

Trends and Issues in Crime and Criminal Justice No. 263**Is there a Genetic Susceptibility to Engage in Criminal Acts?**

By Katherine I. Morley and Wayne D. Hall

Appendix - Candidate genes for antisocial behaviours

Candidate genes are specific genes that contribute among many others to an increased risk of engaging in antisocial behaviour. They are usually selected on the basis of information about the neurobiological bases of behaviour and personality traits. Association studies examine whether one allele, or variant, of a candidate gene occurs more often in individuals who display antisocial behaviour than in some control comparison group. In case-control studies, researchers compare the frequencies of alleles in individuals who engage in antisocial behaviour and in unrelated, unaffected controls who have been matched on age, sex and ethnicity (Burmeister 1999). In family-based studies, such as the transmission disequilibrium test (TDT) and haplotype relative risk (HRR) method, researchers examine which alleles or combinations of genes (haplotypes) are transmitted from parents to affected offspring (Burmeister 1999).

Linkage analyses are used to identify chromosomal regions that may contain genes that influence a complex genetic trait, or to evaluate genes that may be involved in the aetiology of a disorder. These studies trace the inheritance of genetic markers in affected relatives to detect an association between an allele and the disorder (Lander & Schork 1994; Schork 1997). Linkage studies often do not have the power to detect the effects of individual genes that have a small effect on the risks of developing a complex disorder such as antisocial behaviour (Schork 1997).

As has been true in studies of many other personality traits, research on candidate genes for antisocial behaviour has primarily focused on genes that influence neurotransmitter metabolism and function. The main focus of research on antisocial behaviour has been on the serotonergic, dopaminergic and noradrenergic neurotransmitter pathways.

The serotonergic pathway

Serotonin is a neurotransmitter involved in the central and peripheral nervous system and the serotonergic pathway is involved in brain development and synaptic plasticity. It is believed to function as a behavioural inhibition system so any dysfunction in this system is thought to be increase aggressiveness and impulsivity, behaviours that have been correlated with low levels of either serotonin or a serotonin metabolite (Reif & Lesch 2003).

Tryptophan hydroxylase

Tryptophan hydroxylase (TPH1) is an enzyme that increases the conversion of the amino acid tryptophan to serotonin. In a study of individuals with personality disorder, New et al. (1998) found that the “LL” TPH1 genotype was associated with higher levels of impulsive aggression. Manuck et al. (1999) produced conflicting results using a sample of volunteers from the general population. These authors found an association between the U allele of the TPH1 polymorphism and aggressive personality traits. However, a subsequent study examining a population of individuals who had engaged in deliberate self-harm found a weak association between the L allele and impulsiveness in male patients (Evans et al. 2000). A study using a patient-based population identified an association between the 218C allele of a different TPH1 polymorphism and impulsive behavioural tendencies (Staner et al. 2002). A study of TPH1 and ADHD found no association between the two (Tang et al. 2001).

Serotonin receptors

Serotonin interacts with a number of different receptors, a few of which have been investigated in relation to traits predictive of antisocial behaviour. Evans et al. (2000) identified an association between the serotonin receptor 2C gene (HTR2C) and impulsivity in males. Other work on the serotonin receptors has focused on ADHD. Quist et al. (2000) found that the 452Tyr allele of the serotonin receptor 2A gene (HTR2A) is associated with ADHD, but research by Hawi et al. (2002) has suggested that it is the 452His allele that predicts susceptibility to ADHD. One variant of the serotonin receptor 1B gene (HTR1B) has also been associated with ADHD (Hawi et al. 2002).

Serotonin transporter

Solute carrier family 6, member 4 (SLC6A4), otherwise known as the serotonin transporter, increases the reuptake of serotonin, which leads to the termination of its action (Reif & Lesch 2003). A number of studies have identified an association between a particular variant of this gene and ADHD. Manor et al. (2001) first identified this association, which has subsequently been confirmed by a number of additional studies (Kent et al. 2002; Retz et al. 2002; Zoroglu et al. 2002).

The dopaminergic pathway

Dopamine is one of a group of neurotransmitters called catecholamines that, like serotonin, is involved in the nervous system. The dopaminergic system is involved in “reward pathways” in the midbrain (Reif & Lesch 2003). Genes involved in this pathway have primarily been investigated for involvement in ADHD.

Dopamine receptors

There are five known dopamine receptors, but studies have only found associations between three of these receptors and antisocial behaviour. The dopamine receptor D4 (DRD4) has been the most heavily researched. Although the results of individual studies of this gene have been inconsistent, two meta-analyses have found a modest association between DRD4 and liability to ADHD (Faraone et al. 2001; Maher et al. 2002). Only a few studies have been carried out on the dopamine receptor D5 (DRD5) and ADHD and although all have produced positive results, they disagree about which allele is associated with the disorder (Barr et al. 2000; Tahir et al. 2000; Payton et al. 2001). A recent meta-analysis of these studies confirmed the association between DRD5 and ADHD (Maher et al. 2002). Investigations of the dopamine receptor D3 (DRD3) and ADHD have not found evidence of an association (Payton et al. 2001; Muglia et al. 2002). However, a recent study did find an association between a DRD3 variant and both impulsivity and ADHD-related symptoms in violent offenders (Retz et al. 2003).

Dopamine transporter

The dopamine transporter (solute carrier family 6, member 3 or SLC6A3) increases the uptake of dopamine that has been released into the neurons thereby stopping its action. SLC6A3 has been associated with ADHD but findings have been inconsistent. A recent meta-analysis of these studies did not find an association between SLC6A3 and ADHD, although the authors noted that this was mainly due to a single large negative study (Maher et al. 2002).

The noradrenergic pathway

Like dopamine, norepinephrine is also a catecholamine neurotransmitter. The noradrenergic systems functions as a central arousal system (Reif & Lesch 2003). Disruptions to the regulation of the noradrenergic pathway have been implicated in psychological disorders such as anxiety and depression.

Dopamine beta hydroxylase

The dopamine beta hydroxylase (DBH) enzyme increases the conversion of dopamine to norepinephrine. A number of studies have found evidence that one DBH polymorphism is involved in susceptibility to ADHD, although in two of the studies the results did not reach significance (Daly et al. 1999; Roman et al. 2002; Wigg et al. 2002; Smith et al. 2003).

α -adrenergic receptors

This class of receptors bind to catecholamine neurotransmitters. The adrenergic alpha 2A receptor (ADRA2A) has been associated with impulsivity and hostility (Comings et al. 2000). ADRA2A and two other receptors, adrenergic alpha 2C receptor (ADRA2C) and adrenergic alpha 1A (ADRA1A) have been investigated for involvement in ADHD, but all studies have produced negative results (Barr et al. 2001; Xu et al. 2001).

Other genes

Dopa decarboxylase

Dopa decarboxylase (DDC) is involved in the serotonergic and dopaminergic systems in which it increases the production of both serotonin and dopamine. Only a few studies

have been carried out on this gene and ADHD, but its role in neurotransmitter metabolism makes it an interesting candidate gene. A study conducted by Hawi et al. (2001) suggested that one DDC haplotype may increase the risk for developing ADHD. A subsequent study identified a marginally significant association between ADHD and DDC (Kirley et al. 2002), although this research examined only one of the polymorphisms involved in the haplotype identified by Hawi et al.

Monoamine oxidase A

Monoamine oxidase A (MAOA) is an enzyme that metabolises serotonin, dopamine and norepinephrine. MAOA has become the focus of much genetic research on criminal or antisocial behaviour because the study by Brunner et al. (1993) identified an association between a mutation in MAOA and impulsive aggression. Although this relationship has not been confirmed outside the family examined in the original study, MAOA has been the focus of a number of studies on antisocial behaviours.

Vanyukov et al. (1995) examined a dinucleotide repeat (DNR) polymorphism in the gene, but found no association with aggressiveness or conduct disorder. This negative result was reproduced by another study whose authors found an association between a variable number of tandem repeats (VNTR) polymorphism in MAOA and variation in impulsivity and aggression (Manuck et al. 2000). A recent study by Caspi et al. (2002) identified a relationship between MAOA and antisocial behaviour. The authors found that males with a low enzyme-activity genotype, who were also maltreated during childhood, were more likely to develop CD and be convicted of a violent crime than maltreated males with a high-activity genotype.

MAOA has also been investigated for a relationship with ADHD. Payton et al (2001) identified a trend for an association between MAOA and ADHD, although the results did not reach statistical significance. A subsequent study by Manor et al. (2002) also supported this finding. A more recent investigation of MAOA and ADHD could find no association between the two, although MAOA was found to be associated with ADHD in patients with symptoms of comorbid CD (Lawson et al. 2003).

Glossary

Allele: One of the variant forms of a gene at a particular locus, or location, on a chromosome. Different alleles produce variation in inherited characteristics such as hair colour or blood type. In an individual, one form of the allele (the dominant one) may be expressed more than another form (the recessive one).

Autosomal inheritance: The pattern of inheritance shown by a disorder or trait determined by a gene on one of the non-sex chromosomes.

Candidate gene: A gene, located in a chromosome region suspected of being involved in a disease, whose protein product suggests that it could be the disease gene in question.

Chromosomes: The structures found within a cell that contain the genetic information of an organism.

Dominant: A genetic term used to describe how the characteristics expressed by one allele (the dominant one) masks the characteristics expressed by another, known as the recessive allele.

Gene: The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

Haplotype: One of the alternative forms of the genotype of a set of genes that are inherited as a unit. This term is applied to gene complexes rather than the term allele, which refers to one of the forms of a single gene.

Heritability: A measurement of the extent to which individual genetic differences contribute to individual differences in observed behaviour.

Mendelian inheritance: Simple forms of inheritance which follow the laws of segregation and independent assortment as proposed by Mendel. Examples of Mendelian inheritance include autosomal dominant and autosomal recessive.

Mutation: a change in a chromosome or gene, either through an alteration in the nucleotide sequence of the DNA coding for a gene or through a change in the physical arrangement of a chromosomes.

Polymorphism: A common variation in the sequence of DNA among individuals.

Recessive: See dominant

Most of these definitions are taken from the Talking Glossary of Genetic Terms at the National Human Genome Research Institute (<http://www.genome.gov/glossary.cfm>)

References

- Barr, C.L., Wigg, K., Zai, G., Roberts, W., Malone, M., Schachar, R., Tannock, R. & Kennedy, J.L. 2001, "Attention-deficit hyperactivity disorder and the adrenergic receptors alpha 1C and alpha 2C", *Molecular Psychiatry*, vol. 6, no.3, pp. 334-7.
- Barr, C.L., Wigg, K.G., Feng, Y., Zai, G., Malone, M., Roberts, W., Schachar, R., Tannock, R. & Kennedy, J.L. 2000, "Attention-deficit hyperactivity disorder and the gene for the dopamine D5 receptor", *Molecular Psychiatry*, vol. 5, no.5, pp. 548-51.

- Brunner, H.G., Nelen, M., Breakefield, X.O., Ropers, H.H. & van Oost, B.A. 1993, "Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A", *Science*, vol. 262, no.5133, pp. 578-80.
- Burmeister, M. 1999, "Basic concepts in the study of diseases with complex genetics", *Biological Psychiatry*, vol. 45, pp. 522-32.
- Caspi, A., McClay, J., Moffitt, T.E., Mill, J., Martin, J., Craig, I.W., Taylor, A. & Poulton, R. 2002, "Role of genotype in the cycle of violence in maltreated children", *Science*, vol. 297, pp. 851-54.
- Comings, D.E., Johnson, J.P., Gonzalez, N.S., Huss, M., Saucier, G., McGue, M. & MacMurray, J. 2000, "Association between the adrenergic alpha 2A receptor gene (ADRA2A) and measures of irritability, hostility, impulsivity and memory in normal subjects", *Psychiatric Genetics*, vol. 10, no.1, pp. 39-42.
- Daly, G., Hawi, Z., Fitzgerald, M. & Gill, M. 1999, "Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children", *Molecular Psychiatry*, vol. 4, no.2, pp. 192-6.
- Evans, J., Reeves, B., Platt, H., Leibenau, A., Goldman, D., Jefferson, K. & Nutt, D. 2000, "Impulsiveness, serotonin genes and repetition of deliberate self-harm (DSH)", *Psychological Medicine*, vol. 30, no.6, pp. 1327-34.
- Faraone, S.V., Doyle, A.E., Mick, E. & Biederman, J. 2001, "Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder", *American Journal of Psychiatry*, vol. 158, no.7, pp. 1052-7.
- Hawi, Z., Dring, M., Kirley, A., Foley, D., Kent, L., Craddock, N., Asherson, P., Curran, S., Gould, A., Richards, S., Lawson, D., Pay, H., Turic, D., Langley, K., Owen, M., O'Donovan, M., Thapar, A., Fitzgerald, M. & Gill, M. 2002, "Serotonergic system and attention deficit hyperactivity disorder (ADHD): a potential susceptibility locus at the 5-HT(1B) receptor gene in 273 nuclear families from a multi-centre sample", *Molecular Psychiatry*, vol. 7, no.7, pp. 718-25.
- Hawi, Z., Foley, D., Kirley, A., McCarron, M., Fitzgerald, M. & Gill, M. 2001, "Dopa decarboxylase gene polymorphisms and attention deficit hyperactivity disorder (ADHD): no evidence for association in the Irish population", *Molecular Psychiatry*, vol. 6, no.4, pp. 420-4.
- Kent, L., Doerry, U., Hardy, E., Parmar, R., Gingell, K., Hawi, Z., Kirley, A., Lowe, N., Fitzgerald, M., Gill, M. & Craddock, N. 2002, "Evidence that variation at the serotonin transporter gene influences susceptibility to attention deficit hyperactivity disorder (ADHD): analysis and pooled analysis", *Molecular Psychiatry*, vol. 7, no.8, pp. 908-12.
- Kirley, A., Hawi, Z., Daly, G., McCarron, M., Mullins, C., Millar, N., Waldman, I., Fitzgerald, M. & Gill, M. 2002, "Dopaminergic system genes in ADHD: toward a biological hypothesis", *Neuropsychopharmacology*, vol. 27, no.4, pp. 607-19.
- Lander, E.S. & Schork, N.J. 1994, "Genetic dissection of complex traits", *Science*, vol. 265, pp. 2037-47.
- Lawson, D.C., Turic, D., Langley, K., Pay, H.M., Govan, C.F., Norton, N., Hamshere, M.L., Owen, M.J., O'Donovan, M.C. & Thapar, A. 2003, "Association analysis of

- monoamine oxidase A and attention deficit hyperactivity disorder", *American Journal of Medical Genetics*, vol. 116B, no.1, pp. 84-9.
- Maher, B.S., Marazita, M.L., Ferrell, R.E. & Vanyukov, M.M. 2002, "Dopamine system genes and attention deficit hyperactivity disorder: a meta-analysis", *Psychiatric Genetics*, vol. 12, no.4, pp. 207-15.
- Manor, I., Eisenberg, J., Tyano, S., Sever, Y., Cohen, H., Ebstein, R.P. & Kotler, M. 2001, "Family-based association study of the serotonin transporter promoter region polymorphism (5-HTTLPR) in attention deficit hyperactivity disorder", *American Journal of Medical Genetics*, vol. 105, no.1, pp. 91-5.
- Manor, I., Tyano, S., Mel, E., Eisenberg, J., Bachner-Melman, R., Kotler, M. & Ebstein, R.P. 2002, "Family-based and association studies of monoamine oxidase A and attention deficit hyperactivity disorder (ADHD): preferential transmission of the long promoter-region repeat and its association with impaired performance on a continuous performance test (TOVA)", *Molecular Psychiatry*, vol. 7, no.6, pp. 626-32.
- Manuck, S.B., Flory, J.D., Ferrell, R.E., Dent, K.M., Mann, J.J. & Muldoon, M.F. 1999, "Aggression and anger-related traits associated with a polymorphism of the tryptophan hydroxylase gene", *Biological Psychiatry*, vol. 45, no.5, pp. 603-14.
- Manuck, S.B., Flory, J.D., Ferrell, R.E., Mann, J.J. & Muldoon, M.F. 2000, "A regulatory polymorphism of the monoamine oxidase-A gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsivity", *Psychiatry Research*, vol. 95, no.1, pp. 9-23.
- Muglia, P., Jain, U. & Kennedy, J.L. 2002, "A transmission disequilibrium test of the Ser9/Gly dopamine D3 receptor gene polymorphism in adult attention-deficit hyperactivity disorder", *Behavioural Brain Research*, vol. 130, no.1-2, pp. 91-5.
- New, A.S., Gelernter, J., Yovell, Y., Trestman, R.L., Nielsen, D.A., Silverman, J., Mitropoulou, V. & Siever, L.J. 1998, "Tryptophan hydroxylase genotype is associated with impulsive-aggression measures: a preliminary study", *American Journal of Medical Genetics*, vol. 81, no.1, pp. 13-7.
- Payton, A., Holmes, J., Barrett, J.H., Hever, T., Fitzpatrick, H., Trumper, A.L., Harrington, R., McGuffin, P., O'Donovan, M., Owen, M., Ollier, W., Worthington, J. & Thapar, A. 2001, "Examining for association between candidate gene polymorphisms in the dopamine pathway and attention-deficit hyperactivity disorder: a family-based study", *American Journal of Medical Genetics*, vol. 105, no.5, pp. 464-70.
- Quist, J.F., Barr, C.L., Schachar, R., Roberts, W., Malone, M., Tannock, R., Basile, V.S., Beitchman, J. & Kennedy, J.L. 2000, "Evidence for the serotonin HTR2A receptor gene as a susceptibility factor in attention deficit hyperactivity disorder (ADHD)", *Molecular Psychiatry*, vol. 5, no.5, pp. 537-41.
- Reif, A. & Lesch, K.-P. 2003, "Toward a molecular architecture of personality", *Behavioural Brain Research*, vol. 139, pp. 1-20.
- Retz, W., Rosler, M., Supprian, T., Retz-Junginger, P. & Thome, J. 2003, "Dopamine D3 receptor gene polymorphism and violent behavior: relation to impulsiveness and ADHD-related psychopathology", *Journal of Neural Transmission*, vol. 110, no.5, pp. 561-72.

- Retz, W., Thome, J., Blocher, D., Baader, M. & Rosler, M. 2002, "Association of attention deficit hyperactivity disorder-related psychopathology and personality traits with the serotonin transporter promoter region polymorphism", *Neuroscience Letters*, vol. 319, no.3, pp. 133-6.
- Roman, T., Schmitz, M., Polanczyk, G.V., Eizirik, M., Rohde, L.A. & Hutz, M.H. 2002, "Further evidence for the association between attention-deficit/hyperactivity disorder and the dopamine-beta-hydroxylase gene", *American Journal of Medical Genetics*, vol. 114, no.2, pp. 154-8.
- Schork, N.J. 1997, "Genetic of complex disease: approaches, problems, and solutions", *American Journal of Respiratory and Critical Care Medicine*, vol. 156, pp. S103-9.
- Smith, K.M., Daly, M., Fischer, M., Yiannoutsos, C.T., Bauer, L., Barkley, R. & Navia, B.A. 2003, "Association of the dopamine beta hydroxylase gene with attention deficit hyperactivity disorder: Genetic analysis of the Milwaukee longitudinal study", *American Journal of Medical Genetics*, vol. 119B, no.1, pp. 77-85.
- Staner, L., Uyanik, G., Correa, H., Tremeau, F., Monreal, J., Crocq, M.A., Stefanos, G., Morris-Rosendahl, D.J. & Macher, J.P. 2002, "A dimensional impulsive-aggressive phenotype is associated with the A218C polymorphism of the tryptophan hydroxylase gene: a pilot study in well-characterized impulsive inpatients", *American Journal of Medical Genetics*, vol. 114, no.5, pp. 553-7.
- Tahir, E., Yazgan, Y., Cirakoglu, B., Ozbay, F., Waldman, I. & Asherson, P.J. 2000, "Association and linkage of DRD4 and DRD5 with attention deficit hyperactivity disorder (ADHD) in a sample of Turkish children", *Molecular Psychiatry*, vol. 5, no.4, pp. 396-404.
- Tang, G., Ren, D., Xin, R., Qian, Y., Wang, D. & Jiang, S. 2001, "Lack of association between the tryptophan hydroxylase gene A218C polymorphism and attention-deficit hyperactivity disorder in Chinese Han population", *American Journal of Medical Genetics*, vol. 105, no.6, pp. 485-8.
- Vanyukov, M.M., Moss, H.B., Yu, L.M. & Deka, R. 1995, "A dinucleotide repeat polymorphism at the gene for monoamine oxidase A and measures of aggressiveness", *Psychiatry Research*, vol. 59, no.1-2, pp. 35-41.
- Wigg, K., Zai, G., Schachar, R., Tannock, R., Roberts, W., Malone, M., Kennedy, J.L. & Barr, C.L. 2002, "Attention deficit hyperactivity disorder and the gene for dopamine Beta-hydroxylase", *American Journal of Psychiatry*, vol. 159, no.6, pp. 1046-8.
- Xu, C., Schachar, R., Tannock, R., Roberts, W., Malone, M., Kennedy, J.L. & Barr, C.L. 2001, "Linkage study of the alpha2A adrenergic receptor in attention-deficit hyperactivity disorder families", *American Journal of Medical Genetics*, vol. 105, no.2, pp. 159-62.
- Zoroglu, S.S., Erdal, M.E., Alasehirli, B., Erdal, N., Sivasli, E., Tutkun, H., Savas, H.A. & Herken, H. 2002, "Significance of serotonin transporter gene 5-HTTLPR and variable number of tandem repeat polymorphism in attention deficit hyperactivity disorder", *Neuropsychobiology*, vol. 45, no.4, pp. 176-81.