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Genetic influences on the development of childhood psychiatric disorders

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Abstract

This review covers the key types of genetic research design, the methodology involved and emerging, and established findings in relation to child and adolescent psychiatry. Traditional family, twin, and adoption studies show that child and adolescent psychiatric disorders are familial and genetically influenced. Genes and environment contribute to all disorders. Genetic factors seem especially important for autism and attention deficit hyperactivity disorder. Twin and adoption study designs are now being used to examine gene–environment interplay, the effects of environmental risk factors, co-morbidity, phenotype definition, and developmental change. Molecular genetic strategies are increasingly being adopted to identify gene variants that increase risk of specific disorders. The ways in which specific gene variants exert risk effects at cellular and biological system levels are proving to be highly complex. There is also interest in examining the brain mechanisms that may be involved in risk pathways that link gene variant to psychopathology. Finally, molecular genetic studies also highlight the importance of gene–environment interplay, which seems to be especially important in depression and antisocial behaviour.

Keywords

adolescent psychiatry; child psychiatry; family studies; gene–environment interaction; gene–environment interplay; genetics; molecular genetics; twin studies

Introduction

There have been enormous advances in genetics research over the past few decades. Findings from traditional and newer studies are informing us about the aetiology, development, and course of psychiatric disorders in childhood and adolescence. First, there are traditional genetic epidemiological designs, in which the genetic contribution to disorder is inferred. These designs are based on studying relatives who differ in their degree of genetic relatedness, and include family, twin, and adoption studies. Second, molecular genetic studies of child psychiatric disorders are being used to identify specific susceptibility genes in the laboratory, test how they work at a molecular and clinical level, and examine their phenotypic effects.

Family, twin, and adoption studies

Table 1 shows the key methodological features of family, twin, and adoption studies that have been described in detail elsewhere.¹

Family studies

Family studies involve investigating whether there are increased rates of a given disorder in relatives of affected probands compared with rates in a control group. Some family studies examine the risk in relatives of affected children; others examine the offspring of affected parents. All child psychiatric disorders show familial transmission, and this can arise through both genetic influences and environmental factors that impact on all family members in such a way as to make them more similar for that condition. This type of environment is known as a shared environment. Familial risk is expressed as an odds ratio or relative risk. The familial risk estimates vary considerably for different disorders, with odds ratios of around 2–4 for child and adolescent depression, 5 for attention deficit hyperactivity disorder (ADHD) and over 50 for autism. As family studies cannot distinguish genetic and shared environmental influences, twin and adoption designs are needed to separate these effects.

Twin studies

Twins include monozygotic (MZ) and dizygotic (DZ) twin pairs. MZ twin pairs are genetically identical, whereas DZ twin pairs, like full biological siblings, share on average 50% of their genes (see Table 1). For genetically influenced traits, MZ twin pairs show greater similarity (indexed by higher correlation coefficients or probandwise concordance rates) than DZ twin pairs. Twin studies can be used to estimate the proportion of population variation in a given phenotype (e.g. depression) attributable to genetic influences (heritability, h^2) and shared (c^2) and non-shared environmental influences (e^2). Twin studies have shown that child psychiatric disorders and symptoms are influenced by both genes and environment. The exact heritability estimate is not important as this will be specific to the population being studied, and will also vary as different studies use different measures and raters. In general, heritability estimates are highest for autism (90%) and ADHD (80–90%), and generally lower for depression, anxiety, and antisocial behaviour (usually less than 50%).

Twin studies are also used to answer more interesting questions than simply whether or not a disorder is heritable. They are being used to examine the following:

- co-morbidity
- developmental change
- phenotype definition
- gender effects
- gene–environment interplay
- whether environmental factors have risk effects on child psychopathology.

Gene–environment interplay and the risk effects of environmental factors are considered below. Examples of other types of twin study findings in child psychiatry are provided in Table 2.

Adoption studies

Adoption studies involve examining the degree of similarity between genetically related individuals compared with individuals who are related by virtue of adoption (Table 1). A genetic contribution to disorder is inferred when individuals are more similar to their biological relatives than to their adoptive relatives. This type of study design is also useful for testing the contribution of environmental factors, including the family context. There are three types of adoption design.

- Examining the biological offspring of parents with a disorder. Such studies have shown increased rates of schizophrenia in adopted-away offspring of mothers with schizophrenia.
- Examining rates of disorder in the adoptive and biological relatives of affected adoptees. Such studies show genetic contributions to ADHD and antisocial behaviour.
- Cross-fostering design where children at high genetic risk adopted into families at low environmental risk families are compared with children at low genetic/high environmental risk and those at high genetic/high environmental risk. Such designs have shown that high genetic risk makes a greater contribution to antisocial behaviour and childhood IQ in the context of environmental risk (gene–environment interaction; see later).

Gene–environment interplay

Genes can also influence traits and disorders indirectly by working together with environmental factors. Such effects may be subsumed within the heritability estimate in traditional twin studies.

Gene–environment interaction

This phenomenon is where genetic susceptibility has only risk effects, or where risk effects are greatly increased, in the presence of environmental risk.^{2,3} Genetic susceptibility can be (a) inferred, as in twin or adoption study designs, or (b) indexed by a specific variant in a gene. Twin study designs have shown evidence of gene–environment interaction for childhood psychopathology.

- Life events and adolescent depression – risk effects are increased in those at increased genetic risk of depression.⁴
- Physical maltreatment and conduct problems – risk effects are increased in those at higher genetic risk.⁵

Molecular genetic studies also show the contribution of gene–environment interaction.⁶ Examples of gene–environment interaction findings in psychiatry include the following. All of these gene variants are functional; that is, they alter activity of the enzymes monoamine oxidase A (MAOA) and catechol-*O*-methyltransferase (COMT), and the serotonin transporter.

- *MAOA* gene variant linked to antisocial behaviour in the presence of childhood maltreatment – finding replicated and shown in meta-analysis.^{7,8}
- *5HTT* (serotonin transporter) gene variant linked to depression in the presence of adverse life events⁷ – findings replicated, but mixed.⁹ Not yet shown in meta-analysis.
- *COMT* gene variant linked to schizophrenia in the presence of heavy cannabis use in adolescence (but not later).¹⁰ Finding not yet replicated completely.

Gene–environment correlation

The presence and severity of many important environmental risk factors for child psychiatric disorders, such as family conflict and life events, can be related to an individual's genetic make-up. This phenomenon of gene–environment correlation, in which genetic and environmental risk factors co-occur in a non-random fashion, gives rise to several important issues.

- Genetic and environmental risks are not distinct or mutually exclusive.
- Genes may influence psychiatric disorder by increasing the risk of exposure to environmental adversity (or by reducing exposure to protective factors).
- Environmental risk factors may be associated with disorder but may not have true 'environmentally mediated' effects because the association has arisen through genetic factors that influence both the environmental predictor and the outcome (Figure 1). Genetically sensitive designs (e.g. twin studies) are a useful epidemiological tool for testing whether environmental risk factors have environmentally mediated effects on psychopathology.

Testing the effects of environmental risk factors using genetic designs

By using genetically sensitive designs that include genetic pathways (see Figure 1), it becomes possible to test whether the link between a specific environmental risk factor and psychiatric disorder is attributable to a true environmentally mediated risk effect.¹¹ Below are some examples of findings in child and adolescent psychiatry.

- Dependent life events and adolescent depression – twin studies show the presence of gene–environment correlation (genetic pathways) and environmentally mediated risk effects.^{12,13}
- Negative parenting and antisocial behaviour – adoption studies show gene–environment correlation; some environmentally mediated risk effects.^{14,15}
- Maltreatment and antisocial behaviour – twin studies show environmentally mediated risk effects.¹⁶
- Exposure to maternal smoking in pregnancy and antisocial behaviour in offspring – a study based on children who were genetically related and unrelated to women who became pregnant by virtue of assisted reproductive technologies¹⁷ and a study of siblings showed gene–environment correlation and no environmentally mediated risk effects¹⁸ (Rice *et al.*, unpublished results).

Molecular genetics

Gene and chromosome structure

In the past few years, genetics research has moved from identifying causal genes for single gene disorders to identifying genetic risk factors for complex disorders such as psychiatric disorders, cardiovascular disease, and diabetes, which represent a great part of the global burden of disease. However, no matter what the disease or disorder studied, the same principles apply. The information that is inherited from one generation to the next is contained in DNA and, more specifically, in the sequence of its building blocks, the nucleotides. There are four types of nucleotide: guanine (G), cytosine (C), adenine (A), and thymine (T). The most important unit of information is the gene, which encodes, in its sequence of nucleotides, the instructions necessary for protein synthesis. Genes account for less than 30% of total human DNA. The rest of the genome consists of non-coding sequences, which were thought to be 'junk' DNA. However, there is now evidence that these sequences can influence the coding sequences and thus have a regulatory effect on gene expression.

All DNA sequences are organized in chromosomes. Each human cell (apart from gametes) contains 22 pairs of autosomes and one pair of sex chromosomes (XX for females and XY for males). Autosomes are given a number from 1 to 22 according to their size, with 1 being the largest. All chromosomes consist of two arms, a short arm (p) and a long arm (q), connected in the middle by the centromere. This nomenclature facilitates the description of

the physical location of genes. For example, the gene coding for tyrosine hydroxylase, which is the rate-limiting enzyme in the synthesis of catecholamines, is located on chromosome 11p15.5. As everyone has two pairs of all chromosomes (apart from sex chromosomes in males), they have two copies of each gene. These two copies are not necessarily exactly the same, and are known collectively as alleles.

For some disorders, called single gene disorders, Mendel's laws of inheritance can be easily seen to be followed because only one gene is responsible for them. One example is tuberose sclerosis, an autosomal recessive disorder that can be associated with autism; another is fragile X syndrome, which is X-linked. Psychiatric disorders are categorized as complex disorders; this means that, although they follow Mendel's laws, they are the result of multiple gene co-action, gene–gene and gene–environment interactions.

Pathological conditions can also result from chromosomal anomalies. These include differences in chromosome number (aneuploidy; e.g. trisomy 21, Down's syndrome), chromosomal losses (deletions), chromosomal gains (insertions), and chromosomal inversions. These anomalies can be visible microscopically or submicroscopic; for example, a chromosome 22q11 microdeletion that results in velocardiofacial syndrome is associated with an increased rate of psychosis. More recently there has been much interest in submicroscopic (up to 1 kb) chromosomal anomalies that are not always pathogenic and are known as copy number variants (CNVs). Although CNVs are challenging to study at the moment, they could have an important role in psychiatric disorders.

Another factor to be taken into account is that gene expression is regulated by non-coding sequences and other genes, as well as by inherited genetic factors. This is well demonstrated by the influence of epigenetic effects, which are basically changes in gene expression resulting from changes in the chromatin structure and not in the DNA sequence. The most important epigenetic phenomenon is imprinting, which results in selective silencing of only one allele depending on parental origin. In humans, the region on chromosome 15q12 carries a cluster of imprinted genes. Loss of the paternal chromosome causes Prader–Willi syndrome, whereas loss of the maternal chromosome causes Angelman syndrome, with very different effects.¹⁹ For more information about the basic genetics of psychiatric disorders, see Thapar and Rutter²⁰ and Skuse and Seigel.²¹

Identifying complex disorder susceptibility genes

This process has been based on the variation that normally exists in the DNA of different individuals without necessarily being pathogenic. This variation provides genetic markers.

Types of marker used in molecular genetics: a number of studies have used markers called restriction fragment length polymorphisms (RFLPs). The method involves digesting the DNA with enzymes that cut in specific positions and finding differences in the length of the resulting fragments. RFLPs were replaced by microsatellites, which are basically repeated DNA sequences that differ in size in different individuals. Single nucleotide polymorphisms (SNPs) are differences among individuals at the level of a nucleotide. The use of SNPs has revolutionized the field because there are large numbers of this type of marker covering a substantial part of the genome, and their genotyping is cheaper and more robust than with other markers. Advances in technology have made mass genotyping of large numbers of SNPs for very big samples possible and more economical. Information (which is still growing) about a large number of SNPs can be found in a public database called HapMap. There are three methods for identifying susceptibility genes for psychiatric disorders:

- whole genome linkage studies

- candidate gene association studies
- whole genome association studies (WGA).

Whole genome linkage studies are based on families with multiple affected individuals, mainly affected sibling pairs, and aim to identify broad regions in the genome that could harbour susceptibility genes. The principle is that, if an allele of a marker is linked to a susceptibility locus, affected relatives will share more of this allele than expected. Linkage studies have been applied in ADHD and autism. In brief, fine mapping of linkage results has not been able to identify susceptibility genes, probably because linkage studies are better at picking up regions that harbour genes of larger effect and not genes of small effects, which are very important in psychiatry.

Candidate gene association studies are based on selecting specific genes based on evidence from other studies and then testing marker alleles in two different groups: one group of affected individuals (cases) and one group of matched healthy individuals (controls). There are two types of candidate gene.

- Positional – where the genes are selected following significant findings from linkage studies or by studying families who present with a disorder and a specific chromosomal rearrangement. One example of such an approach led to the identification of a susceptibility gene for schizophrenia, *DISC*, in a family presenting with schizophrenia and bipolar disorder, and a translocation on chromosome 1.22
- Functional – when selection is based on assumptions about the pathophysiology of the disorder derived from animal, pharmacological, or imaging studies.

These studies have not been very successful in complex disorders, possibly because the assumptions about the pathogenesis were not correct. One notable exception is ADHD; evidence from animal, imaging, and pharmacological studies has pointed to the involvement of dopaminergic pathways in ADHD. Study of a variable number tandem repeat (VNTR) polymorphism in the dopamine D4 receptor gene provided significant evidence that the seven-repeat unit allele is associated with ADHD. This result has been replicated independently in meta-analyses and pooled analyses,^{23,24} as have findings of association with a dopamine D5 receptor gene marker.

Whole genome association studies are now the most promising method for systematically searching for susceptibility genes. They involve testing several hundreds of thousands of SNPs across the genome without an *a priori* hypothesis, and it is believed that they will also be able to pick up genes of small effect. A major limitation is that they require extremely large sample sizes to overcome the problem of multiple testing and to avoid false-positive results that are simply associated by chance. A whole genome association study for autism has revealed that changes in the number of copies of a gene or locus (i.e. deletions or duplications) can be an important part of the aetiology. Copy number variation in chromosomal region 16p11.2 has been found to be responsible for approximately 1.5% of cases of autism.²⁵ Whole genome association studies are under way for ADHD as well, and have been published for bipolar disorder and schizophrenia in adults.

Gene–phenotype links: psychiatric disorders are complex disorders, and this means that there can be different risk factors operating through different mechanisms but having very similar clinical manifestations, or that the same risk factor can have different effects. For this reason, there has been interest in examining the following.

- Intermediate phenotypes – for example, identifying susceptibility genes that influence cognitive function.

- Imaging genomics – to examine the relationship between genes, brain function, structure, and disorder.
- Phenotype variation – that genes can have a modifying phenotypic effect without necessarily increasing risk of the disorder itself is shown by the association between a *COMT* gene variant and conduct disorder symptoms in ADHD. A polymorphism that encodes a valine (val) to methionine (met) amino acid change has been studied in four independent samples. Possession of the val allele was found to be associated with conduct disorder symptoms in ADHD in three samples and a pooled analysis.²⁶

Clinical implications

We have reviewed key aspects of genetics research in relation to child and adolescent psychiatry, and highlighted important findings. What impact might this research have in terms of clinical practice?

- Prediction. Family studies provide global but not personalized risk estimates. Identified gene variants thus far are of small effect size and thus not useful in prediction.
- Treatment and prevention. Identifying genetic risk factors and aetiological mechanisms can inform new drug targets and interventions. Pharmacogenomics may be helpful in the future for individual tailoring of medications.
- Understanding the origins and course of psychiatric disorder. Both genes and environment work together in complex ways. It is not helpful to consider a condition as genetic or environmental.
- Environmental intervention can alter the clinical course or be used to treat conditions, even where there is a strong genetic aetiology.
- Patient education. The clinician has a role in interpreting new published findings and understanding complex disease genetics.
- Risk reduction interventions. Identifying environmental protective factors that modify genetic risk may be helpful in the future.
- Genetics may help in understanding diagnostic boundaries and overlap, such as the distinction between hyperkinetic disorder and hyperkinetic conduct disorder.

Conclusion

Genetics is an important and rapidly moving area of neuroscience. Modern molecular genetic approaches and traditional designs are highlighting that genes and environment work closely together and that the biological underpinnings of psychiatric disorder are complex. Child and adolescent psychiatrists and trainees need to keep abreast of these findings.

REFERENCES

1. Thapar, A.; McGuffin, P. Quantitative genetics. In: Gelder, M., editor. New Oxford textbook of Psychiatry. Oxford University Press; Oxford: 2008.
2. Moffitt TE, Caspi A, Rutter M. Strategy for investigating interactions between measured genes and measured environments. *Arch Gen Psychiatry*. 2005; 62:473–81. [PubMed: 15867100]
3. Thapar A, Harold G, Rice F, Langley K, O'Donovan M. The contribution of gene–environment interaction to psychopathology. *Dev Psychopathol*. 2007; 19:989–1004. [PubMed: 17931430]
4. Silberg J, Pickles A, Rutter M, et al. The influence of genetic factors and life stress on depression among adolescent girls. *Arch Gen Psychiatry*. 1999; 56:225–32. [PubMed: 10078499]

5. Jaffee SR, Caspi A, Moffitt TE, et al. Nature X nurture: genetic vulnerabilities interact with physical maltreatment to promote conduct problems. *Dev Psychopathol.* 2005; 17:67–84. [PubMed: 15971760]
6. Institute of Medicine. Report on genes, behavior, and the social environment: moving beyond the nature/nurture debate. National Academies Press; Washington, DC: 2006.
7. Caspi A, McClay J, Moffitt TE, et al. Role of genotype in the cycle of violence in maltreated children. *Science.* 2002; 297:851–54. [PubMed: 12161658]
8. Taylor A, Kim-Cohen J. Meta-analysis of gene–environment interactions in developmental psychopathology. *Dev Psychopathol.* 2007; 19:1029–37. [PubMed: 17931432]
9. Zammit S, Lewis G, Thapar A, et al. Phenotypic variation between parent–offspring trios and non-trios in genetic studies of schizophrenia. *J Psychiatr Res.* 2006; 40:622–26. [PubMed: 16038933]
10. Caspi A, Moffitt TE, Cannon M, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene $\times$ environment interaction. *Biol Psychiatry.* 2005; 57:1117–27. [PubMed: 15866551]
11. Academy of Medical Sciences. Identifying the environmental causes of disease: how should we decide what to believe and when to take action?. Academy of Medical Sciences; London: 2007.
12. Eaves L, Foley D, Silberg J. Has the ‘Equal Environments’ assumption been tested in twin studies? *Twin Res.* 2003; 6:486–89. [PubMed: 14965458]
13. Rice F, Harold G, Thapar A. Negative life events as an account of the age related differences in the aetiology of depression in childhood and adolescence. *J Child Psychol Psychiatry.* 2003; 44:977–87. [PubMed: 14531580]
14. Ge X, Conger RD, Cadoret RJ, et al. The developmental interface between nature and nurture: a mutual influence model of child antisocial behaviour and parent behaviors. *Dev Psychol.* 1996; 32:574–89.
15. O'Connor TG, Deater-Deckard K, Fulker D, Rutter M, Plomin R. Genotype–environment correlations in late childhood and early adolescence: antisocial behavioral problems and coercive parenting. *Dev Psychol.* 1998; 34:970–81. [PubMed: 9779743]
16. Jaffee SR, Caspi A, Moffitt TE, Taylor A. Physical maltreatment victim to antisocial child: evidence of an environmentally mediated process. *J Abnorm Psychol.* 2004; 113:44–55. [PubMed: 14992656]
17. Thapar A, Harold G, Rice F, et al. Do intrauterine or genetic influences explain the foetal origins of chronic disease? A novel experimental method for disentangling effects. *BMC Med Res Methodol.* 2007; 22:7–25.
18. D'onofrio B, Van Hulle CA, Waldman ID, et al. Smoking during pregnancy and offspring externalizing problems: an exploration of genetic and environmental confounds. *Dev Psychopathol.* 2008; 20:139–64. [PubMed: 18211732]
19. Davies W, Isles AR, Wilkinson LS. Imprinted gene expression in the brain. *Neurosci Biobehav Rev.* 2005; 29:421–30. [PubMed: 15820547]
20. Thapar, A.; Rutter, M. Genetics. In: Rutter, M.; Bishop, D.; Pine, D.; Scott, S.; Stevenson, J.; Thapar, A., editors. *Rutter's textbook on child and adolescent psychiatry.* 5th edn. Blackwell; Oxford: 2008.
21. Skuse, D.; Seigel, A. Behavioral phenotypes and chromosomal disorders. In: Rutter, M.; Bishop, D.; Pine, D.; Scott, S.; Stevenson, J.; Thapar, A., editors. *Rutter's textbook on child and adolescent psychiatry.* 5th edn. Blackwell; Oxford: 2008.
22. Owen MJ, Craddock N, O'Donovan MC. Schizophrenia: genes at last? *Trends Genet.* 2005; 21:518–25. [PubMed: 16009449]
23. Faraone SV, Doyle AF, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *Am J Psychiatry.* 2001; 158:1052–57. [PubMed: 11431226]
24. Li D, Sham PC, Owen MJ, He L. Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Hum Mol Genet.* 2006; 15:2276–84. [PubMed: 16774975]

25. Weiss LA, Shen Y, Korn JM, et al. Association between microdeletion and microduplication at 16p11.2 and autism. *N Engl J Med*. 2008; 358:667–75. [PubMed: 18184952]
26. Caspi A, Langley K, Milne B, et al. A replicated molecular genetic basis for subtyping antisocial behavior in children with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*. 2008; 65:203–10. [PubMed: 18250258]

Figure 1. Testing for environmental mediation: genetic and environmental pathways linking an environmental risk factor and outcome

Table 1
Methodological features of family, twin, and adoption study designs

Study design	Methodological features of design
Family Studies	<p>Choice of control group important – using those with another psychiatric disorder provides a stricter test</p> <p>Familial risk calculation depends on estimated prevalence rate of disorder in population (e.g. higher prevalence estimates of autism in recent years, mean lower estimates of familial risk now)</p> <p>Ascertainment biases possible unless population-based sample (volunteer bias may inflate familial risk estimates)</p> <p>Adjustment needed for whether or not individuals have passed through age of risk</p>
Twin studies	<p>Comparability with singletons – twins at higher risk prenatally and perinatally, but no evidence that increased rates of psychiatric disorder</p> <p>Equal environment assumption – twin design assumes monozygotic and dizygotic twins share environment to same extent, but not necessarily the case; needs to be tested in the study</p> <p>Some monozygotic twins share a placenta (may lead to increased prenatal environmental sharing); others do not</p> <p>Monozygotic twins may not be completely genetically identical (non-inherited effects such as imprinting)</p>
Adoption studies	<p>Adoptions are less common than they used to be</p> <p>Low-risk adoptive families</p> <p>May be selective placements</p>

Table 2
Examples of twin-study findings in child and adolescent psychiatry

Co-morbidity

- Anxiety and depression have a shared genetic liability
- ADHD and conduct disorder have a shared genetic liability

Developmental change

- Symptoms of depression show increased heritability over time – probably due to increased gene–environment interplay in adolescence
- Early anxiety is linked to later depression through genetic factors and gene–environment interplay
- Early-onset persistent conduct disorder appears to be a more strongly genetically influenced form of conduct disorder

Phenotype boundaries and definitions

- Autism genetic liability extends to an increased risk of milder social and cognitive deficits
 - ADHD appears to lie on a continuous distribution
 - Conduct problems accompanied by ADHD appear to be more strongly heritable than other forms of conduct problem
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ADHD, attention deficit hyperactivity disorder.