# Sex steroid–related candidate genes in psychiatric disorders

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Sex steroids readily pass the blood-brain barrier, and receptors for them are abundant in brain areas important for the regulation of emotions, cognition and behaviour. Animal experiments have revealed both important early effects of these hormones on brain development and their ongoing influence on brain morphology and neurotransmission in the adult organism. The important effects of sex steroids on human behaviour are illustrated by, for example, the effect of reduced levels of these hormones on sexual drive and conditions such as premenstrual dysphoric disorder, perimenopausal dysphoria, postpartum depression, postpartum psychosis, dysphoria induced by oral contraceptives or hormonal replacement therapy and anabolic steroid–induced aggression. The fact that men and women (as groups) differ with respect to the prevalence of several psychiatric disorders, certain aspects of cognitive function and certain personality traits may possibly also reflect an influence of sex steroids on human behaviour. The heritability of most behavioural traits, including personality, cognitive abilities and susceptibility to psychiatric illness, is considerable, but as yet, only few genes of definite importance in this context have been identified. Given the important role of sex steroids for brain function, it is unfortunate that relatively few studies so far have addressed the possible influence of sex steroid–related genes on interindividual differences with respect to personality, cognition and susceptibility to psychiatric disorders. To facilitate further research in this area, this review provides information on several such genes and summarizes what is currently known with respect to their possible influence on brain function.

Les stéroïdes sexuels franchissent facilement la barrière hémato-encéphalique et les récepteurs de ces agents sont abondants dans des régions du cerveau importantes pour la régulation des émotions, la cognition et le comportement. Des expériences effectuées sur des animaux ont révélé que ces hormones avaient des effets importants durant le développement du cerveau et des effets continus sur la morphologie du cerveau et la neurotransmission dans l'organisme adulte. Les effets importants des stéroïdes sexuels sur le comportement humain sont illustrés, par exemple, par l'effet qu'une baisse des concentrations de ces hormones a sur la libido et sur des problèmes comme le trouble dysphorique prémenstruel, la dysphorie périménopausique, la dépression postnatale, la psychose postnatale, la dysphorie causée par les contraceptifs oraux ou une hormonothérapie de remplacement et l'agressivité provoquée par les stéroïdes anabolisants. Les différences entre les hommes et les femmes (comme groupes) en ce qui a trait à la prévalence de plusieurs troubles psychiatriques, à certains aspects de la fonction cognitive et à certaines caractéristiques de la personnalité sont peut-être aussi le reflet d'une influence des stéroïdes sexuels sur le comportement humain. Le caractère héréditaire de la plupart des traits de comportement, y compris la personnalité, les aptitudes cognitives et la vulnérabilité aux maladies psychiatriques, est important, mais jusqu'à maintenant, on a identifié quelques gènes seulement qui ont une importance définitive dans ce contexte. Étant donné le rôle important des stéroïdes sexuels dans la fonction cérébrale, il est malheureux que l'on ait peu étudié jusqu'à maintenant l'influence possible des gènes reliés aux stéroïdes sexuels sur les différences entre individus en ce qui a trait à la personnalité, à la cognition et à la vulnérabilité aux troubles psychiatriques. Afin de faciliter des recherches plus poussées dans ce domaine, cette synthèse présente de l'information sur plusieurs de ces gènes et résume ce que l'on connaît actuellement de leur influence possible sur la fonction cérébrale.

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## Introduction

Sex steroids readily enter the brain, and receptors for them are found in brain areas known to be of importance for emotions, cognition and behaviour. Animal experiments have revealed that these hormones have both an important early and permanent influence on brain development and an ongoing influence on brain neurotransmission in the adult organism. The influence exerted by sex steroids on animal behaviour, including sexual activity and aggression, is exerted by both these mechanisms.[1–4] That sex steroids also influence behaviour in humans is shown by the reduction in libido that often follows a decrease in serum sex steroids and by conditions such as premenstrual dysphoric disorder (where the symptoms coincide with sex steroid fluctuations in serum and can be abolished by means of ovariectomy or treatment with ovulation inhibitors), postpartum depression, dysphoria induced by oral contraceptives and changes in behaviour induced by anabolic steroids.[5–8]

Although some aspects of sexual dimorphism may be attributable to factors other than sex steroids,[9,10] the hypothesis that sex hormones play a role in the regulation of mood and behaviour also gains support from the fact that a large number of psychiatric conditions, including depression, panic disorder, generalized anxiety disorder, social phobia and eating disorders, are more prevalent in women than in men. In contrast, alcoholism, attention-deficit hyperactivity disorder and autism are more common in men. As well, with respect to normal personality traits, there are subtle but clear differences between women and men at the group level (e.g., with respect to anxiety-related traits). Similarly, certain aspects of cognitive abilities appear to differ slightly between the sexes.[3,4]

Autism is a disorder of particular interest in regard to the possible role of sex steroids; there is evidence suggesting that subjects with autism are characterized by a brain that, in certain aspects, may be regarded as unusually masculinized.[3] Transsexualism is another condition for which aberrations in the early organizational influence of sex steroids on the brain is likely to be of critical importance (see below).

Knowing from twin and family studies that most psychiatric disorders are to a greater or lesser extent hereditary, numerous research groups are currently engaged in the search for candidate genes influencing the risk for psychiatric morbidity. This line of research has been characterized by considerable enthusiasm that has lately, however, been combined with a certain disappointment: identifying susceptibility genes for common psychiatric disorders has proven more difficult than anticipated by many researchers. The list of genes found to be associated with certain psychiatric disorders or certain aspects of behaviour is nevertheless slowly expanding and now includes the serotonin transporter gene, which is associated with anxiety traits[11]; the catechol-*O*-methyltransferase (*COMT*) gene, which is associated with cognition[12]; the apolipoprotein E gene, which is associated with Alzheimer disease[13]; and several genes, such as the disrupted in schizophrenia (*DISC1*) and neuregulin 1 genes, which are associated with schizophrenia.[14]

In regard to the association between sex steroids and psychiatric disorders or traits showing a clear sex difference in prevalence, the genes regulating sex steroids should be worthy candidates for exploration. As yet, studies on the possible influence of such genes on mood and behaviour have been relatively sparse. To facilitate further research in this area, this review provides information on several candidate genes related to sex steroids and summarizes what is currently known about their possible relation to brain and behaviour. Obviously, a large number of genes may directly or indirectly influence sex steroids and, hence, be regarded as sex steroid–related. For the sake of brevity, we focus on genes encoding sex steroid receptors (for which we summarize most published findings in Table 1) and receptor coregulators; however, we also mention certain genes coding for relevant enzymes. Given the scarcity of studies in this area, we also mention studies with small sample sizes or otherwise marred by shortcomings in design or methods.

Given the organism's remarkable capacity for compensation and adaptation, it may seem counterintuitive that a single polymorphism in a single gene should exert any major impact on the activity of the sex steroids and on aspects of the phenotype that are under the influence of these hormones. Because one should therefore probably not expect large effect sizes in association studies focusing on a single polymorphism, a reasonable strategy in future studies might be to assess the possible influence of interactions between several polymorphisms within the same gene (polymorphism × polymorphism interactions) or between polymorphisms in different genes that influence the sex steroid pathway in different ways (gene × gene interactions). As yet, there are few studies of sex steroids investigating the importance of polymorphism × polymorphism interactions and gene × gene interactions. Consequently, with some exceptions,[47–50] most studies discussed in this review have addressed the possible importance of a single polymorphism (or haplotype) in a single gene.

## Sex steroid receptors

### *General comments*

The sex steroid receptors are ligand-activated transcription factors that bind to specific hormone response elements in their target genes. They are abundant in brain areas known to be important for the regulation of emotions, cognition and behaviour (i.e., the hypothalamus, amygdala, cerebral cortex, hippocampus and brain stem).[1,51,52] The expression of these receptors is often characterized by a certain sexual dimorphism.[53]

There are 2 subtypes of estrogen receptors: α and β.[54] In addition, several isoforms of each subtype have been reported.[55] The 2 estrogen receptor subtypes have comparable affinities to estradiol, but many other ligands show preferential binding to one or the other of them. The 2 subtypes also differ with respect to tissue distribution and coregulator interactions.[56,57]

So far, there seems to be only a single subtype of the androgen receptor and the progesterone receptor. Alternative splicing of the amino terminal of androgen receptor and

progesterone receptor genes, however, results in different isoforms displaying differences in both expression and function.[58,59]

### *Estrogen receptor α gene*

The human estrogen receptor α gene (*ESR1*) is located on chromosome 6q25.1[60] and composed of 8 exons. A large number of polymorphisms in this gene have been identified,[61–64] none of which has as yet been shown beyond doubt to be functional. However, it has been speculated that a TA repeat located upstream from exon 1 may influence the tissue-specific expression of the gene. This repeat is in strong linkage disequilibrium with other polymorphisms in the 5′ region of the gene, such as the PvuII (IVS1–397 T/C; rs2234693) and XbaI (IVS1–351 A/C; rs9340799) polymorphisms in intron 1. It has been suggested that the PvuII single nucleotide polymorphism (SNP) produces a binding site for a specific transcription factor[61] that may affect gene expression.

In several studies with high power to detect associations, the TA repeat, PvuII and XbaI polymorphisms in the *ESR1* gene have been found to influence bone mineral density, fracture risk,[65,66] risk for cardiovascular disease[62,67,68] and risk for breast cancer.[64,69,70] Although strong, these associations are not undisputed.[71]

Given the well-established role of estrogen receptor α on brain development and function, it is not surprising that possible associations between the *ESR1* gene and various behavioural phenotypes have been the subject of several studies (Table 1). Comings and coworkers[31] have reported an association between a long TA repeat polymorphism in *ESR1* and high anxiety scores in men; moreover, in 2 subsequent studies assessing a large number of genes by means of multivariate analysis, the same research group confirmed an association between this polymorphism and personality traits (measured by means of the Temperament and Character Inventory [TCI])[37] as well as an association with conduct disorder.[38] Using the the Karolinska Scales of Personality (KSP), we examined the possible association between the same estrogen receptor α repeat polymorphism and personality traits in women recruited from the normal population[39]; this study revealed an association between short length of the estrogen receptor α TA repeat polymorphism and high scores on scales related to neuroticism, psychoticism and irritability. In a longitudinal study of children and adolescents, haplotypes comprising the TA repeat as well as the PvuII and XbaI polymorphisms also were associated with anxiety-related personality traits.[40] Moreover, in a large sample from the elderly population, a PvuII and XbaI haplotype was associated with the likelihood of displaying anxiety in women but not in men; in contrast, there was no association with depression.[41] Conversely, in another study, the PvuII polymorphism was found to be associated with depression in Chinese women.[36]

In a recent study investigating 16 SNPs in *ESR1* in a sample of patients with premenstrual dysphoric disorder and symptom-free control subjects, an association was found between diagnosis and a haplotype in intron 4. Further, the significant associations with *ESR1* haplotypes were observed only in those with the Val/Val genotype of the Val158Met polymorphism in the *COMT* gene (see below).[30] Although this finding is intriguing, it must, because of the small sample size, be considered as preliminary until replicated.

Interestingly, recent data suggest that the PvuII polymorphism is associated with an increased risk for schizophrenia as well as with ESR1 expression in the human brain.[72] Moreover, the same polymorphism has been associated with amygdala volume measured with magnetic resonance imaging in a large, elderly population.[73] Finally, it has been suggested that *ESR1* polymorphisms (PvuII and XbaI) are associated with various forms of cognitive impairment.[74,75]

Taken together, the evidence for associations between *ESR1* polymorphisms and anxiety traits, not least in women, is fairly strong. Intriguing but still preliminary reports suggest that *ESR1* variants may be important also for premenstrual dysphoric disorder, depression and schizophrenia.

### *Estrogen receptor β gene*

The human estrogen receptor β gene (*ESR2*) is located on chromosome 14q22–24. The gene is composed of 8 exons[76] and has several polymorphsisms,[44,64,77,78] of which a polymorphic CA repeat in intron 5[79] and 2 common SNPs — 1 at position 1730 (G730A; rs4986938) in the 3′ untranslated region and 1 silent mutation at position 1082 (G1082A; rs1256049)[43] in exon 5 — are the most studied. To date, only a single clearly functional polymorphism in *ESR2* (F289L), identified specifically in African populations, has been reported[80]; this polymorphism leads to reduced estrogen binding affinity and impaired response to transactivation induced by 17β-estradiol. Associations between *ESR2* polymorphisms and breast cancer,[64] bone mass density,[77] prostate cancer[78] and risk factors for cardiovascular disease[81] have been reported in studies based on large populations.

Several investigations also suggest an influence of *ESR2* variants on the brain (Table 1). For example, associations have been reported between *ESR2* polymorphisms and Alzheimer disease[82,83] and also with early-onset Parkinson disease.[84] Moreover, 2 studies have revealed associations between the G1082A polymorphism and anorexia nervosa,[42,43] and another study has suggested an association between the *ESR2* gene and bulimic disease.[44] Preliminary evidence from a small group of postmenopausal Japanese women suggests an association between menopausal complaints, including mood symptoms, and the CA repeat of *ESR2*.[45] Further, a recent report provides some evidence for an association between longer CA repeats and risk for depression in an adolescent population.[29] No associations between the G1730A polymorphism and bipolar disorder could be seen in a sample comprising parent and proband trios.[85]

Taken together so far, few association studies of psychiatric disorders have included the estrogen receptor β gene. There is some weak evidence for associations between *ESR2* polymorphisms and eating disorders in women. However, because animal data indicate that this gene is of considerable importance for behaviour, it clearly deserves further study.

*Progesterone receptor gene*

The human progesterone receptor gene (*PGR*) is located on chromosome 11q22–23[86] and composed of 8 exons. The receptor exists in 2 molecular forms, PR-A and PR-B; these differ only at the amino terminus, with PR-B containing an addi-

**Table 1: Investigations of polymorphisms in sex steroid receptor genes in relation to psychiatric disorders and behaviour**

| Gene | Polymorphism | Trait | No. of patients; (M/F) | No. of subjects or control subjects; (M/F) | Ethnicity | Main finding | Study |
|---|---|---|---|---|---|---|---|
| *AR* | CAG/GGC repeats | Tourette syndrome, ADHD and conduct disorder scores | 250 (202/48) | 52 (19/33) | White | Individuals with long CAG and long GGC had lower ADHD, CD, ODD scores. | Comings et al.[15] |
| *AR* | CAG/GGC repeats | Personality (TCI) | | 204 (204/0) | White | Individuals with long CAG or long GGC had higher self-transcendence scores. | Comings et al.[16] |
| *AR* | GGC repeat | Measures of aggression, hostility (Buss–Durkee Inventory, DSQ, TCI, LOC, sexual habits in men, parental divorce and age of menarche in women. | | 285 (121/164) | White | In men, the presence of the 16 repeat allele of the GGC was associated with traits related to aggression, hostility and impulsivity, as well as with sexual compulsions and the lifetime number of sex partners. In women, homozygosity for the 16 repeat allele was associated with divorce of parents, absent father and earlier age of menarche. | Comings et al.[17] |
| *AR* | GGC repeat | Adverse childhood experiences | | 1702 (794/908) | White | No associations. | Jorm et al.[18] |
| *AR* | CAG repeat | Eysenck psychoticism | | Adults: 588 (0/588) Adolescents: 912 (457/455) | White | Weak associations between short CAG repeats and high psychoticism scores in women, and low psychoticism scores in adolescent boys. | Loehlin et al.[19] |
| *AR* | CAG/GGC repeats | Eysenck psychoticism | | 1698 (793/905) | White | Short CAG repeats associated with high psychoticism in men. | Turakulov et al.[20] |
| *AR* | CAG repeat | Personality (KSP) | | 340 (186/154) | White | Long CAG repeats associated with high scores for Muscular Tension and Lack of Assertiveness. No associations after correction for multiple testing. | Jönsson et al.[21] |
| *AR* | CAG repeat | Antisocial behavioural traits | | 2096 (1007/1089) | White | Men with medium CAG repeat lengths scored higher for antisocial traits. | Prichard et al.[22] |
| *AR* | CAG repeat | Schizophrenia | 225 (108/117) | 247 (125/122) | Chinese | No associations. | Tsai et al.[23] |
| *AR* | CAG repeat | Violent criminal activity | 146 (146/0) | 108 (108/0) | Chinese | No association between the *AR* repeat length and violent convicts. More violent/criminal cases than control cases carried a short CAG repeat polymorphism. | Cheng et al.[24] |
| *AR* | Mutation screen | Alcoholism, social phobia, schizophrenia, bipolar disorder, ADHD, autism | 173 | | | R726L was found in 1 of 17 scanned alcoholics, and P516S was identified in 1 of 3 phobia patients. | Yan et al.[25] |
| *AR* | CAG repeat | Depression | | 1000 (1000/0) | 958 white | Men with low total testosterone levels and short CAG repeats had increased risk for depression. | Seidman et al.[26] |
| *AR* | CAG repeat | Depression | | 1246 (1246/0) | 525 black, 721 white | Interactive effect of CAG repeat length and testosterone levels on depressive symptoms. | Colangelo et al.[27] |
| *AR* | CAG repeat | Depression | | 266 (266/0) | | No associations. | T Sjoen et al.[28] |
| *AR* | CAG repeat | Depression | 102 (0/102) | 150 (0/150) | Chinese | Female adolescent patients with depression had shorter mean CAG repeat length than control subjects. | Geng et al.[29] |
| *ESR1* | 16 SNPs of *ESR1*; *COMT* Val/Met | PMDD | 91 (0/91) | 56 (0/56) | White | 4 SNPs in intron 4 were associated with PMDD. The significant associations were only seen in carriers of the *COMT* Val/Val genotype. | Huo et al.[30] |
| *ESR1* | TA repeat | Personality (SCL-90) | | 179 (179/0) | Mainly white | Individuals homozygous for the long TA repeat displayed higher anxiety scores. | Comings et al.[31] |
| *ESR1* | PvuII, XbaI | Schizophrenia | 125 (50/75) | 142 (60/82) | Chinese | No associations. | Ouyang et al.[32] |
| *ESR1* | PvuII, XbaI | Bipolar disorder, puerperal psychosis | 219 (92/127) | 219 (94/125) | White | No associations. | Jones et al.[33] |

*Continued*

tional stretch of amino acids.[58] This domain plays an important role in identifying target genes that can be activated by the PR-B protein but not by the PR-A protein. The expression ratio of the 2 PR isoforms in the brain varies during fetal development[87,88] and as a result of the estrous cycle[89,90] and also differs between males and females.[91–93] Administration of

**Table 1 continued**

| Gene | Polymorphism | Trait | No. of patients; (M/F) | No. of subjects or control subjects; (M/F) | Ethnicity | Main finding | Study |
|---|---|---|---|---|---|---|---|
| *ESR1* | Mutation screen | Schizophrenia, bipolar disorder, puerperal psychosis, autism, ADHD, alcoholism | 240 | | White | 3 missense mutations (H6Y, K299R, P146Q) were found in 1 patient each with bipolar disorder, puerperal psychosis and alcoholism. | Feng et al.[34] |
| *ESR1* | Mutation screen | Bipolar disorder, puerperal psychosis | 231 (39/192) | 110 (38/72) | White | No association to the involvement of any of the rare *ESR1* variants. | Middle et al.[35] |
| *ESR1* | PvuII, XbaI | MDD | 154 (65/89) | 226 (100/126) | Chinese | P allele of the PvuII SNP was more frequent in female patients with depression compared with female control subjects. No association in men or in suicide attempters. | Tsai et al.[36] |
| *ESR1* | TA repeat | Personality (TCI) | | 204 (204/0) | Mainly white | TA repeat length associated with personality traits. | Comings et al.[37] |
| *ESR1* | TA repeat | Conduct disorder | 250 (202/48) | 52 (19/33) | Mainly white | TA repeat length associated with conduct disorder. | Comings et al.[38] |
| *ESR1* | TA repeat | Personality (KSP) | | 172 (0/172) | White | A short TA repeat associated with higher anxiety and nonconformity scores. | Westberg et al.[39] |
| *ESR1* | PvuII, XbaI, TA repeat | Personality (many different scales used) | | 680 | White | 2-locus genotypes of the PvuII or XbaI SNPs and the TA repeat was associated with high anxiety scores in children and adolescents. | Prichard et al.[40] |
| *ESR1* | TG repeat | Antisocial behavioural traits | | 2096 (1007/1089) | White | Long TG repeat alleles were associated with higher scores for antisocial traits in men. Associations did not survive correction for multiple testing. | Prichard et al.[22] |
| *ESR1* | PvuII, XbaI | Anxiety/ depression | | Anxiety: 2468 (1133/1335) Depression: 4098 (1694/2404) | White | An *ESR1* haplotype was associated with anxiety in women, but not in men. No relation observed with depressive symptoms. | Tiemeier et al.[41] |
| *ESR1* | PvuII, XbaI, TA repeat | Anorexia nervosa | 170 (0/170) | 152 (0/152) | White | No associations. | Eastwood et al.[42] |
| *ESR2* | 6 SNPs | PMDD | 91 (0/91) | 56 (0/56) | White | No associations. | Huo et al.[30] |
| *ESR2* | G1082A, A1730G, mutation screen | Anorexia nervosa, bulimia nervosa, obesity | Anorexia nervosa: 50 Bulimia nervosa: 28 Obesity: 96 | 25 | White | A 21 bp deletion (codons 238–244) was detected in 2 obese probands and an underweight individual. A 846G→A transition leading to a nonconservative amino acid substitution (G-250-S) was found in 2 obese male probands. 1082G allele was more frequent in anorexia nervosa patients. | Rosenkranz et al.[43] |
| *ESR2* | G1082A, A1730G | Anorexia nervosa | 170 (0/170) | 152 (0/152) | White | 1082A allele was more frequent in anorexia nervosa patients. | Eastwood et al.[42] |
| *ESR2* | G1082A; A1730G; cx+56 | Bulimic disease | 76 (0/76) | 60 (0/60) | White | 1730A and cx+56A alleles were more frequent in patients than in control subjects. A conserved mutation (R221G) was identified in 1 patient. | Nilsson et al.[44] |
| *ESR2* | CA repeat | Perimenopausal symptoms | 51 (0/51) | | Japanese | The CA repeat length associated with menopausal problems such as vasomotor symptoms, psychological symptoms (including depressed mood) and premenstrual symptoms. | Takeo et al.[45] |
| *ESR2* | CA repeat | Depression | 102 (0/102) | 150 (0/150) | Chinese | Patients had shorter mean *ESR2* CA repeat length than control subjects. Short repeats were more prevalent in patients. No effects of *ESR1* TA repeat. | Geng et al.[29] |
| *PGR* | G331A | Panic disorder | 72 (24/48) | 452 (199/253) | White | 331A allele associated with panic disorder in women. | Ho et al.[46] |

ADHD = attention-deficit hyperactivity disorder; *AR* = androgen receptor gene; CD = conduct disorder; *COMT* = catechol-*O*-methyltransferase gene; DSQ = Defense Style Questionnaire; *ESR1* = estrogen receptor $\alpha$ gene; *ESR2* = estrogen receptor $\beta$ gene; F = female; KSP = Karolinska Scales of Personality; LOC = Locus of Control Test; M = male; MDD = major depressive disorder; ODD = oppositional defiant disorder; *PGR* = progesterone receptor gene; PMDD = premenstrual dysphoric disorder; SCL-90 = Symptom Checklist-90; SNP = single nucleotide polymorphism; TCI = Temperament and Character Inventory.

estrogen and progesterone has been shown to influence the expression ratio, and some of these variations may therefore be induced by these hormones.[89,92,94] Notably, PR-A has recently been shown to play a key role in both hormone-dependent and hormone-independent facilitation of female sexual behaviour.[95]

The *PGR* gene contains several genetic variants.[64,70,96–99] For example, intron 7 of the gene contains a 306 bp ALU insertion polymorphism[97] called PROGINS that has recently been shown to decrease the stability of the PGR transcript, which diminishes the response of the receptor to progesterone.[100] The PROGINS polymorphism has been thoroughly studied in relation to ovarian[101] and breast[99] cancer, but with conflicting results.

The PROGINS polymorphism is linked with an SNP in exon 4 causing a valine-to-leucine substitution (V660L), as well as with a silent SNP in exon 5. Functional characterization of the V660L variant in an in vitro study revealed that the progesterone receptor encoded by the less common variant had a similar hormone binding capacity and hormone dissociation rate but higher transcriptional activity, compared with the wild-type receptor.[101]

There is also a functional polymorphism at position +331 (rs10895068) in the promoter region of the *PGR* gene that has been shown to increase the transcription of the gene and to favour the expression of the PR-B isoform in an endometrial cancer cell line.[96] This polymorphism is located adjacent to a binding site for the GATA family of transcription factors. GATA5, which is expressed in breast cancer cell lines but not in normal mammary tissue, activated progesterone receptor expression in cells expressing the +331A variant of the receptor more strongly than in cells expressing the G allele.[102] The G331A polymorphism has been found to be associated with risk for endometrial cancer,[96,103] ovarian cancer[104] and breast cancer,[102,105] as well as with serum prolactin levels in healthy women.[106]

According to the false suffocation alarm hypothesis, panic disorder is due to abnormalities in the brain stem regulation of ventilation.[107] Because progesterone is important for the regulation of breathing,[108,109] an involvement of this hormone in panic disorder is well in line with this hypothesis and has been suggested by Klein.[107] Prompted by this and by the fact that panic disorder displays a considerable sex difference with respect to prevalence, with women being afflicted more often than men,[110] we studied the possible association between *PGR* variants and panic disorder and found the A allele of the G331A SNP to occur more frequently in patients than in control subjects.[46] After the cohort was split according to sex, this association was seen in female patients only, with an odds ratio of 3.5. The PROGINS polymorphism was, however, not associated with the disorder.

### *Androgen receptor gene*

The androgen receptor gene (*AR*) is located on chromosome Xq11–12 and composed of 8 exons.[111,112] Exon 1 of the gene, encoding the amino terminal domain, contains 2 polymorphic trinucleotide repeats: a CAG repeat encoding a polyglutamine stretch and a GGC repeat encoding a polyglycine stretch.

The polymorphic polyglutamine stretch appears to influence the function of the receptor as transcription factor, and relatively long fragments are associated with a low level of receptor function.[113–115] Studies aiming to elucidate the molecular mechanism for this relation between repeat length and receptor function suggest that the CAG repeat influences interactions between *AR* and its coactivators. In one study, long repeat regions were shown to act as inhibitors of the interactions between coactivators and the receptor protein[116]; in another study, *AR*s with deleted polyglutamine regions showed enhanced interactions with coactivators.[117] Conversely, the functional consequences of the GGC repeat polymorphism remain inconsistent: 3 studies indicate a positive correlation between GGC repeat number and *AR* gene activity or protein amount,[59,118,119] 1 suggests an inverse correlation between repeat length and AR protein amount,[120] and 1 suggests higher activity for the most common allele.[121]

Clinical studies strongly support the notion that the CAG repeat sequence of the *AR* gene is of functional importance. The normal size range of the repeat is between 4 and 36. A substantial expansion (40–72 repeats) is the cause of a rare X-linked motor neuron disorder in men (Kennedy disease, or spinal and bulbar muscular atrophy)[122] that is associated with moderate androgen insensitivity.[123–125] A large number of studies have reported associations between short CAG or GGC repeats and increased risk of prostate cancer and benign prostate hyperplasia,[126–129] as well as decreased risk of infertility.[130–132] Moreover, associations between these repeat polymorphisms and several other androgen-related diseases and traits in men have been reported, including male-pattern baldness, bone density and cardiovascular risk factors.[133,134]

There are also an increasing number of studies on the importance of *AR* gene repeats in women. In female populations, associations have been suggested between repeat length and serum androgen levels,[135] breast cancer,[136,137] ovarian cancer,[138] bone mass density,[139] obesity[140] and left-handedness.[141]

Recent investigations also suggest an influence of *AR* repeat polymorphisms on the brain (Table 1). In 2 small studies of CAG repeat length in the androgen receptor gene and Alzheimer disease, short androgen receptor alleles were associated with increased disease risk[142,143]; moreover, in men, this effect was strengthened if short androgen receptor alleles were combined with low levels of serum testosterone.[143] Conversely, in a prospective study of older men, short CAG repeat alleles were associated with better performance on 3 cognitive tests.[144]

In a recent study, we found a relation between *AR* repeat length and the personality traits of impulsiveness and monotony avoidance as measured with the KSP in 2 separate samples of men, one comprising 141 middle-aged subjects from the normal Swedish population and one comprising a smaller group of subjects from a forensic psychiatry cohort (Westberg and colleagues, unpublished). Similarly, others have reported associations between *AR* repeat length and personality traits, externalizing behaviour and antisocial traits.[15,19–22]

Several studies, although not entirely consistently, suggest that low serum testosterone levels are associated with risk for depression and/or depressive symptoms in men.[145] Three studies have investigated whether *AR* CAG repeat length

may influence this possible relation between testosterone levels and depression.[26–28] Two of these studies, conducted in large samples of young[26] and middle-aged[27] men, suggest that individuals having short CAG repeats and low testosterone display enhanced risk for depression. However, this relation was not observed in a smaller population of older men.[28]

Studies on the possible association between *AR* repeat polymorphisms and schizophrenia[23] or violent criminal activity[24] have yielded negative results. Rare mutations in *AR* have been observed in patients with alcoholism and social phobia.[25]

Taken together, investigations conducted so far suggest that a short CAG repeat in combination with low testosterone levels may increase the risk for depression in men. Preliminary evidence from several studies also suggests that *AR* repeat polymorphisms may be of importance for interindividual differences in personality traits.

## Other sex steroid–related genes

### *Coregulators*

Coregulators of sex steroid receptors play an important role for tissue-specific actions of sex steroids.[57] Several coregulators of importance for brain function have been identified[146]; for example, both the steroid receptor coactivator gene and CREB-binding protein have been shown to be involved in estrogen receptor–mediated effects on sexual behaviour.[147] Moreover, the coactivator estrogen receptor–associated protein 140, which interacts with both estrogen receptor α and estrogen receptor β, displays its highest expression in the brain.[148] Another protein expressed in the brain that, among other tasks, serves as coactivator for sex steroid receptors, is E6-associated protein (UBE3A),[149] which is involved in the pathophysiology of Angelman syndrome.

Although there are as yet no studies on the possible influence of genes encoding sex steroid receptor coregulators on human behaviour, this group of genes clearly deserves further investigation.

### *Membrane-coupled receptors*

Rapid effects of sex steroids on neuronal cell firing as well as on behaviour, by means of nongenomic mechanisms, have been reported.[150] At least some of the rapid effects exerted by estrogens are probably mediated by a recently discovered G protein–coupled receptor, GPR30,[151] which is expressed in the brain.[152] *GPR30* should therefore be another interesting candidate for future association studies on behaviour related to sex steroids as well as psychiatric disorders. Moreover, the fact that progesterone metabolites interact with the γ-aminobutyric acid A ($GABA_A$) receptor[153] makes the different subunits of this receptor complex important candidates when the genetic basis for interindividual differences in progesterone responsiveness is addressed.

### *Genes regulating sex steroid levels in serum and brain*

The aromatase enzyme converts androgens into estrogens. The human aromatase gene (*CYP19*) is located on 15q21.1 and contains several genetic variants.[154,155] Associations have been revealed with hormone levels,[156–158] bone metabolism,[157,158] risk factors for prostate cancer,[129,159] endometriosis[160] and obesity.[156,161] Moreover, several reports have recently suggested that a variant of *CYP19* is a substantial risk factor for Alzheimer disease.[162,163] However, there are as yet few studies of this gene in other psychiatric disorders.

Transsexualism is a rare condition that has been suggested to be caused by aberrations in the early sexual differentiation of the brain, a process believed to involve estrogen receptors, androgen receptors and the aromatase enzyme. We have reported preliminary data indicating that interactions between the repeat polymorphisms in the *CYP19*, *ESR2* and *AR* genes may be of importance for male-to-female transsexualism.[48] When short and long repeat lengths were compared between groups, significant effects on the risk for developing transsexualism were revealed for all 3 polymorphisms as well as for the interaction between the *AR* and *CYP19* polymorphisms. Given the small number of transsexuals in this study, the results should be interpreted with caution. In a more recent study, however, we also found a nonsynonymous SNP in the aromatase gene to be associated with male-to-female transsexualism (Bergman and colleagues, unpublished).

A large number of studies have reported associations between other CYP genes and serum hormone levels.[164,165] Notably, polymorphisms in *CYP1A1*, *17HSD* and *CYP19* were recently shown to be associated with depressive symptoms in middle-aged women.[166] Moreover, in 2 recent studies, a functional polymorphism in the *CYP2C19* gene, encoding an enzyme that metabolizes sex steroids as well as serotonin, was associated with personality traits assessed with the TCI.[167,168] The *CYP2C19* polymorphism results in 3 phenotypic groups: homozygous extensive metabolizer, heterozygous extensive metabolizer and poor metabolizer. In a study by Ishii and colleagues,[167] the female extensive metabolizer group showed high scores on reward dependence, cooperativeness and self-transcendence. In contrast, a study by Yasui-Furukori and colleagues[168] showed an association between the extensive metabolizer genotype and low scores in harm avoidance but no associations with the other TCI dimensions.

The enzyme COMT metabolizes both estrogens and catecholamines such as dopamine and noradrenaline. The human *COMT* gene is located on chromosome 22q11.2 and contains many genetic variants,[169] several of which seem to be of functional importance.[170,171] The most studied of these is the valine-to-methionine substitution at codon 158 (rs4680) resulting in a protein with a lower enzyme activity, as shown both in vitro[172] and in vivo.[173] Strong evidence has been provided for associations between the *COMT* val-158-met polymorphism and cognitive function,[12,174] and there are also studies suggesting that this polymorphism is associated with both panic disorder[175,176] and obsessive–compulsive disorder,[177] as well as with personality traits.[178,179]

Usually, the association between the *COMT* gene and central nervous system–related traits such as cognition has been attributed to the importance of this gene for the metabolism of catecholamines. The possible importance of estrogen, which is

also metabolized by COMT, in this context should however not be ignored; notably, the val-158-met polymorphism has been associated with estrogen levels in both women[180,181] and men,[182] as well as with other estrogen-related phenotypes such as risk for breast cancer[183] and bone mineral density.[181,184] Interestingly, as recently reviewed,[185] most of the strong associations between *COMT* polymorphisms and psychiatric disorders, as well as personality traits, appear to be sex-specific.

Estrogens are known to downregulate COMT expression by estrogen receptor–mediated actions.[186] There is one polymorphism described in the vicinity of one of the estrogen response elements (ERE6) in the promoter region of the *COMT* gene[187] that may affect the estrogen receptor–mediated regulation of COMT expression. Sweet and colleagues[47] have reported that joint actions of alleles of the rs4680 and ERE6 polymorphisms exert a strong impact on risk for Alzheimer disease with psychosis. In women, a strong linear relation between the number of ERE6 C and rs4680 G alleles and the risk for Alzheimer disease with psychosis was reported, whereas in men the outcome was more complex.

Notably, enzymes required for the synthesis of sex steroids, as well as for functionally active sex steroid metabolites, are expressed locally within the brain; some of the sex steroids present in the central nervous system are thus probably produced locally.[188] For example, within the brain, progesterone is metabolized to allopregnanolone[189,190] that may influence behaviour by interacting with $GABA_A$ receptors (see above). The genes for the 5 α-reductase type 1 and type 2 enzymes, which are critical for this conversion, contain functional polymorphisms[191] that could be relevant for the study of psychiatric disorders for which allopregnanolone has been attributed importance, such as premenstrual dysphoric disorder. Given the importance of this enzyme for the formation of the active metabolite dihydrotestosterone from testosterone, the same genes are obviously also relevant candidates for any condition hypothesized to be related to the influence of androgens.

Polymorphisms in the sex hormone–binding globulin gene encoding the protein essential for the transport of sex steroids in blood have also been reported to influence sex hormone levels.[120,192] To date, however, there are no studies on the possible importance of these polymorphisms for behavioural traits.

It should be added that, needless to say, serum levels of sex steroids may also be influenced by other genes than those coding for enzymes and transporting proteins, including, for example, the genes coding for sex steroid receptors.[135,193,194] A further discussion on the complex regulation of sex steroid levels is, however, beyond the scope of this review.

## Concluding remarks

Despite the fact that sex steroids play a clear role in several psychiatric disorders, such as premenstrual dysphoric disorder and postpartum depression, and are likely to contribute to sex differences characterizing a number of other psychiatric disorders, the possible influence of polymorphisms in sex steroid–related genes on behaviour and psychiatric morbidity is still poorly explored. Accumulating data showing polymorphisms in several such genes to be of importance for various somatic conditions should encourage further research on their possible influence on brain and behaviour. The purpose of this review has been to summarize findings obtained in this area so far, with special focus on the genes coding for sex steroid receptors.

Whenever an association between a sex steroid–related gene variant and a certain behavioural trait is observed, this could of course indicate that sex steroids exert an ongoing influence on the trait in question. Importantly, however, given the critical role of sex steroids during brain development, such an association might, as well, be caused by an early organizing effect on the architecture of the brain.

Data available at this point suggest that *ESR1* polymorphisms influence interindividual differences in anxiety, at least in women, and that the CAG repeat of the *AR* gene, if combined with low testosterone levels, influences the risk for depression in men. There are also several other associations of potential importance that have been reported and warrant attempts for replication, as well numerous important issues that still wait to be addressed. Rather than focusing on single polymorphisms or genes, future studies in this field would probably benefit from examining possible interactions between different genes affecting sex steroid activity by means of different mechanisms. In addition, whenever possible, it is probably advantageous to combine genetic studies with assessment of hormone levels in serum.

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