases mainly contain data from high-status individuals in 'Western, educated, industrialised, rich and democratic' – or, memorably, WEIRD – countries, and they are thus fairly homogeneous. Much more data is needed to capture the full genetic diversity of humankind: the published studies may also be difficult to generalise to cultures a long way from Western ones. Including data from more disadvantaged families, and not only from those who volunteer for trials, may also increase the clinical utility of these studies.

The researchers also discuss how genomic data is used in family study designs other than those presented in the main text. These include the 'classical twin study' design, which compares pairs of identical and fraternal twins. In this, the genetic component of a particular trait will correlate with the extent to which identical twins are more similar than fraternal ones. There are also studies that include stepfamilies, and children reared apart from their parents and siblings. Both these study types will yield more information once genetic data is available for more examples of each class, perhaps particularly when this covers three (or more) generations of the same families. Some data gaps can be filled by specific, family-based genetic databases, but these are logistically difficult and expensive to create.

McAdams and his colleagues sum up their wide-ranging and detailed review by commenting that genetic data can add an enormous amount to any study of human populations, not only the quasi-experimental approaches to the nature-nurture debate that they discuss. The combined methods can already help probe the root causes of mental distress between generations, and their contribution will only grow as more genomic data becomes available. And this, in turn, should make an important contribution to the emotional well-being of our youngest children.

Dr Clare Sansom