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REVIEW ARTICLE

# Genetics of human aggressive behaviour

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**Abstract** A consideration of the evolutionary, physiological and anthropological aspects of aggression suggests that individual differences in such behaviour will have important genetic as well as environmental underpinning. Surveys of the likely pathways controlling the physiological and neuronal processes involved highlight, as obvious targets to investigate, genes implicated in sexual differentiation, anxiety, stress response and the serotonin neurotransmitter pathway. To date, however, association studies on single candidates have provided little evidence for any such loci with a major effect size. This may be because genes do not operate independently, but function against a background in which other genetic and environmental factors are crucial. Indeed, a series of recent studies, particularly concentrating on the serotonin and norepinephrine metabolising enzyme, monoamine oxidase A, has emphasised the necessity of examining gene by environmental interactions if the contributions of individual loci are to be understood. These findings will have major significance for the interpretation and analysis of data from detailed whole genome association studies. Functional imaging studies of genetic variants affecting serotonin pathways have also provided valuable insights into potential links between genes, brain and aggressive behaviour.

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## Evolutionary origins of aggression

The various facets of human aggression can be considered as evolutionary advantageous traits and as important predictors of success in a competitive modern world; they may also provide an impediment to social cohesion. It is not difficult to imagine how aggression, particularly for males in animal communities, provides a competitive edge in securing resources and in intra-sexual competition via combat. High aggression may even compensate for lack of physical prowess in establishing hierarchy and dominance with respect to reproductive success. Aggression in females can provide protection of their offspring against a range of threats. Such behaviour also has negative attributes and in certain circumstances represents a high-risk strategy with associated possibilities of injury or death. Given such a high likelihood of both potentially positive and negative selective discrimination throughout evolution, it is not surprising that human aggression appears to have a strong genetic underpinning (Maynard Smith et al. 1988).

It should be noted that two types of aggressive behaviour are frequently distinguished, one resulting from a lack and the other from an excess of emotional sensitivity. The former behaviour is often described as instrumental, or proactive, aggression and is pre-meditated and frequently goal-directed. It is characteristically associated with psychopathy, lacking both empathy and remorse. This is in contrast to, so called, reactive aggression which is typically triggered by negative experiences and emotions including anger and/or anxiety (e.g. Tremblay et al. 2005). It appears to result from exaggerated threat perception and response to it, together with an inability to control the resultant enhanced emotional state (e.g. see Blair 2004; Blair et al. 2006; Crick and Dodge 1996).

In respect of reactive aggression and the response to threat, there appears to be a complex relationship between anxiety and aggression and a strong evolutionary conservation of the brain regions implicated for both in mammals. The neural circuits involved centre on the amygdala and its linked pathways which control avoidant, defensive or aggressive behaviour (e.g. see Lesch 2005). Indeed, it has been posited that dysfunction of the neural circuits regulating emotion represent an aetiological factor of impulsive violence (Davidson et al. 2000). These circuits embrace not only the amygdala, but also the anterior cingulated cortex and regions of the prefrontal cortex. Some individuals who show impulsive, violent tendencies have dysfunctional serotonergic projection to this region, consistent with the long held belief that disruption of the serotonin system is a highly significant feature in predisposing aggression (see Siever 2008; Berman et al. 2009).

## Heritability of aggression

A detailed evaluation and meta-analysis of 24 genetically informative studies concerning aggression concluded that heritability accounted overall for about 50% of the variance (Miles and Carey 1997; Rhee and Waldman 2002). Miles and Carey concluded that "heritability and common environment are definitely responsible for individual differences in aggression". They noted, however, that heritability changed with time; whilst genetic factors and common environment were equally important in childhood, heritability became even more prominent in adulthood. It also appeared that male heritability for the trait was slightly higher than that for females.

## Genetic features and likely pathways implicated in aggression

### Sex differences and aggression

As noted above, there are likely to be different evolutionary aggression strategies for males and females resulting in different proactive and reactive responses in level and frequency. In humans, very clear cut distinctions between the sexes can be made on the basis of crime statistics which indicate that males are overwhelmingly more likely to be implicated in crimes involving aggression. In the USA, government data indicate males to be ten times more likely than females to commit murder and more than five times as likely to be under 'correctional supervision' for criminal offences (see http://www.ojp.usdoj.gov/bjs/). This appears to be a general finding in other populations; for example, in New Zealand, a longitudinal study of about 1,000 individuals over the period from 3 to 21 years, males were found to be 2.4 times more likely to be involved in antisocial behaviour than females (Moffitt et al. 2001). The widespread and consistent pattern of male excess in aggression statistics is remarkable given that it generally emerges irrespective of the measures employed and the age of the individuals surveyed.

A wealth of studies has demonstrated a correlation between testosterone levels and aggression in animals. The situation with humans is much less clear and the data more conflicting. Whilst some research has suggested that aggression and testosterone are indeed positively correlated (Archer 1991), there are contrary observations. For instance, Turner (1994) showed that whilst testosterone was positively correlated with aggressive behaviour in 12–13-year-old boys, it was not in 15–16-year-old boys. Subsequently, a meta-analysis, based on 45 independent studies encompassing 9,760 individuals and reflecting a range of both negative and positive correlations provided support for an overall weak positive effect ($r = 0.14$) (Book et al. 2001). Interpretation of the relationship is, however, complicated in humans, not only because of methodological problems, but also because of fluctuations in hormone levels in response to environmental conditions and circadian rhythm. Age is also a confound both in regard to changing response and actual levels.

Many investigations have concentrated on the aggressive behaviour of adolescent and young adult males referred to by Wilson and Daly (1985) as the ''Young Male Syndrome". Indeed, it is males between the ages of 12 and 25 who are the principal perpetrators and victims of violence, and this may be due to increasing testosterone levels which start to rise in early adolescence (e.g. Mazur 1983). Puberty signals increasing sexual maturity, a concomitant rise in androgen levels, and an increase in inter-male competition—a combination with a presumptive selection for confrontational competitive abilities (Wilson and Daly 1985; Book et al. 2001). This male-associated aggression suggests the possibility that genes in androgen synthesis and function are potentially implicated.

It appears that not only is the Y chromosome important in contributing to aggression through its role in male determination, but that other Y-linked loci may be significant. By sophisticated manipulations, it has been possible to delete the normal male determining gene (*Sry*) from the Y chromosome in mice (designated $Y^-$) and to provide it as an autosomal copy against a background of different X, Y and $Y^-$ sex chromosome combinations. Analysis of the behaviours of the strains created clearly shows an effect on aggression independent of the *Sry* locus (Gatewood et al. 2006). This implies that other specific genes on the X and or Y chromosome are involved in aggression. With regard to the Y chromosome, this provides a restricted search field for any genes implicated; however, apart from some evidence suggesting the

implication of the steroid sulphatase locus, *Sts* (which incidentally is non-functional in humans, and hence unlikely to contribute to genetic variability) no other Y-chromosome loci have been confirmed as contributing to aggression.

## Stress and the HPA axis

It follows from the hypothesis that failure to regulate emotional balance can result in impulsive reactive aggression that the stress response itself and its genetic components are likely to be implicated (see Craig 2007a). The hypothalamus, pituitary and adrenal (HPA) axis, frequently monitored through cortisol levels, which are directly affected by stress, has consequently been a focus for attention. Research into potential association between cortisol levels and aggression have, however, been hampered by the sampling protocols employed and the complications presented by diurnal variation together with immediate contextual mediated changes. Furthermore, the pubertal stage in the young individuals surveyed is an important variable. In an attempt to surmount such difficulties and to establish a trait-like, as opposed to a state-like, measure, Shirtcliff et al. (2005) monitored individual differences in a large number (724) of youths concentrating on early morning saliva samples. For the males only, higher externalising problem behaviour was consistently associated with lower salivary cortisol. Other recent studies have provided some support for this pattern. Loney et al. (2006) found that male adolescents exhibiting elevated callous unemotional traits had low cortisol levels compared to equivalent controls, and Popma et al. (2007) found that adolescent boys, who had disruptive behaviour disorder, showed significantly lower levels in the first hour after waking. Most recently, radio-immune assays were employed to compare key components in the saliva of 20 aggressive and 20 non-aggressive students matched for gender, age and pubertal development. Interestingly, although the male aggressive students manifested lower cortisol levels, higher testosterone levels predicted aggression in the girls (but not the boys) examined (Yu and Shi 2009). There are deviations from this apparent consensus, for example, van Bokhoven et al. (2005) employing a longitudinal approach to behavioural monitoring found consistently higher cortisol levels in boys with conduct disorder (particularly reactive aggression) than those without; however, levels were only monitored at age 13, thereby restricting more general interpretations.

## The serotonin pathway

A rich history of research indicating the key role of serotonin in aggression indicates that the genetic control of all aspects of serotonin metabolism and particularly of its synthesis, its release from neurons and its action via the various receptors represent a rich field for the selection of candidate genes. One strand of evidence for this is the generally consistent observation for both humans and macaques that reduced levels of the serotonin metabolite 5-hydroxy-indole acetic acid (5-HIAA) in cerebrospinal fluid (CSF) are associated with violent behaviour (e.g. Birger et al. 2003; Coccaro et al. 1997). There has also been a persisting documentation of an association of low levels of 5-HIAA in the spinal fluid of suicide attempters and specifically in those employing violent means (see Birger et al. 2003 for review).

The action of serotonin is mediated by a range of cognate receptors. In addition to the receptors on the postsynaptic neuron, the involvement of the 5-HT1A and 5-HT1B autoreceptors on the pre-synaptic neuron also provide a routes for the regulation of aggressive behaviour, and there is evidence for this role in rodents. For example, up-regulation of somatodendritic 5-HT1A and terminal 5-HT1B autoreceptors is observed in highly aggressive rats, which is further enhanced following victorious aggressive experiences (Caramaschi et al. 2007). Such up-regulation may be part of a normal compensatory mechanism to the elevated activity of the serotonin system in such aggressive animals. If this autoreceptor response overshoots, it is possible that the resultant damping of the serotonergic neurons' activity leads to violent and aggressive behaviour (Caramaschi et al. 2007).

In contrast to the apparent damping down effect of serotonin, Coccaro et al. (1998) found in studies on CSF arginine vasopressin (AVP) and 5-HIAA levels that whilst the former were positively correlated with life history of aggression, the latter were correlated inversely. It therefore seems that loci implicated in the synthesis of and response to AVP may represent a further category of genetic variables for consideration.

## Aggression and low blood sugar levels

Abnormally low levels of blood sugar (hypoglycaemia) may trigger a series of physiological changes and behaviours including aggression. Two types of non-diabetic hypoglycaemia are recognised. The term "reactive hypoglycaemia" describes recurrent episodes of symptomatic hypoglycaemia occurring 2–4 h after a high carbohydrate meal (or oral glucose load, OGL). It is thought to represent a consequence of excessive and persisting levels of insulin release triggered by the intake of carbohydrate/glucose. The second type is "fasting hypoglycaemia" also called post-absorptive hypoglycaemia, which may be related to an underlying disease state. Other predictors include hormonal deficiencies, intake of certain medications and/or alcoholic beverages (particularly "binge drinking"). The symptoms associated with significant hypoglycaemia include fatigue, dizziness, headaches and irritability; hence, there have been

several investigations of the association between low blood sugar and aggression. Virkkunen and Huttunen (1982) tested offenders who had committed one or more serious assaults and noted that they also responded in the OGL challenge with atypically low glucose levels and slow recovery times. Subsequently, Virkkunen (1983, 1986) found that insulin secretion was enhanced (with presumptive glucose level depletion) during tests on atypical responders and was associated with pronounced antisocial characteristics. Benton (1988) concludes that moderate falls in blood glucose may predispose individuals to aggression, but because the levels are not clinically within the range for hypoglycaemia, other normally observed symptoms may not manifest, thereby muddying the clarity of a formal demonstration between reactive hypoglycaemia and aggression. It seems, therefore, that moderate falls in glucose levels, caused for whatever reason (but including excessive alcohol intake), may cause irritability and depending on the levels of provocation and aggression.

Various studies have attempted to link serotonin mechanisms, insulin levels and glucose metabolism with aggression and impulse control, leading to the proposal of a "low serotonin syndrome" (e.g. Linnoila and Virkkunen 1992). It is predicted that a decrease in serotonin activity in the Raphe nuclei (which can result from excessive alcohol intake) causes a chain reaction, first in suppressing pancreatic insulin release, resulting in hypoglycaemia with concomitant increases in impulsivity and aggressive or violent behaviour (Yamamoto et al. 1984). Unfortunately, although it is reasonable to assume that the interactions between serotonin, glucose and alcohol metabolism are significant features of aggression, these findings are not conclusive enough as yet to have predictive value (e.g. see Virkkunen et al. 2007).

## Evidence for the implication of specific genes

In the following sections, the evidence for the involvement of specific genes is considered. Following a brief review of genome wide studies, the functional variation in candidate genes, selected on the basis of their likely involvement in relevant pathways (as described in the preceding sections), will be reviewed.

### Genome scans for aggression loci

Surprisingly, there appears to have been very few linkage or association whole genome scans for aggression apart from a search for quantitative trait loci in mice (Brodkin et al. 2002). In this study, outcrosses and backcrosses between the extremely aggressive strain, NZB/B1NJ, and the markedly unaggressive A/J strain have enabled two significant chromosomal regions to be identified and potential candidate loci to be suggested (Brodkin et al. 2002). The regions implicated were distal chromosome 10 and proximal chromosome X, with corresponding putative loci designated *Aggr1* and *Aggr2*. Candidate genes within the regions include the diacylglycerol kinase subunit gene (*Dagk1*) and the glutamate receptor subunit AMPA3 gene (*Gria3*), respectively. Plausible arguments can be made for both as candidates. Diacylglycerol kinases are involved in the phosphatidylinositol signal transduction system important in brain neurotransmission. In rats, glutamate receptor genes impart different pharmacologic and kinetic properties on currents evoked by L-glutamate or its analogue, AMPA. Indeed, subsequent evidence has shown that a selective agonist of glutamate receptors 2 and 3 can reduce the isolation-induced aggression in male mice (Navarro et al. 2008). Nevertheless, there appears to be no direct evidence that either locus is implicated in human aggression.

### Candidate genes related to sex differences

#### *Androgen receptor (AR)*

The best established, highly polymorphic and functional locus with regard to sex determination is the androgen receptor (*AR*), which embraces two trinucleotide repeats. In a preliminary finding which will require replication, Jonsson et al. (2001) observed tendencies (not reaching statistical significance levels) in healthy Swedish males for an association of shorter (and presumptively higher expressed) CAG repeats with muscular tension and with verbal aggression. More recently, Rajender et al. (2008) have attempted to replicate this observation in Indian males convicted for various aggression-related offences (murder and/or rape) together with controls. They found a highly significant association of the shorter CAG repeats motifs with the somewhat more dramatic phenotype, in this case, of violent criminal activity.

### Candidate genes in the serotoninergic system

#### *Monoamine oxidases (MAOA and MAOB)*

MAOA and MAOB are two closely related enzymes, the products of two abutting X-linked genes which play an important role in the metabolism of biogenic amines in the central nervous system and in the periphery. In general, whilst MAOA preferentially oxidises biogenic amines such as serotonin (5-HT), norepinephrine (NE) and epinephrine, MAOB is important in dopamine metabolism and degrades dietary amines including phenylethylamine. Of the two, by far the most investigated with respect to human aggression is *MAOA*. An important watershed in the candidature of

this locus followed the correlation between null mutations (leading to imbalances in serotonin and NE metabolism) and aggression observed in both human and mice (Brunner et al. 1993; Cases et al. 1995). Subsequently, most interest has centred on detecting behavioural associations with SNPs, microsatellites and/or promoter VNTR variants in *MAOA*. The latter are known to confer significant functional variation and given the high LD across the locus, it is possible that the associations with aggression and violence observed with other markers result from their acting as surrogates for the tandem repeat (reviewed in Craig 2007a; D'Souza and Craig 2008). This VNTR polymorphism has established functional effects on reporter genes and expressed proteins. It is located 1.2 kb upstream of the coding region and comprises a 30-bp repeated sequence normally present in 3, 3.5, 4 or 5 copies. The 3 and 4 repeats are predominant and have been classified as low or high expression forms, respectively (Deckert et al. 1999; Denney et al. 1999; Sabol et al. 1998); however, one study has failed to detect associated significant transcriptional differences (Balciuniene et al. 2002) employing human cortical brain tissue as opposed to cultured cells. Interestingly, Pinsonneault et al. (2006), also working with human brain observed that other *cis* acting factors may obscure any differential transcriptional effect of the 4 versus the 3 repeat (see also Cirulli and Goldstein 2007). There are conflicting reports of a direct association of low activity alleles and a range of aggressive behaviours (see Craig 2005). The complex interactions between functional variation at this locus, exposure to environments and sex hormones that may be responsible for the inconsistencies are reviewed in a later section.

*Serotonin transporter (SLC6A4)*

Surprisingly, given the role of serotonin modulation and aggression, the well-established long and short versions of the promoter region (*5-HTTLPR*) encoding high and low activity variants have figured only slightly in context of a potential role in human aggression. Support is mainly provided by a study on violent and non-violent adult males referred for forensic assessment. The results interestingly showed an interaction effect between childhood high adversity impacting only on later-life violence if the short (low activity) promoter alleles were present (Reif et al. 2007).

*Tryptophan hydroxylases 1 and 2 (TPH1 and TPH2)*

The traditionally investigated tryptophan hydroxylase enzyme (TPH1) catalyses the rate-limiting step in the synthesis of serotonin and was thought to be widely expressed in the brain. Its candidature in behavioural studies was, however, somewhat complicated by the discovery in 2003 of a second form of the enzyme, TPH2 (Walther and Bader 2003). In mice, whilst *Tph2* is predominantly expressed in brain stem, *Tph1* is expressed in a wide range of tissues, but not predominantly in the brain. Some reports indicate that two human isoforms are both expressed in brain tissues (e.g. Zill et al. 2007); however, very recently Gutknecht et al. (2009) were unable to detect TPH1 by immuno-histochemistry or in situ hybridisation in adult human or mice brain, not in brain of developing mice.

*TPH1* has two well-characterised SNPs (A218C and A779C) in intron 7, which are in strong linkage disequilibrium. The 779A allele (also referred to as U) has been associated with lower CSF 5-HIAA in control males (but not females); however, the lowest 5-HIAA levels were found in homozygous individuals for the C allele in impulsive alcoholic violent offenders (Nielsen et al. 1994). Manuck et al. (1999) also investigated the A218C polymorphism in a sample comprising 124 men and 127 women. Overall, individuals with an A allele scored significantly higher on measures of aggression and tendency to experience unprovoked anger. The co-variation of *TPH1* genotype with aggression and anger measures was found to be statistically robust in men, but non-significant amongst women. Hence, the overall conclusion from several studies suggest that the two SNPs (although given their high LD unlikely to be operating independently) are probably directly, or indirectly, implicated in both the regulation of CSF 5-HIAA levels and in aggression, as well as having a possible role in suicidal behaviour (see Hennig et al. 2005). The latter authors examined the association of the A779C SNP with aggression subdivided into aggressive hostility (AH) and neurotic hostility (NH)—corresponding roughly to "proactive" and "reactive" aggression. Similar to the observations of Manuck et al. (1999), individuals homozygous for the A allele showed the highest aggression and CC individuals the lowest; but only for AH and not NH. Hennig et al. conclude that the dichotomy observed for the subdivisions may explain some of the inconsistencies in the literature; however, the study was relatively small and requires replication.

There is an inter-strain polymorphism of the *Tph2* gene in mice. This C1473G variation encodes a Pro447 to Arg447 substitution and is associated with brain TPH activity and inter-male aggressiveness across ten mouse strains (Kulikov et al. 2005); a study extended and confirmed by Osipova et al. (2009). The Pro447Arg substitution corresponds to the Pro449Arg polymorphism in the human enzyme TPH2 (Zhang et al. 2004). Although this has been associated with affective disorders, there is surprisingly as yet no evidence presented for a role in aggression. Transmission disequilibrium analysis has, however, suggested a role for variants in the transcriptional control region of TPH2 in ADHD (Walitza et al. 2005).

*Serotonin receptors*

5-HT1A and 5-HT1B receptors associated with serotonergic neurons appear to be key players in the control of offensive aggression in rodents. 5-HT1B hetero-receptors (i.e. modulating neurotransmitter release on non-5-HT nerve terminals) have also been identified as important in modulating offensive aggression. Together with the serotonin transporter, control of 5-HT release, via presynaptic 5-HT1A and 5-HT1B, (auto) receptors may also have important influences on aggression under certain conditions (for review see Olivier and van Oorschot 2005). Several studies have sought to establish whether, or not, altered function of the 5-HT1B (hetero) receptor in humans may contribute to changes in aggressive behaviour. There are a number of polymorphisms in the coding sequence and surrounding 5′- and 3′-untranslated regions, and more than 20 association studies with aggression have been published with varying results (Sanders et al. 2002). A functional polymorphism, G861C, has been identified which affects binding of serotonin (Huang et al. 1999), and associations have been found with antisocial alcoholism (Hasegawa et al. 2002; Lappalainen et al. 1998; Soyka et al. 2004) and also with a history of suicide attempts (New et al. 2001); however, other investigations failed to link the polymorphism with suicidal behaviour or suicide (Nishiguchi et al. 2001; Rujescu et al. 2003; Stefulj et al. 2004), whilst yet other studies have reported associations with pervasive aggression in children (Davidge et al. 2004).

There are several polymorphisms reported also for *5HT2A*; however, there is scant evidence for the functional importance of any. Most studies have focused on a single SNP providing a silent T102C polymorphism (rs6313) and have provided support for association with a range of behaviours, including psychosis, agitation, aberrant motor behaviour and depression (e.g. see Prichard et al. 2008); however, these authors were unable to replicate a previous association reported for the CC genotype with agitation and aggression in Alzheimer's disease patients (Lam et al. 2004). A second well-studied polymorphism is the G-1438A promoter SNP which is in nearly complete linkage disequilibrium with the silent T102C SNP has been examined in context of antisocial behaviours in alcohol dependents, and has been found to have significant association with impulsive behaviour but not borderline or antisocial, personality disorders (Preuss et al. 2001).

## Candidate genes in the stress response pathway

Two separate elements in the stress pathway exist, the autonomic reaction to stressful situations (commonly typified by the fight or flight paradigm) and the neuroendocrine stress response. The list of possible genetic factors interacting with these systems is open-ended; however, potential significant functional variation in a selection of the top candidate genes has been reviewed recently (Craig 2007b). It is worth noting, however, in spite of the key position occupied by the glucocorticoid receptor and the extensive variation reported for the *GR* locus including 16 SNPs (Bray and Cotton 2003), there have been no consistent observations linking these directly to aggressive behaviour.

*Dopamine-beta-hydroxylase (DBH)*

DBH is a key enzyme in the synthesis of norepinephrine, and there is an abundance of literature describing the genetic control of DBH levels (in serum) and some indication that this may underpin aspects of antisocial behaviour. In an early study, Rogeness et al. (1982) reported that children with conduct disorder (under-socialised type) had low plasma DBH levels. Subsequently, it was observed that males with early experience of maltreatment (and consequently potentially at risk for the subsequent development of aggressive traits) had relatively low DBH levels (Galvin et al. 1991); furthermore, similar low levels were observed in young boys with behavioural disorders and whose fathers showed antisocial behaviour (Gabel et al. 1995).

Several polymorphisms including a SNP (C-1021T, rs1611115), which accounts for about 50% variance in plasma levels, and a dinucleotide repeat 4 kb upstream have been employed in association studies. Most recently, Hess et al. (2009) have provided evidence that the *DBH*-1021TT genotype was significantly associated with increased neuroticism scores and impulsive and/or aggressive behaviour in ADHD.

*Catechol-O-methyl transferase (COMT)*

The COMT enzyme catalyses the transfer of a methyl group from *S*-adenosylmethionine to catecholamines, including dopamine and epinephrine; this provides a major degradative pathway for the catecholamine transmitters. Knock out of *COMT* in mice leads to increased aggressive behaviour but only in males (Gogos et al. 1998). There are, however, contradictory reports on the relationship between *COMT* and aggressive behaviour in humans. The studies have mainly concentrated on the functional SNP (val158met) in the coding region, with the met substitution leading to approximately 40% reduction in enzyme activity by conferring thermolability. Some authors have found a correlation of the met allele with increased aggressiveness particularly for males and frequently associated with schizophrenia. Recently, given the ambiguity of the data and the role of sex differences, Kulikova et al. (2008) examined the functional SNP in the manifestation of physical aggression in 114 unselected women. They observed that

the met/met homozygotes are least aggressive, whilst wild type homozygotes (val/val) exhibited maximum aggression ($P < 0.01$).

*Adrenergic receptors*

Evidence for a link between norepinephrine and aggressive behaviour comes from a variety of studies employing animal models. Such research has found in general that there is a positive relationship between noradrenergic activity and fighting/biting behaviour in various rodents and monkeys. In most human studies, a positive relationship between aggressiveness and CSF norepinephrine, or its metabolite 3-methoxy-4-hydroxyphenylglycol and MHPG are found (e.g. Brown et al. 1982; Placidi et al. 2001). It is therefore of some interest that the $\beta$-type noradrenergic receptor blocker (propranolol) has been employed to control aggressive behaviour in violent patients (for review see Yudofsky et al. 1998). Studies that have administered propranolol to a small number of violent patients have reported a reduction of aggressive behaviour in some but not all (Silver et al. 1999). This suggests that genetic variation in the NE receptors—particularly ADRB1 (on which beta blockers typically act) may be important in both stress and aggression responses. A functional SNP (arg389 allele) in *ADRB1* has been associated with changes to heart rate and BMI; however, a direct link between functional variation in the beta adrenergic receptors and aggression remains to be firmly established.

*Noradrenaline transporter (NET1, SLC6A2)*

Although alterations in the concentration of NE in the CNS have been reported with major psychiatric disorders, Robertson et al. (2001), who reviewed a variety of polymorphisms that had been described in the *NET* locus, concluded that there was no evidence that they contributed to any psychiatric illness. Subsequently, however, Kim et al. (2006) identified a −3081A/T polymorphism in the *NET* promoter with the T allele showing significantly decreased promoter function. They also presented preliminary evidence suggesting an association between the −3081T allele and ADHD in Americans of European descent, thereby providing a tenuous link with aggression.

Overall, whilst it seems that there is considerable theoretical and some experimental evidence suggesting the importance of the stress response pathways in modulating aggression, the ability to demonstrate direct and reproducible links between established functional variation in the major genes investigated and human aggression remains elusive.

Candidate genes related to hypoglycaemia

The physiological link between low blood glucose and aggression has yet to be explained adequately. Nevertheless, an interesting development is that variation in the serotonin transporter-linked polymorphic region (*5-HTTLPR*) was found to affect nutritional intervention on fasting blood glucose (FBG) levels in non-diabetic females with the low activity homozygotes showing significantly larger decreases in FBG over the test period than other genotypes (Yamakawa et al. 2005). This provides a tangential aspect to the role of genetic variation in the serotonin transporter in context of aggression. Furthermore, glucose transporters are also thought to have an affect on hypoglycaemia and resultant behaviour, and it can be posited that any decrease in transporter functionality could exacerbate hypoglycaemic symptoms, including an increase in irritability. This is supported by studies on a family, in whom six out of the eight family members with dystonia-18 were found to have a mutation of the glucose transporter *SLC2A1* gene, resulting in irritability and impulsive behaviour (Weber et al. 2008).

Other candidates

*Nitric oxide synthase (NOS1)*

Since the first observation that a knock out of *Nos1* in mice results in increased aggression (Nelson et al. 1995), there have been many animal studies which have supported a role for the enzyme in this and related behaviours. Very recently, Reif et al. (2009) have carried out an in-depth study of the structure of this complex gene and have concentrated their investigations on a functional promoter repeat length variant (*NOS1* Ex1f VNTR). This area contains recognition sites for a range of transcription factors. In a study of more than 3,200 individuals, association was found with traits relating to impulsivity, including hyperactive and aggressive behaviour. Interestingly, the short version of the repeat which was associated is also characterised by lowered transcription of the *NOS1* exon 1f promoter and alterations in the pattern of neuronal transcripts. The lower activity and associated behavioural consequences of the short VNTR allele is reminiscent of those observed for *MAOA* and *SERT*. We suggest that variation at the *NOS1* locus is likely to provide a valuable basis for future investigations.

*Arginine vasopressin receptor (AVPR1A)*

Given the evidence that the levels of arginine vasopressin have been implicated in aggression (Coccaro et al. 1998), it would seem likely that functional variation in the cognate

receptors might have a significant role. The receptor gene *AVPR1a* has promoter repeats, which in lower vertebrates are associated with regulation of brain expression patterns. Furthermore, *Avpr1a* has been implicated in aggressive behaviour in rodents (Ferris et al. 1997). In humans, two microsatellite repeats in the reporter have been shown to be associated with social communication and also autistic traits; however, as yet no direct relationship to aggression has been demonstrated (Bachner-Melman et al. 2005; Kim et al. 2002; Wassink et al. 2004).

## Gene × environment interactions: the role of stress in aggression

The overwhelming conclusion from both linkage and candidate gene studies is that there are few, if any, loci with large effect size, and it is becoming increasingly obvious that it will be necessary to consider the impact of genes, not in isolation, but as part of a multifactorial miasma including both other genetic factors and the environment. Strong evidence that this is the case stems from the replicated observations of interactions between the functional variants in the *MAOA* locus and stressful upbringing. In the first study of this kind, it was found that maltreated males were significantly more likely to develop antisocial problems if they had the low activity genotype in the 5′ regulatory VNTR (Caspi et al. 2002). There have been several subsequent studies, the majority of which have confirmed the basic conclusion that the high activity promoter variant confers protection against stressful and abusive childhood (Foley et al. 2004; Nilsson et al. 2006; Widom and Brzustowicz. 2006). The generality of the observation has been confirmed by meta-analysis (Kim-Cohen et al. 2006) with a stronger interaction effect in males (Taylor and Kim-Cohen 2007). Others have found MAOA genotype and adverse childhood environments act independently of each other in increasing the risk for later-life violent behaviour (Reif et al. 2007).

A separate interpretation has been put forward by Huang et al. (2004) who found a significant correlation of the high expression MAOA-uVNTR polymorphism with lower impulsivity, but only in adult males who report early childhood abuse. They proposed from their observations that the polymorphism may be a marker for impulsivity and consequently provide an increased risk for abuse, which may lead on subsequently to aggressive behaviour. Interestingly, Nilsson et al. (2007) noted that high MAOA activity male individuals were less likely than their low activity counterparts to be involved in destructive behaviour during adolescent alcohol consumption. Most recently, Weder et al. (2009) have investigated the G × E interaction at a range of trauma levels, and whilst confirming a significant interaction between exposure to moderate trauma and the low-activity *MAOA* genotype for both males and females (hemi or homozygous, respectively) found that exposure to extreme levels of trauma resulted in high aggression scores regardless of genotype. Overall, it seems clear that this complex situation remains an area for continued study—with requirements for standardisation of phenotype and environmental assessments.

There are relatively few studies relating to *MAOA* functional variants and female behaviour; however, a G × E interaction has been observed in which girls with high, rather than low, activity alleles appeared to be at increased risk of committing criminal behaviour in the presence of psychosocial risk (Sjoberg et al. 2007). More recently, a main effect of low activity *MAOA* alleles on risk for conduct disorder in females but not in males was detected; but a significant interaction with adversity was not observed (Prom-Wormley et al. 2009).

Furthermore, with regard to the possible interaction with both sex and stress, the evidence that *MAOA* transcription may be regulated by both androgens and glucocorticoids (via the HPA axis) may provide a mechanistic insight (see Craig 2007a). Comprehensive studies show that activation of the *MAOA* promoter region by glucocorticoids and androgens is regulated differently by R1 (RAM2/CDCA7L) and Sp1 transcription factors. It has been demonstrated that androgens interact directly with the third of the glucocorticoid/androgen response elements (GRE/ARE), which also appears to act indirectly with Sp1 (Ou et al. 2006). Glucocorticoid activation of transcription at these sites is stronger than that observed for androgens and, as they compete for the same site; it is possible that high testosterone levels may lead to an overall lower expression of *MAOA* (Ou et al. 2006). This remains to be confirmed. Of additional interest in this context is the recent observation that levels of *MAOA* activity determined by the promoter VNTR appear to interact non-additively with testosterone in predicting antisocial behaviour (as measured by the Brown–Goodwin lifetime scale aggression score). Whilst high levels of testosterone are associated with increased scores, individuals with the high activity MAOA alleles behave similarly to those with lower testosterone levels. As the authors comment, this may explain in part the lack of consistency in attempts to correlate testosterone and violence (Sjoberg et al. 2008).

## Brain imaging results support the involvement of MAOA

Meyer-Lindenberg et al. (2006) have shown that low activity *MAOA* genotype in healthy males appeared to predicate significant reductions in volume of virtually the entire

cingulated gyrus and bilateral amygdalae. There were also genotype-dependent differences in amygdala activation during emotional arousal. They observed a significant sex-specific genotype interaction with only males increasing the volume of their bilateral lateral orbitofrontal cortex (OFC) by 14% volume in low activity genotypes relative to high-activity genotypes; however, no genotype-dependent structural changes were present in this region in women. Blood oxygenation level-dependent (BOLD) fMRI studies showed that in response inhibition task, whilst a greater response in healthy males was observed in the Brodmann's area in high activity *MAOA* genotypes, in low activity genotypes a greater response was observed in the right superior parietal cortex and bilateral extrastriate cortex (Passamonti et al. 2006). In contrast to the general failure to detect main effects of the MAOA genotype in association studies, Eisenberger et al. (2007) reported a direct effect of genotype on aggression traits in their imaging cohort, with both sexes reporting higher trait aggression if they were low activity. They also showed greater dorsal anterior cingulate cortex (dACC) reactivity suggesting that the MAOA–aggression relationship was mediated by greater reactivity of this brain region to social exclusion.

In the first attempt to correlate brain MAOA activity measured by positron emission tomography with the labelled ligand, $C^{11}$chlorgyline, no significant differences were observed between the high- and low-activity genotypes, although a trend for higher activity was observed in the predicted direction for the visual cortex of high *MAOA* individuals (Fowler et al. 2007). In subsequent publications by the same group (Alia-Klein et al. 2008a, b, 2009), it was shown that lower brain activity in cortical and sub-cortical brain regions correlated with higher self reported trait aggression (observed in both high and low genotype groups); however, in a challenge which involved emphatically delivering the word *NO,* carriers of the low *MAOA* genotype differed in reactions of the brain regions involved in the control of anger, which may underlie their greater vulnerability to aggressive behaviour.

It seems, therefore, that genotype–brain and genotype–behaviour relationships are developmentally complex. Other detailed functional, structural and connectivity investigations have suggested that the low activity *MAOA* allele adversely prejudices information processing within the amygdala, rostral cingulate and medial prefrontal cortex. Reduced rates of metabolism of low activity carriers lead to altered serotonin and NE levels. If this occurs during a critical window for the development of corticolimbic circuitry, this may disrupt normal social and emotional adjustment leaving individuals more vulnerable to the influence of adverse early life experience (see Buckholtz and Meyer-Lindenberg 2008).

## Postscript: the potential role of epigenetics

Following the intriguing observations concerning the methylation of the glucocorticoid receptor promoter in rat pups exposed to maternal deprivation and their subsequent behavioural deficits (Weaver et al. 2004), it has been shown that adult male rats which had been exposed to maternal deprivation showed increased inter-male aggressiveness (Veenema et al. 2007). The potential for similar molecular mechanisms in human aggression provides an intriguing area for subsequent research and it is of potential relevance that there is evidence for an apparently analogous methylation of the glucocorticoid receptor gene in humans as revealed by studies on violent suicide victims who had been exposed to early adverse life events (McGowan et al. 2009). Of specific interest in this context is the report of Pinsonneault et al. (2006), who demonstrated CpG methylation of the MAOA promoter region in female, but not male, brain tissue; however, the possible significance of this in context of G × E interactions remains to be elucidated.

It may be that in the absence of substantial and widely replicated main effects of the genes investigated to date, the future of research in the genetics of human aggression lies in the area of epigenetic modifications resulting from environmental interaction. This emphasises the need to document adequately a range of environmental variables, particularly centred on early trauma and persistent stress, for those individuals who will form the next cohorts for whole genome studies. There also remains the possibility that genome features (particularly those lying out of reach of current SNP based screening techniques) may have a major contribution to the aetiology of aggression. Such features may include rare copy number variants and complex tandem repeats. It is clear that there is an exciting range of new directions in which to pursue genome research on human aggression.

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