Genetics and Behaviour

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9.1 Introduction

Behavioural genetics constitutes a wide research field focusing on genetic, as well as environmental contributors to phenotypic variance of behaviour.

There are different research methods to explore genetic contribution to behaviour:

(a) Animal studies: these are based on animal models simulating human behaviour, e.g. aggressive, impulsive, etc. Selective breeding or genetic manipulation allows studying gene effects on brain development and behaviour.
(b) Heritability studies: these involve quantitative research techniques aiming at determining heritability, e.g. genome-wide linkage studies of multiple alleles segregating within family members. Heritability studies include family, twin and adoption studies.
(c) Molecular genetic studies: these focus on the identification of susceptibility genes, e.g. association between DNA polymorphisms and behavioural traits. The most promising susceptibility alleles are the ones altering gene expression and thus protein levels. Molecular genetic studies include linkage and

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association studies. The latter constitute a common approach in the field of behavioural genetics. Roughly, they search for significant differences in genetic variant frequencies between individuals characterised by a specific behaviour and healthy controls.

(d) Mechanism studies: these focus on the investigation of the underlying biological mechanisms triggered by gene polymorphisms.

Still, it is almost impossible to base phenotypic expression of behaviour strictly on genes. A broad range of environmental factors is also influential. Thus, it is widely accepted that genetic factors (nature) and environmental factors (nurture) interact with each other. As a result, environmental factors can trigger behaviours for which there is a genetic predisposition (Caspi et al. 2002; Reif et al. 2007; Cicchetti et al. 2012). Gene-environment interaction or genotype-environment correlation (rGE) may be (a) passive, in which there is an association between inherited genotype and childhood environment, e.g. antisocial parents provide both genetic component and an environment promoting the development of antisocial behaviour, and (b) evocative, in which one factor promotes the other, e.g. a child genetically predisposed for aggression will manifest aggressive behaviour provoking others' harsh responses, which evoke in turn further manifestation of child's aggressive behaviour (Jaffee and Price 2008).

Behaviour varies between individuals, a phenomenon called "population variance". Such variance is statistically represented by a bell curve, depicting a "normal distribution". The tails of normal distribution represent individuals with low or high extremes of variance. The term "heritability" is used to describe the proportion of phenotypic variance that may be attributed to genetic factors, e.g. "heritability of 0.50" means that 50% of the variance across the population is explained by non-specific genotype differences. On the other hand, the term "environmental variance" is used to describe the proportion of phenotypic variance that can be explained by environmental factors.

The aim of this chapter is to provide recent research evidence for the association between genes and behaviour. In this first section, a short introduction revises basic knowledge of genetics and provides descriptive information about behaviours and personality traits studied in relation with genetics.

9.1.1 Genetic Variation

Humans are diploid organisms with 23 pairs of chromosomes, 22 somatic and 1 pair of sex chromosomes (female, XX; male, XY). Chromosomes contain all genetic information, coded for by DNA. DNA consists of two strands. Each strand consists of nucleotides. There are four main nitrogenous nucleotide bases, adenine (A), thymine (T), guanine (G) and cytosine (C). Purines consist of A and G while pyrimidines of T and C. These bases couple with each other forming base pairs (bp). Adenine pairs with thymine and guanine with cytosine, in such the two DNA strands are held together forming a double helix, which resembles graphically a ladder.

A DNA segment coding for a specific protein is called "gene", while the sum of genes forms one's "genome". Gene DNA sequences are not fully identical among all people. For instance, at a particular DNA position, one may have adenine whereas another guanine. This DNA variation is called "allele", resulting in wide phenotypic differences among humans. Each individual is a carrier of two alleles, since chromosomes are paired. One allele is of maternal and the other of paternal origin. An individual is homozygous when alleles are identical. When alleles are different, then there is heterozygosity for that particular gene allele. In most cases, individuals are heterozygous.

Alleles detected in at least one out of a hundred (1%) in a population constitute "DNA polymorphisms". Polymorphisms are the result of DNA damage or incorrect DNA replication. In cases of DNA alterations with deleterious effects, i.e. mutations, severe diseases may emerge. Such mutations are usually rapidly eliminated from a population, since mutant carriers are less likely to reproduce. In a broader sense, DNA polymorphisms are not associated with emerging pathology. They are rather the reason why each person is unique. Depending though on polymorphism, protein amount or protein structure may be altered. In this case, the polymorphism is considered "functional". Functional polymorphisms mapping at important sites may be associated with human traits and disorders. The most common polymorphisms are (a) single nucleotide polymorphisms (SNPs): these are formed by variation in a single nucleotide at a specific position. When a purine is changed into another purine or a pyrimidine into another pyrimidine, the polymorphism is called "transition". When a purine is changed into a pyrimidine, the polymorphism is called "transversion". Although there are some triallelic SNPs (i.e. three different base variations), for most SNPs, there are only two different alleles. Single nucleotide polymorphisms may be found at different locations within the genome, and most of them are "silent", caused by synonymous nucleotide changes leaving protein amino acid sequences unaltered (non-synonymous nucleotide changes are the ones altering amino acid sequence and possibly protein's function). Still, a SNP located at a gene's promoter region could be functional, affecting gene expression; (b) short insertion and deletion polymorphisms (INDELs): these constitute insertions (i.e. nucleotide gain, lengthening overall fragment) or deletions (i.e. nucleotide loss, shortening overall fragment) of up to 50 nucleotides at a single locus; and (c) variable-number tandem repeats (VNTRs): these are formed by genetic elements repeated in tandem arrays. They include micro- and minisatellites, primarily distinguished based on size and repeat pattern. Microsatellites or short tandem repeats (STRs) or simple sequence repeats (SSRs) consist of repeated nucleotide sequences ranging from 2 to 6 bp. Minisatellites consist of repeated sequences ranging from 11 to 65 bp.

In case of behavioural genetics, the term "risk allele" is used to describe polymorphic alleles associated with a specific behavioural phenotype. Still, it is extremely difficult to associate a specific behaviour strictly with a certain allele. Behavioural traits normally distributed in a population are attributed to multiple genes interacting with each other. Each gene shows relative limited effects, either enforcing or limiting a trait. Furthermore, gene expression is based on many other expressed genes. Altogether, "polygenic inheritance" (i.e. a complex gene pattern,

in some cases across different chromosomes) is involved in the phenotypic expression of human behaviour and personality. Lastly, "linkage disequilibrium" (LD) refers to the non-random association of alleles at two or more loci. Neighbouring alleles tend to co-segregate, i.e. be inherited together. Table 9.1 includes a brief glossary of genetic terms and abbreviations used in this chapter.

Table 9.1 Brief glossary of genetic terms and abbreviations

Terms and abbreviations	Definition
Diploid	A cell/organism with two sets of chromosomes, one of maternal and one of paternal origin
Chromosome	Structure located in the cell nucleus and formed by DNA coiled tightly around histones, the proteins supporting chromosome's structure
XX	Female
XY	Male
DNA	Deoxyribonucleic acid composed of nucleotides, encoding genetic information carried by chromosomes
DNA replication	Production of two identical DNA replicas from one original DNA molecule
Nitrogenous nucleotide bases	Adenine (A), thymine (T), guanine (G), cytosine (C)
Purines	Adenine (A) and guanine (G)
Pyrimidines	Thymine (T) and cytosine (C)
bp	Base pair, formed by nucleotide bases' coupling (adenine pairs with thymine and guanine with cytosine)
kb	Kilobase, unit equal to 1000 bp
Double helix	Two DNA strands coiled around each other
Genome	Sum of genes in an individual
Gene	DNA segment coding for a specific protein
Locus	The exact position of a gene on a chromosome
Gene's promoter region	DNA region initiating gene transcription (i.e. the first step of gene expression), in which a DNA segment is copied into messenger RNA (mRNA)
Gene's coding region	DNA sequence composed of exons, coding for a protein
Exon	DNA sequence encoding RNA, produced after introns have been removed via RNA splicing
Intron	DNA sequence removed by RNA splicing
Codon	Nucleotide triplet coding for an amino acid
Initiation or start codon	Nucleotide triplet defining the beginning of translation, i.e. protein formation. The most common start codon is AUG, coding for amino acid methionine
Amino acid	Structural units forming proteins
Allele	Gene variation due to different nucleotide arrangement, resulting in wide phenotypic differences (each individual carries one allele of maternal and one of paternal origin)
Major allele	The most common allele in a population; in most cases it is the ancestral, also called "wild" allele
Minor allele	The second most common allele in a population

Table 9.1 (continued)

Terms and abbreviations	Definition
Genotype	The combination of two alleles at a specific locus
Homo-/heterozygous	Due to chromosomal diploidy, there are two alleles for any given gene. Carriers of identical alleles at a specific position are homozygous, whereas carriers of different alleles are heterozygous for that particular gene
Alleles in phase	In diploids, "alleles in phase" or "gametic phase" refers to allele combination at different loci on the same chromosome, representing the original combination of maternal and paternal alleles
Risk allele	Allele associated with a specific behaviour or personality trait
Differential susceptibility	Vulnerability or protective effects provided by a gene under specific environmental conditions
DNA polymorphism	Allele detected in at least one out of a hundred in a population
SNP	Single nucleotide polymorphism formed by variation in a single nucleotide at a specific position
Transition	SNP, in which a purine is changed into another purine or a pyrimidine into another pyrimidine
Transversion	SNP, in which a purine is changed into a pyrimidine
Silent SNP	SNP caused by synonymous nucleotide changes leaving amino acid sequence unaltered
Functional SNP	SNP caused by non-synonymous nucleotide changes, altering amino acid sequence and possibly protein's function SNP located at gene's promoter region, affecting gene expression
INDEL	Short insertion and deletion polymorphism, including insertions or deletions of up to 50 nucleotides at a single locus
VNTR	Variable-number tandem repeat formed by genetic elements repeated in tandem arrays
Microsatellite	Short tandem repeat (STR) or simple sequence repeat (SSR) consisting of repeated nucleotide sequences of 2–6 bp
Minisatellite	VNTR consisting of repeated nucleotide sequences of 11–65 bp
Polygenic inheritance	Complex gene pattern, in some cases across different chromosomes, affecting phenotypic expression
LD	Linkage disequilibrium, i.e. non-random association of co-segregating alleles at two or more loci

9.1.2 Behaviour and Personality

9.1.2.1 Behaviour

Behaviour is defined by the way an individual acts and functions in response to internal or external stimuli and under specific circumstances. Behaviours are divided into "innate" and "learned". Innate behaviours are governed by genes. An example of human innate behaviour, or fixed action pattern, is a baby's smile when it's looked at. Such a response makes it attractive and maximises the chance of gaining parental care. Although learned behaviours have a genetic background as well, they are also determined by experience and environmental influences. Examples of learned behaviours include habituation, imprinting, classical conditioning, operant conditioning, observational learning, play and insight learning (reasoning).

Different behaviours have been studied in relation with gene polymorphisms, among which impulsive, suicidal, aggressive, antisocial and criminal. Behaviours laying at the extremes of normal distribution are maladaptive and often associated with psychiatric disorders.

Impulsive Behaviour

Impulsive behaviour is characterised by acting without foresight and is associated with a preference for immediate reward, decision-making without realising risky aspects of a decision and poor volitional control (Evenden 1999). In other words, different aspects of impulsivity include non-planning impulsiveness (i.e. behaving without taking future consequences into consideration), cognitive or attentional impulsiveness (i.e. deciding rapidly without focusing on an assignment) and motor impulsiveness (i.e. acting without thinking) (Patton et al. 1995).

Impulsivity as a personality trait is associated with impulsive behaviour. "Adaptive" impulsivity may be a positive personality trait when there is a demand for immediate confrontation with a crucial situation. In short, impulsive actions that turn out beneficial may be characterised as "spontaneous", "unconventional" or "bold", although their true nature remains impulsive. On the other hand, there is "maladaptive" impulsivity, which is dysfunctional, leads to negative consequences and may be associated with aggressive behaviour.

Heritability of trait impulsivity was estimated at around 45–50% (Pedersen et al. 1988; Hur and Bouchard Jr. 1997). The role of heritability in the manifestation of impulsivity was shown to increase with age. Additionally, heritability of risk-taking was shown to increase with age, though only in males (Anokhin et al. 2009). Behavioural expression of impulsivity was associated with suicidal, aggressive and antisocial behaviour. Additionally, impulsive behaviour constitutes a shared phenotype among different psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), impulse control and addictive disorders.

Suicidal Behaviour

Suicidal behaviour or suicidality includes thoughts and actions aiming at causing own death. *S*uicide ideation always precedes a suicide attempt and may be originally expressed by a vague death wish. As suicide ideation becomes more intense, a suicide plan, including suicide method, place and time, may be organised. A suicide attempt is an intentional act aiming at causing own death, without succeeding. Lastly, suicide is defined as an intentional fatal act causing own death.

Suicidal behaviour is more common within the context of psychiatric disorders, such as major depressive disorder and schizophrenia (Nock et al. 2008). There seems to be a genetic contribution to suicidal behaviour independent of the genetic contribution to psychiatric disorders. Many genes were implicated in the manifestation of suicidal behaviour (Clayden et al. 2012). Family history of suicidal behaviour is a severe risk factor for suicidal behaviour, while heritability of serious suicidality was estimated at around 55% (Mann et al. 2001). According to some, suicidal behaviour may constitute another form of aggressive behaviour, in which aggression is directed towards one's self. Suicide attempts may be more related to impulsivity, while completed suicide may be more related to aggression.

Aggressive Behaviour

Aggressive behaviour constitutes a broad phenotype, ranging from verbal to physical aggression, including offensive behaviour against others and objects' destruction. Aggression is categorised into two major subtypes: (a) proactive or instrumental. This form is associated with premeditated, controlled assault. Therefore, it is considered as predatory, offensive aggression, aiming at gaining something or achieving a goal, and is related to psychopathy. Proactive aggressive behaviour is more closely related to antisocial and criminal behaviour; (b) reactive or impulsive. In this case, aggressive behaviour is neither planned nor well considered and is almost always accompanied by intense negative emotions, e.g. fear, anxiety, anger, hostility, increased psychomotor activity and excitation of autonomic nervous system. Reactive aggression is usually provoked by external stimuli, such as insults, threats, physical attacks, and is more closely related to affect dysregulation and impulsive behaviour (Vitiello and Stoff 1997). When reactive aggression constitutes a response to threats posed by others, then it is considered "defensive" and thus beneficial. On the contrary, "dysfunctional" reactive aggression is often disproportionate to the stimulus, associated with reduced control over aggressive impulses and closely related to frustration (Crick and Dodge 1996; Raine et al. 2006).

Aggressive behaviour is far more common in males compared with females. Heritability, which was confirmed by meta-analyses of twin and adoption studies, may be more pronounced during adulthood compared with childhood, during which environmental factors are probably equally important. The genetic component of aggressive behaviour was shown to account for 40–60% of the variance (Miles and Carey 1997; Rhee and Waldman 2002; Craig and Halton 2009).

Antisocial Behaviour

Antisocial behaviour constitutes a broad phenotype, characterised among others by aggressive behaviour, criminal behaviour, delinquency and psychopathy (Baker et al. 2007). Antisocial behaviour can be studied under a different perspective, depending on its definition and measurement tools, and is best considered a dimensional phenomenon, a continuum, within which different manifestation and diverse severity may be observed. Altogether, there seems to be a strong association between the clinical manifestation (e.g. aggressive behaviour), the legal aspects (e.g. criminal behaviour, court conviction) and the personality traits (e.g. hostility, dishonesty, psychopathy) related to antisocial behaviour.

Antisocial personality traits include beliefs and attitudes aiming at using or harming others. Still, someone with antisocial personality traits does not necessarily perform aggressive or illegal acts. Since the relation between antisocial personality traits and aggressive or criminal behaviour is not bidirectional, genetic studies should differentiate aggressive versus non-aggressive antisocial behaviour.

Antisocial behaviour is far more common in males compared with females (Craig and Halton 2009). Still, the effect of genetic factors on the manifestation of antisocial behaviour seems to be higher in females during childhood. This sex difference disappears throughout adolescence and in adulthood, since the effect of genetic and environmental factors becomes roughly the same in both sexes (Jacobson

et al. 2002). Quantitative genetic studies yielded diverse results, possibly due to heterogeneous definition and assessment of antisocial behaviour. Roughly, the genetic component of antisocial behaviour was shown to account for 40–60% of the variance (Gunter et al. 2010; Fergusson et al. 2011).

Criminal Behaviour

Criminal behaviour, defined as "an act violating public law" or as "failure to act according to public law", was mainly studied within the context of antisocial behaviour/antisocial personality disorder.

9.1.2.2 Personality

Personality is formed by a pattern of relatively permanent traits and unique mental, emotional and behavioural characteristics providing consistency and individuality to one's behaviour. A personality "trait" is a relatively stable characteristic, enduring and consistent across a variety of situations, as well as typical for an individual. Traits are considered to predispose a person to respond in a certain way, regardless of the situation. For instance, an individual with high trait anxiety is prone to interpreting ambiguous stimuli as more threatening, while an individual with high trait anger is prone to reacting with anger towards situations that are least provoking. On the other hand, "state" is a temporary emotional-personality change, constituting a reaction to different stimuli.

Cloninger introduced the Temperament and Character Inventory (TCI), a self-report personality questionnaire, based on his "psychobiological model of personality". According to Cloninger, personality consists of temperament (i.e. heritable-stable traits) and character (i.e. traits influenced by learning and experience, maturing throughout life). Temperament has four dimensions: (a) novelty seeking, (b) harm avoidance, (c) reward dependence and (d) persistence. Character consists of three dimensions: (a) self-directedness, (b) cooperativeness and (c) self-transcendence (Raeymaekers and Van Broeckhoven 1998).

Currently, another widely used taxonomy of personality traits identifies five major personality dimensions: (a) neuroticism, (b) introversion-extraversion, (c) agreeableness, (d) conscientiousness and (e) openness to experience. Each personality trait is represented by a normal distribution. Based on twin studies, heritability of aforementioned dimensions was estimated at around 40% (Borkenau et al. 2001). Neuroticism constitutes a dimensional trait with six different facets: (a) anxiety, (b) depression, (c) hostility, (d) self-consciousness, (e) impulsiveness and (f) vulnerability (Miller et al. 2009). Altogether, twin studies revealed that genetic factors contribute to phenotypic expression of all aforementioned personality facets, accounting for 41–61% of the variance (Jang et al. 1996).

Personality traits laying at the extremes of normal distribution are putatively maladaptive and may predispose to the manifestation of psychiatric disorders. For instance, anxiety-related traits increase vulnerability for the development of anxiety disorders. Different personality traits have been studied in relation with gene polymorphisms, among which trait anxiety, trait impulsivity, trait anger, novelty seeking, sensation seeking, harm avoidance and psychopathy.

Novelty Seeking

High novelty seeking individuals appear quick-tempered, impulsive, curious, exploratory, enthusiastic-excitable, disorderly and extravagant. According to Cloninger's Tridimensional Personality Questionnaire (TPQ, the old version of TCI, measuring novelty seeking, harm avoidance and reward dependence), individuals scoring high in novelty seeking are characterised by impulsive and exploratory behaviour, while those scoring low tend to be rigid, frugal, reflective, stoic and low-tempered. Novelty seeking was correlated with extraversion (Lepine et al. 1994; Tsuchimine et al. 2009). Novelty seeking and extraversion were correlated in turn with suicide ideation and attempt (Brezo et al. 2006). Heritability of novelty seeking was shown to account for 36% of the variance (Heiman et al. 2004).

Sensation Seeking

Sensation seeking is defined as an individual's need for novel, varied, sensory and mental experiences (Zuckerman et al. 1972) and is expressed by four facets: (a) experience seeking, characterised by an attraction towards new experiences (e.g. through travel or various lifestyle choices); (b) disinhibition, characterised by a tendency towards sensation pursuit (e.g. alcohol or sexual intercourse); (c) thrill/adventure seeking, characterised by an engagement in adventurous activities (e.g. extreme sports, reckless driving); and (d) boredom susceptibility, characterised by an aversion to boredom, routine and repetition as well agitation when there is lack of a variety of stimuli.

Sensation seekers pursue new sensations, feelings and experiences in all life aspects, including personal and professional life. Although risk is not the driving force, risk can be underestimated or even considered an additional stimulant for acquiring desired sensations. Behaviours associated with thrill and adventure components of sensation seeking are referred to as "thrill" or "adrenaline seeking behaviours". Individuals exhibiting dysfunctional sensation seeking may engage in sexual risk-taking and gambling.

It was shown that sensation seeking is a highly heritable trait. In males, highly heritable sensation seeking facets included experience seeking (60%) and disinhibition (59%), while thrill/adventure seeking was the least heritable facet (34%). In females, highly heritable facets included thrill/adventure seeking (62%) and disinhibition (52%), while boredom susceptibility was the least heritable facet, accounting for 29% of the variance (Stoel et al. 2006). Sensation seeking was correlated with novelty seeking (McCourt et al. 1993).

Harm Avoidance

Harm avoidance is characterised by anticipatory worry, fear of the unknown, cautiousness, self-doubt, shyness and fatigability. Individuals exhibiting this trait are often characterised as cautious, fearful, discouraged, insecure, negativistic-pessimistic, asthenic and reserved with strangers (Cheung 2007). Harm avoidance was positively correlated with neuroticism and negatively correlated with novelty and sensation seeking (Cloninger 1986; McCourt et al. 1993). Harm avoidance and neuroticism were associated with suicide ideation and attempts (Brezo et al. 2006). Heritability of harm avoidance was shown to account for 36% of the variance (Heiman et al. 2004).

Psychopathy
Psychopathy is a personality trait characterised by lack of empathy (i.e. response congruent to the other's emotional state) and remorse. Psychopathy is related to antisocial behaviour and was shown to have a genetic component ranging from 50% to 80% (Retz et al. 2004; Gunter et al. 2010).

9.2 Genes and Behaviour

This second section focuses on the association between different gene polymorphisms and behaviour/personality. Emphasis was given on human studies, since data from animal studies cannot be easily interpreted in relation to humans. Some animal studies will be presented when there is no available data on humans. Due to the large amount of literature, emphasis was drawn away from genes that have not been extensively studied (Clayden et al. 2012). For instance, although the norepinephrine system has been associated with aggression, genes for which there is lack of consistent evidence, e.g. norepinephrine transporter gene (Kim et al. 2006a), will not be described. Overall, focus was placed on meta-analytic studies, whenever these were available.

9.2.1 Serotonergic System

The serotonergic system is involved, among others, in mood and behaviour regulation. There is evidence for the implication of the serotonergic system in the manifestation of impulsive (Bevilacqua and Goldman 2013), suicidal (Mann et al. 2001), aggressive and antisocial behaviour (Lesch and Merschdorf 2000).

Specifically, it was serotonergic system hypofunction that was associated with impulsive and risk-taking behaviour (Mann 2003). Low 5-hydroxyindoleacetic acid (5-HIAA) levels in cerebrospinal fluid (CSF), indicative of serotonergic system deficiency, were associated with suicidal behaviour within the context of different psychiatric disorders, independent of diagnosis (Asberg et al. 1986; Olivier and van Oorschot 2005). Furthermore, different serotonergic gene polymorphisms were associated with suicidal behaviour (Arango et al. 2003).

The serotonergic system was particularly implicated in the manifestation of aggressive behaviour (Craig and Halton 2009). The theory of a negative association between serotonergic activity and aggression, i.e. low serotonin activity is related to increased aggression levels (Olivier and van Oorschot 2005), was supported by the anti-aggressive effects of selective serotonin reuptake inhibitors (SSRIs) (Fuller 1996; Reist et al. 2003) and other anti-aggressive drugs with serotonergic function, called "serenics", which are under investigation (Miczek et al. 2002; Olivier and van Oorschot 2005). Still, such a direct association may be an oversimplified hypothesis due to serotonin receptors' wide variety, as well as serotonin system's complex regulation (de Almeida et al. 2005).

Lastly, it should be mentioned that research evidence relating different behavioural phenotypes to serotonergic system's dysfunction emphasises the detrimental effects of environmental stressors on the serotonergic system. Tables 9.2, 9.3, 9.4, and 9.5 present meta-analyses of studies investigating serotonergic genes in relation with behaviour and personality.

Table 9.2 MAOA gene polymorphism and behaviour

Gene (chromosome location)	Encoded protein	Polymorphism	Alleles	Behavioural phenotype	Meta-analyses
MAOA (Xp11.3)	Monoamine oxidase A	MAOA-uVNTR, 30 bp repeat element	MAOA-H: high-activity allele, transcribed 2–10 times more efficiently MAOA-L: low-activity allele	Suicidal behaviour	Meta-analysis of five studies (862 suicidal cases versus 1239 healthy controls) Results: no association (Clayden et al. 2012)
				Aggressive/ antisocial behaviour	Meta-analysis of five studies (around 2570 males) Results: childhood adversity/abuse was associated with antisocial behaviour in male MAOA-L genotype carriers (Kim-Cohen et al. 2006)
					Meta-analysis of 31 studies (case and healthy control number not mentioned) Results: MAOA-L was proven a risk allele for broadly defined antisocial behaviour (Ficks and Waldman 2014)
					1. Meta-analysis of 20 studies of strictly male or mixed male-female, mainly non-clinical populations (11,064 participants) Results: male MAOA-L carriers with a background of childhood maltreatment (e.g. domestic violence, physical/sexual abuse and parental neglect) exhibited higher levels of aggression/violence, non-violent antisocial behaviour as well as aggressive/violent antisocial behaviour during childhood/adolescence, as well as during adulthood 2. Meta-analysis of 12 studies of female, mainly non-clinical populations (7588 participants) Results: an interaction was observed between MAOA-H genotype and childhood maltreatment (e.g. domestic violence, physical/sexual abuse and parental neglect) in relation with antisocial outcomes. This finding depended though on meta-analysis' study inclusion and requires further investigation (Byrd and Manuck 2014)

Table 9.3 SLC6A4 gene polymorphisms and behaviour/personality

Gene (chromosome location)	Encoded protein	Polymorphisms	Alleles	Behavioural phenotype	Meta-analyses
SLC6A4 (17q11.1–q12)	Serotonin transporter	5-HTTLPR, 20–23 bp repeat element	L: long allele; it was associated with increased gene transcriptional efficiency and exists as LA and LG (low-expressing) S: short allele; it was associated with reduced gene transcriptional activity and is therefore considered low-expressing	Suicidal behaviour	Meta-analysis of 12 studies (three studies of completed/nine studies of attempted suicide; 1168 suicidal cases versus 1371 healthy controls) Results: S allele was proven a risk factor for suicide attempt (Anguelova et al. 2003)
					1. Meta-analysis of 18 studies (1521 suicide attempters and completers versus 2429 healthy controls) Results: no association; subanalysis of 15 studies of only Caucasian populations revealed again no association
					2. Meta-analysis of two studies of patients with a schizophrenia spectrum disorder (146 suicide attempters and 374 non-attempters) and two studies of patients with alcohol dependence (107 suicide attempters and 166 non attempters), leading to a meta-analysis of four studies altogether (258 suicide attempters versus 291 non-attempters) Results: S allele was proven a risk factor for suicide attempt in patients diagnosed with the same psychiatric disorders (the association was significant only in patients with alcohol dependence, when diagnostic categories were considered separately)
					3. Meta-analysis of five studies (190 violent attempters/suicide completers versus 733 healthy controls) Results: association between S allele and violent suicide behaviour (no association when non-violent attempters were compared with healthy controls) (Lin and Tsai 2004)

Gene (chromosome location)	Encoded protein	Polymorphisms	Alleles	Behavioural phenotype	Meta-analyses
					Meta-analysis of 39 studies (3096 suicidal cases versus 5936 healthy controls) Results: overall association between 5-HTTLPR polymorphism and suicidal behaviour, independent of psychiatric diagnoses (Li and He 2007)
					Meta-analysis of 31 studies (6324 suicidal cases versus 10,285 healthy controls) Results: no overall association Subanalysis of 25 studies of suicide attempters revealed an association between S allele and suicide attempt (S allele increased risk for suicide attempt by 13%) Subanalysis of six studies of suicide completers revealed no association (Clayden et al. 2012)
				Aggressive/ antisocial behaviour	Meta-analysis of 18 studies (case and healthy control number not mentioned) Results: S was proven a risk allele for broadly defined antisocial behaviour (Ficks and Waldman 2014)
				Trait anxiety	Meta-analysis of 26 studies (7657 participants) Results: no association (slight association, provided the fact that trait anxiety was assessed by a particular scale addressing the five-factor model of personality) (Schinka et al. 2004)
		STin2, 17 bp repeat element	STin2.9: contains nine copies STin2.10: contains ten copies STin2.12: contains 12 copies and constitutes a more potent positive transcriptional regulator	Suicidal behaviour	Meta-analysis of 10 studies (case and healthy control number not mentioned) Results: no association (Li and He 2007)

Table 9.4 Serotonin receptor gene polymorphisms and behaviour

Gene (chromosome location)	Encoded protein	Polymorphisms	Alleles	Behavioural phenotype	Meta-analyses
5-HTR1A (5q11.2–13)	Serotonin 1A receptor	rs6295: C(-1019)G SNP	C G: it was associated with higher receptor expression	Suicidal behaviour	Meta-analysis of four studies (three Caucasian/one Asian population; 957 suicidal cases versus 957 healthy controls) Results: no association, even when only suicide completers were included in analysis (Angles et al. 2012)
					Meta-analysis of six studies (2022 suicidal cases versus 2135 healthy controls) Results: no association (Clayden et al. 2012)
					Meta-analysis of nine studies (seven Caucasian/one Asian/one Mexican population; 2366 suicidal cases versus 2943 healthy controls) Results: no association, even when only Caucasians were included in analysis (Gonzalez-Castro et al. 2013a, b)
5-HTR1B (6q14.1)	Serotonin 1B receptor	rs6296: G861C SNP	G: G/G genotype was associated with higher receptor binding C	Suicidal behaviour	Meta-analysis of seven studies (789 suicidal cases versus 1247 healthy controls) Results: no association (Kia-Keating et al. 2007)
					Meta-analysis of ten studies (2947 suicidal cases versus 4066 healthy controls) Results: no association, even when suicide completers were excluded from analysis (Clayden et al. 2012)

5-HTR2A (13q14–q21)	Serotonin 2A receptor	rs6313: T102C SNP	T C	Suicidal behaviour	Meta-analysis of nine studies (three studies of suicide attempters; 596 suicidal cases versus 1003 healthy controls) Results: no association (Anguelova et al. 2003)
					Meta-analysis of 25 studies (1954 suicidal cases versus 2860 healthy controls) Results: no association, even when analysing different subgroups, e.g. Europeans, Asians, suicidal ideation versus healthy controls, suicide attempt versus healthy controls, violent versus non-violent, etc. (Li et al. 2006)
					Meta-analysis of 18 studies (3759 suicidal cases versus 5692 healthy controls) Results: no association, even when suicide completers were excluded from analysis (Clayden et al. 2012)
					Meta-analysis of 23 studies [2566 suicide attempters and completers versus 3989 healthy controls, as well as 612 suicidal cases and 1129 healthy controls included in a previous meta-analysis (Li et al. 2006); 13 Caucasian/six Asian/four populations of other ethnic origin] Results: no association, even when Caucasian and Asian populations, as well as schizophrenia patients, were analysed separately (Gonzalez-Castro et al. 2013a)
					Meta-analysis of 13 studies [1729 suicide attempters diagnosed with a psychiatric disorder (710 Asians/1019 European-Americans); 1794 non-suicide attempters diagnosed with a psychiatric disorder (759 Asians/920 European-Americans); 2398 healthy controls (906 Asians/1492 European-Americans)] Results: no association when suicide attempters were compared with healthy controls, even when data were analysed separately based on ethnicity No association when suicide attempters were compared with non-attempters diagnosed with the same psychiatric disorders, even when data were analysed separately based on ethnicity Analysis taking psychiatric diagnosis into consideration revealed an association between C/C genotype and suicide attempt in schizophrenia patients. Genotype C/C was not proven a risk factor for suicide attempt in bipolar and in patients with alcohol dependence (Wang et al. 2015)
		rs6311: G-1438A SNP	G A	Suicidal behaviour	Meta-analysis of seven studies (six Asian populations, further data not shown) Results: genotypic analysis with allele A combined [(AA+AG)/GG] revealed an association with suicidal behaviour (Li et al. 2006)
5-HTR2C (Xq23)	Serotonin 2C receptor	rs6318: C68G SNP	C G	Suicidal behaviour	Meta-analysis of seven studies (2297 suicidal cases versus 3431 healthy controls) Results: no association (Clayden et al. 2012)

Table 9.5 TPH1 gene polymorphisms and behaviour

Gene (chromosome location)	Encoded protein	Polymorphisms	Alleles	Behavioural phenotype	Meta-analyses
TPH1 (11p15.1)	Tryptophan hydroxylase, isoform 1	rs1800532: A218C SNP	218A (U allele) 218C (L allele)	Suicidal behaviour	Meta-analysis of seven studies (Caucasian populations only; 898 suicide attempters and completers versus 1179 healthy controls) Results: association between 218A allele and suicide-related behaviours (Rujescu et al. 2003b)
					Meta-analysis of seven studies (Caucasian populations only; 860 suicidal cases versus 1279 healthy controls) Results: association between 218A allele and suicide-related behaviours (Bellivier et al. 2004)
					Meta-analysis of 21 studies (4829 suicidal cases versus 7945 healthy controls) Results: no overall association; association between 218A allele and suicide attempt (Clayden et al. 2012)
		rs1799913: A779C SNP	779A (U allele): it was associated with lower CSF 5-HIAA levels 779C (L allele)	Suicidal behaviour	Meta-analysis of eight studies (1512 suicidal cases versus 3408 healthy controls) Results: no association (Clayden et al. 2012)
		rs1800532 (A218C SNP) together with rs1799913 (A779C SNP)	Described above	Suicidal behaviour	1. Meta-analysis of 15 studies of A218C and/or A779C (3585 suicide attempters and completers versus 2295 healthy controls) Results: no overall association 2. Meta-analysis of nine studies of psychiatric patients (two alcohol dependence/seven major depression, bipolar disorder and schizophrenia; 625 suicide attempters versus 1475 non-attempters) Results: no association (Lalovic and Turecki 2002)
					Meta-analysis of 34 studies of A218C and/or A779C (3922 suicidal cases versus 6700 healthy controls) Results: overall association between A218C/A779C SNPs and suicidal behaviour (different alleles implicated, based on different study characteristics) (Li and He 2006)
					Meta-analysis of 13 studies of psychiatric patients (three schizophrenia/two bipolar disorder/two major depression/three alcohol dependence/one borderline personality disorder/two mixed diagnoses; 1272 suicide attempters versus 1727 non-suicide attempters) Results: no association, independent of mental health status (Saetre et al. 2010)

9.2.1.1 Monoamine Oxidase A Gene (MAOA)

The MAOA Gene Polymorphism

The monoamine oxidase A, MAO-A, is a mitochondrial enzyme in neuronal presynaptic terminals, implicated in the degradation of biogenic amines, i.e. the neurotransmitters dopamine, serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine, after reuptake from the neuronal synaptic cleft. Decreased brain MAO-A levels were associated with impulsive aggression and mental retardation in a study of a Dutch family and specifically in male carriers of a MAOA gene mutation (C936T MAOA stop codon) of maternal origin (Brunner et al. 1993a,b). Additionally, low MAO-A activity in different cortical and subcortical regions detected by positron emission tomography was related to trait aggression, accounting for more than 30% of variance (Alia-Klein et al. 2008).

The MAOA gene, linked to the short arm of X chromosome (Xp11.3), is mainly expressed in catecholaminergic neurons (Hunter 2010). There is a functional polymorphism within the gene's promoter region, located 1.2 kb upstream of the MAOA coding region. This length polymorphic region (MAOA-LPR), a VNTR (MAOA-uVNTR) consisting of a specific 30 bp nucleotide sequence repeated 2, 3, 3.5, 4 or 5 times, was shown to influence gene's transcriptional activity. It was reported that high-activity MAOA gene variants (MAOA-H), containing alleles with 3.5 or 4 copies, were transcribed 2–10 times more efficiently than low-activity MAOA gene variants (MAOA-L), containing alleles with 2, 3 or 5 copies. Thus, the nucleotide repeat number was shown to affect MAO-A enzyme abundance, since MAOA-H genotype was associated with higher, while MAOA-L genotype with reduced MAO-A expression and therefore increased synaptic serotonin levels (Sabol et al. 1998; Buckholtz and Meyer-Lindenberg 2008; Guo et al. 2008).

The MAOA-uVNTR Polymorphism and Behaviour/Personality

The MAOA-L allele was associated with personality traits related to aggressiveness and impulsivity in a community male sample (Manuck et al. 2000). Furthermore, it was suggested that MAOA-L allele association with trait aggression in both healthy males and females may be mediated by increased sensitivity towards negative experiences (Eisenberger et al. 2007). The MAOA-L allele was also associated with antisocial and aggressive/violent behaviour in different psychiatric populations, such as in patients diagnosed with substance abuse and cluster B personality disorders (Reif et al. 2007), as well as in male criminal alcoholics with increased CSF testosterone levels (Sjoberg et al. 2008).

The MAOA genotype was shown to moderate the effects of childhood maltreatment on the manifestation of antisocial behaviour in adulthood. Specifically, male MAOA-L carriers with a background of childhood maltreatment were more prompt to the development of antisocial behaviour compared with male MAOA-H carriers. This was the outcome of a core longitudinal study, emphasising the combined effect of genetic and environmental factors on behavioural outcome (Caspi et al. 2002). Further studies of gene-environment interactions showed that the MAOA-L genotype predicted aggressive behaviour in males with a history of traumatic life events,

e.g. separation from parents or family violence, especially during the first 15 years of life (Frazzetto et al. 2007), the presence of at least one short MAOA allele (MAOA-L, 2 or 3 copies) in males and one or two long MAOA alleles (MAOA-H, 3.5, 4 or 5 copies) in females was associated with higher levels of delinquency in adolescents with a history of maltreatment (Aslund et al. 2011), and MAOA-L genotype was associated with aggressive behaviour in males under high provocation (McDermott et al. 2009).

On the other hand, MAOA-L was proven a risk allele for violent behaviour in a population of psychiatric patients, independent of childhood adversity (Reif et al. 2007), while others found no interaction between MAOA genotype and childhood adversity (Haberstick et al. 2005; Huizinga et al. 2006). Lastly, there were studies that did not find an association between MAOA genotype and aggressive/antisocial behaviour at all (Haberstick et al. 2005; Jacob et al. 2005; Widom and Brzustowicz 2006; Prichard et al. 2007a; Weder et al. 2009).

Altogether, different meta-analyses revealed an association between MAOA-L allele and aggressive/violent/antisocial behaviour, while MAOA-H was shown to be the low-risk allele. The first one, a meta-analysis of five independent studies (around 2570 males), reported that childhood adversity (domestic violence, parental neglect, physical or sexual abuse, harsh discipline, etc.) was associated with antisocial behaviour in male MAOA-L genotype carriers (Kim-Cohen et al. 2006). A subsequent meta-analysis of 31 studies confirmed MAOA-L as a risk allele for aggressive and antisocial behaviour (Ficks and Waldman 2014). Lastly, a more recent extended meta-analysis investigated the effect of the interaction between childhood adversity and MAOA genotype on later manifestation of aggressive-antisocial behaviour in both males and females. The meta-analysed studies were mainly conducted in non-clinical populations. Firstly, 20 studies of strictly male or mixed male-female samples (11,064 participants) were meta-analysed. Results revealed that male MAOA-L carriers with a background of childhood maltreatment and other adversities exhibited higher levels of aggression/violence, non-violent antisocial behaviour as well as aggressive/violent antisocial behaviour during childhood/adolescence, as well as during adulthood. When early environmental adversity was more closely investigated, it was shown that MAOA-L genotype increased the risk for aforementioned behavioural outcomes specifically in cases of childhood maltreatment (e.g. domestic violence, physical/sexual abuse and parental neglect), and not in cases of other childhood adversities (e.g. separation, marital difficulties, parental psychopathology). Secondly, 12 studies of female populations (7588 participants) were meta-analysed. Overall, results did not reveal any significant interaction between MAOA genotype and maltreatment/other adversities, predicting aggressive/antisocial outcomes. An interaction was observed between MAOA-H genotype and childhood maltreatment in relation with antisocial outcomes. This association depended though on study inclusion and therefore requires further investigation (Byrd and Manuck 2014).

On the other hand, a meta-analysis of five studies (862 suicidal cases versus 1239 healthy controls) investigating the association between MAOA-L (three copies), MAOA-H (four copies) and suicidal behaviour did not reveal any significant associations (Clayden et al. 2012) (Table 9.2).

9.2.1.2 Serotonin Transporter Gene (SLC6A4)

The SLC6A4 Gene Polymorphisms

The serotonin transporter, SERT or 5HTT, is a monoamine transporter protein at serotonergic neurons' cell body and synaptic terminals, regulating synaptic signalling by removing serotonin from synaptic cleft back to presynaptic neurons.

The transporter is coded for by the gene "solute carrier family 6 member 4" (SLC6A4), located at chromosome 17 (17q11.1–q12) (Nakamura et al. 2000). The polymorphism "5-HTTLPR" constitutes a 20–23 bp repeat element in gene's promoter region (44 bp insertion/deletion), giving rise to up to 14 different alleles (Nakamura et al. 2000). The most common and best studied alleles include the "long" ("L", 16 copies, 528 bp) and the "short" ("S", 14 copies, 484 bp) variant (Heils et al. 1996; Hariri and Weinberger 2003). Homozygosity for the long variant (L/L) was associated with increased transcriptional efficiency compared with the L/S and S/S genotypes (Heils et al. 1996; Cadoret et al. 2003), resulting in higher amounts of serotonin transporter and thus higher serotonin reuptake in blood platelets and lymphoblasts. Contrary, the S allele was associated with reduced SLC6A4 gene transcriptional activity (Lesch et al. 1996; Greenberg et al. 1999), since the S/S genotype corresponded to almost half of SERT protein levels compared with the L/L genotype (Collier et al. 1996). Still, another study reported no association between the 5-HTTLPR genotype and serotonin transporter binding (Jacobsen et al. 2000). Lately, a common polymorphism (rs25531), a single-base substitution (SNP A/G), was reported within the first of two 22 bp imperfect repeats of the L allele. This SNP gives rise to the LA and the LG allele. Thus, together with the S allele, the locus is considered triallelic. The LG allele carries a binding site for a transcription factor (AP2) that possibly suppresses gene expression. Thus, similarly to the S allele, the LG was considered a low-expressing allele (Hu et al. 2006).

Another SLC6A4 gene polymorphism is a 17 bp VNTR in the second intron (STin2), a triallelic polymorphism existing in the form of 9 (STin2.9), 10 (STin2.10) and 12 (STin2.12) copies. Allele STin2.12 was proven a more potent positive transcriptional regulator compared with STin2.10 (MacKenzie and Quinn 1999).

The 5-HTTLPR Polymorphism and Behaviour/Personality

Studies of 5-HTTLPR polymorphism in a Japanese (Sakado et al. 2003) and a Korean male population (Lee et al. 2003b) showed that the S/S genotype was associated with higher levels of trait impulsivity compared with the L/S and the L/L genotype. Similarly, in another study of a non-clinical Caucasian population recruited from the University of Oslo, S/S carriers showed higher levels of impulsivity compared with L/S carriers displaying intermediate and L/L carriers displaying lower levels of impulsiveness. The effect of S allele on the expression of impulsivity was sex-dependent, since males were more likely to exhibit impulsiveness (Walderhaug et al. 2010). On the other hand, a study of a non-clinical Caucasian-Brazilian population did not find any association between the 5-HTTLPR polymorphism and impulsivity (Lage et al. 2011).

A study of German suicide completers with undefined psychiatric diagnoses reported an association between the S allele and violent suicide (Bondy et al. 2000a). The same association was reported in another study of suicide attempters (40 with and 11 without a history of a major psychiatric disorder) (Courtet et al. 2001). Contradictory reports supported an association between the L allele and suicidal behaviour within the context of affective disorders (Du et al. 1999), while other studies did not find any association between the 5-HTTLPR polymorphism and suicidal behaviour (Anguelova et al. 2003). A meta-analysis including nine studies of suicide attempters and three studies of suicide completers analysed a total number of 1168 suicidal cases in comparison with 1371 healthy controls. The results supported an association between the S allele and suicidal behaviour. Still, further analysis showed that this association was credited to studies of suicide attempters only, since meta-analysis of 991 suicide attempters confirmed an association between suicidal behaviour and the S allele, while meta-analysis of 177 suicide completers did not (Anguelova et al. 2003). The following meta-analysis of 18 studies (1521 suicidal cases versus 2429 healthy controls) did not find any association between the 5-HTTLPR polymorphism and suicidal behaviour. In order to rule out confounding effects of ethnicity, a separate analysis included only Caucasians. Again, no significant association was revealed. The same meta-analysis focused only on psychiatric patients, comparing patients with and without suicidal behaviour (4 studies of mood disorder patients, 258 suicide attempters versus 291 non-attempters; 2 studies of schizophrenia/schizoaffective patients, 146 suicide attempters versus 374 non-attempters; 2 studies of alcohol-dependent patients, 107 suicide attempters versus 166 non-attempters). The results revealed a significant association between the S allele and suicide attempts in patients with a positive psychiatric history. Lastly, meta-analysis of five studies (190 cases of violent suicide attempters or completers versus 733 healthy controls) revealed a significant association between the S allele and violent suicidal behaviour. Additionally, S allele frequency was higher in violent compared with non-violent suicide attempters (Lin and Tsai 2004). A subsequent meta-analysis of 39 studies (3096 suicidal cases versus 5936 healthy controls) confirmed overall association of the 5-HTTLPR polymorphism and suicidal behaviour, suggesting though that based on study design and genotypic analysis, both the S and the L allele contribute to risk (Li and He 2007). Lastly, an even more recent meta-analysis of 31 studies (6324 suicidal individuals versus 10,285 healthy controls; 25 studies of suicide attempters, 6 studies of suicide completers) confirmed an association between the S allele and suicidal behaviour in attempted suicide only, emphasising once more the phenotypic heterogeneity between suicide attempt and completed suicide. Based on results, the S allele increased risk for suicide attempt by 13% (Clayden et al. 2012).

In regard to aggression, a study reported a significant association between genotypes with low-expressing alleles (S/S, S/LG and LG/LG) and aggressive behaviour in children aged 5–15 years (Beitchman et al. 2006). Another study emphasised the importance of gene-environment interaction, since a highly adverse childhood environment was associated with later manifestation of violent behaviour only in psychiatric patients being S/S and S/L carriers. Vice versa, the L/L genotype was

considered a protective factor against manifestation of violence in adults with a high childhood adverse environment index (Reif et al. 2007). This finding was confirmed in male Caucasian offenders with a history of childhood ADHD. The S allele and the S/S genotype were associated with violent behaviour, explaining 5% of the variance of violent behaviour (Retz et al. 2004). Lastly, a study of a Chinese population of convicted criminals reported an association between the S/S genotype and violent crime, but not antisocial personality disorder (Liao et al. 2004). On the other hand, there were studies that reported no association between the 5-HTTLPR genotype and aggressive behaviour in children (Davidge et al. 2004). Altogether, a recent meta-analysis of 18 studies of the 5-HTTLPR polymorphism confirmed an association between the S allele and the increased risk for antisocial behaviour. Still, the authors noted an effect of publication bias on results, since it was shown that there was a trend towards more publications reporting positive associations (Ficks and Waldman 2014).

Lastly, the S allele (both S/S and S/L genotype) was also associated with neuroticism, reflected by increased trait anxiety (Lesch et al. 1996), specifically within the context of cluster C personality disorders (Jacob et al. 2004). In addition, a study reported an association between the S allele and different aspects of neuroticism, such as trait anxiety, affective temperament (depressive, cyclothymic, irritable and anxious), guilt, hostility and somatisation in a non-clinical Hungarian sample (Gonda et al. 2009). Still, an association between the 5-HTTLPR polymorphism and neuroticism was not always confirmed (Ball et al. 1997). A meta-analysis of 26 studies (7657 subjects) did not reveal a significant association between the 5-HTTLPR genotype and trait anxiety. However, a slight association was indicated, provided the fact that anxiety was assessed by a particular scale addressing the five-factor model of personality (Schinka et al. 2004).

The STin2 Polymorphism and Behaviour/Personality

Based on a post-mortem study of Croatia/Southern Slavic suicide victims, the lower activity STin2.10 allele was associated with suicidal behaviour (Jernej et al. 2004). Altogether though, a meta-analysis of ten studies (case and healthy control number were not reported) failed to support an association between the STin2 polymorphism and suicidal behaviour (Li and He 2007).

According to a study of children displaying aggressive behaviour, in several cases within the context of ADHD, oppositional defiant and conduct disorder, STin2.10 allele frequency was significantly lower compared with STin2.12 allele frequency. Still, this difference was not statistically significant when aggressive children were compared with a control population of healthy adults (Davidge et al. 2004).

The STin2 polymorphism was also studied in relation to different personality traits, measured by the Eysenck Personality Inventory and the TCI. Carriers of the 10-repeat allele scored lower in neuroticism and harm avoidance, while they scored higher in extraversion. Contrary to STin2.10 carriers, STin2.12 carriers scored higher in harm avoidance and lower in extraversion and novelty seeking (Kazantseva et al. 2008) (Table 9.3).

9.2.1.3 Serotonin Receptor Genes

The Serotonin Receptor 1A Gene (5-HTR1A)

The serotonin receptor family includes at least 14 different 5-HT receptors (Hoyer et al. 2002). The serotonin receptor 5-HTR1A is a protein regulating serotonin release by functioning both as a presynaptic autoreceptor in dorsal and medial raphe nuclei serotonergic neurons and a postsynaptic heteroreceptor in non-serotonergic neurons.

The 5-HTR1A receptor is encoded by a gene located at chromosome 5 (5q11.2–13) (Kobilka et al. 1987). There is a common functional SNP (rs6295) in 5-HTR1A gene promoter, C(-1019)G (Wu and Comings 1999). The G allele was associated with higher receptor expression, leading to increased negative feedback inhibition in raphe nuclei serotonergic neurons (mediated by 5-HTR1A autoreceptors) and thus decreased serotonergic activity (Lemonde et al. 2003).

In a study of a Hungarian population, G/G carriers displayed significantly higher impulsivity levels, compared with G/C and C/C carriers (Benko et al. 2010).

The G allele was also recognised as a risk factor for completed suicide in a population of French-Canadian origin (Lemonde et al. 2003) and for suicide attempt in a Polish study (Sawiniec et al. 2007). Still, the latter association was not supported in Ukrainian families of suicide attempters (probands and both parents) (Wasserman et al. 2006) and in a Mexican population of suicide attempters (Gonzalez-Castro et al. 2013b).

The first meta-analysis of four studies of the C(-1019)G polymorphism in relation to suicidal behaviour (three Caucasian and one Asian population; 957 suicidal cases versus 957 healthy controls) did not find any association between the G risk allele and suicidal behaviour (Angles et al. 2012). Lack of an association was confirmed in a subsequent meta-analysis of six studies (2022 suicidal cases versus 2135 healthy controls) (Clayden et al. 2012), as well as in a more recent meta-analysis of nine studies (seven Caucasian, one Asian and one Mexican population; 2366 suicidal cases versus 2943 healthy controls) (Gonzalez-Castro et al. 2013b).

Furthermore, the C(-1019)G polymorphism was investigated in relation with personality traits. The G allele was associated with different anxiety- and depression-related personality traits, such as neuroticism and harm avoidance, in a non-clinical German population (Strobel et al. 2003), though such an association was not always supported (Koller et al. 2006). Another study also failed to report an association between the C(-1019)G polymorphism and different personality traits in a German population of suicide attempters and healthy controls, as well as in an Italian population of patients diagnosed with a mood disorder (Serretti et al. 2009).

Lastly, a few studies of other SNPs, such as *Pro16Leu* (rs1800041, amino acid proline is substituted by amino acid leucine at codon 16), Gly272Asp (rs1800042, amino acid glycine is substituted by amino acid aspartic acid at codon 272) (Anguelova et al. 2003) as well as a C to T transition (rs878567) (Gonzalez-Castro et al. 2013b), did not reveal an association with suicidal behaviour.

The Serotonin Receptor 1B Gene (5-HTR1B)

The serotonin receptor 5-HTR1B is a protein functioning both as a presynaptic autoreceptor in serotonergic neurons, as well as a postsynaptic heteroreceptor in non-serotonergic neurons. The activation of 5-HTR1B autoreceptor modulates neuronal function by inhibiting serotonin release, preventing neuron's overstimulation. There is evidence that 5HTR1B heteroreceptors modulate offensive aggression (Olivier and van Oorschot 2005).

The 5-HTR1B receptor is coded for by a short intronless gene located at chromosome 6 (6q14.1). Several gene polymorphisms have been described, among which a G861C SNP (rs6296). Although G861C is a silent SNP, it is in LD with other functional polymorphisms. There is some evidence that G861C, or another allele in LD with G861C, affects receptor binding (Sanders et al. 2002). Based on a post-mortem study, homozygosity for the G allele was associated with higher receptor binding compared with the G/C heterozygous genotype (Huang et al. 1999).

Although a study found an association between the G allele and history of suicidal behaviour within the context of personality disorders (New et al. 2001), other studies of the G861C SNP did not prove 5-HTR1B a risk gene for manifestation of suicidal behaviour in a Japanese (Nishiguchi et al. 2001), a German (Rujescu et al. 2003c) and a Slavic/Croatian population (Stefulj et al. 2004b). Altogether, lack of an association between the G861C polymorphism and suicidal behaviour was confirmed by a meta-analysis of seven studies (789 suicidal cases versus 1247 healthy controls), in which results were not affected by study heterogeneity, age, gender or ethnicity (Kia-Keating et al. 2007), as well as by a meta-analysis of ten studies (2947 suicidal cases versus 4066 healthy controls) (Clayden et al. 2012).

A study of children displaying aggressive behaviour, in several cases within the context of ADHD, oppositional defiant and conduct disorder, reported a trend towards higher C allele frequency in these children compared with a control population of healthy adults (Davidge et al. 2004), an observation that requires though further verification. Increased C allele frequency was also observed in a Finnish cohort of antisocial alcoholics compared with non-antisocial alcoholics and healthy controls (Lappalainen et al. 1998). Contrary, a previous post-mortem study did not reveal an association between the G861C genotype and pathological aggression (Huang et al. 1999).

The Serotonin Receptor 2A Gene (5-HTR2A)

The serotonin receptor 5-HTR2A is a G *protein*-coupled receptor, regulated by many different interacting proteins and distributed in many different central nervous system areas. This receptor has been implicated in the manifestation of affective and cognitive disorders (Zhang and Stackman Jr. 2015).

The receptor is encoded by the 5-HTR2A gene located at chromosome 13 (13q14–q21). There is a silent SNP in exon 1 (rs6313) as a result of a T/C substitution at position 102. The polymorphism T102C is in almost complete LD with the promoter G-1438A SNP (rs6311), which is also non-functional. Still, a post-mortem study of suicide victims and healthy controls showed that the T102C and the G-1438A SNP affected serotonin binding in both study groups. Specifically, the

haplotype 102T/-1438A was associated with increased serotonin binding compared with the haplotype 102C/-1438G (Turecki et al. 1999). Other 5-HTR2A gene SNPs include rs6314 (within gene's coding region; amino acid histidine is substituted by amino acid tyrosine at codon 452, His452Tyr), rs7322347 (an intron 2 SNP, T/A), rs643627 (A/G) and rs594242 (C/G).

Studies of the association between the T102C polymorphism and suicidal behaviour were rather controversial, indicating the C as the risk allele (Zhang et al. 1997), T as the risk allele (Gonzalez-Castro et al. 2013a, b) or no association at all (Bondy et al. 2000b). A meta-analysis of nine studies (596 suicidal attempters and completers versus 1003 healthy controls) did not find any association between the T102C polymorphism and suicidal behaviour (Anguelova et al. 2003). A subsequent meta-analysis of 25 studies (1954 suicidal cases versus 2860 healthy controls) investigated the association between the T102C polymorphism and suicidal behaviour performing several subanalyses, e.g. Europeans only, Asians only, suicidal ideation versus healthy controls, suicide attempt versus healthy controls, violent versus non-violent, etc. Overall, study findings did not support an association between the T102C polymorphism and suicidal behaviour (Li et al. 2006). Lack of an association was confirmed by another meta-analysis of 18 studies (3759 suicidal cases versus 5692 healthy controls) (Clayden et al. 2012).

An even more recent meta-analysis of 23 studies, including 2566 suicide attempters and completers versus 3989 healthy controls (13 Caucasian, 6 Asian and 4 populations of other ethnic origin), as well as 612 suicidal cases and 1129 healthy controls included in a previous meta-analysis (Li et al. 2006), reported no association between the T102C polymorphism and suicidal behaviour, after using allelic models for both C and T allele. No associations were found even when Caucasian and Asian populations were analysed separately, as well as when only schizophrenia patients were considered (Gonzalez-Castro et al. 2013a). A latest meta-analysis of 13 studies [1729 suicide attempters diagnosed with a psychiatric disorder (710 Asians/1019 European-Americans); 1794 non-suicide attempters diagnosed with a psychiatric disorder (759 Asians/920 European-Americans); 2398 healthy controls (906 Asians/1492 European-Americans)] conducted two separate analyses. In the first one, suicide attempters were compared with healthy controls. Results indicated that the C/C genotype was not associated with suicide attempt, even when data was analysed separately based on ethnicity. In the second analysis, suicide attempters were compared with non-attempters diagnosed with the same psychiatric disorders. Again, there was no association between the T102C polymorphism and suicide attempt, even when different ethnic groups were analysed separately. Still, when data was analysed separately based on psychiatric diagnosis, the C/C genotype was proven a risk factor for suicide attempt in schizophrenia patients. On the other hand, this association was confirmed neither in bipolar patients nor in patients with alcohol dependence (Wang et al. 2015).

Although a few data on other polymorphisms, such as His452Tyr and G-1438A, did not reveal an association between 5-HTR2A gene polymorphisms and suicidal behaviour (Anguelova et al. 2003), a meta-analysis of seven studies (six Asian populations) conducting genotypic analysis with the G-1438A SNP allele A combined

[(AA+AG)/GG] reported a significant association with suicidal behaviour (Li et al. 2006). The G-1438A polymorphism was also not associated with different personality traits, such as novelty seeking and harm avoidance. Still, an association was found between the A-1438A genotype and impulsive behaviour assessed by a behavioural task (go/no-go task) in healthy Japanese study participants (Nomura et al. 2006), as well as contradictory evidence for an association between the A-1438A genotype and low levels of impulsive behaviour in a German population of patients with alcohol dependence. The latter association was independent of the presence of comorbidity with a personality disorder (Preuss et al. 2001).

Another study of a non-clinical Caucasian Hungarian population investigated the relation between a set of different 5-HTR2A SNPs and aggressive traits. An association was reported between the intronic SNP T/A (rs7322347) and aggressive traits, in such T/T genotype carriers displayed more aggressive traits compared with allele A carriers (Banlaki et al. 2015).

Lastly, a study of German suicide attempters, diagnosed with an affective, schizophrenia spectrum or borderline personality disorder, searched for an association between different 5-HTR2A gene polymorphisms (rs643627, rs594242 and rs6311) and inwardly/outwardly state and trait anger, as well as aggressive behaviour. Results showed that the A-C-T haplotype (polymorphism/allele, rs643627/A, rs594242/C and rs6311/T), the C-T haplotype (polymorphism/allele, rs594242/C and rs6311/T) and the T allele (rs6311) decreased risk for suicidal behaviour. Additionally, the rs6311 SNP was associated with trait anger, in such the risk genotype C/C was related to higher levels of trait anger, specifically anger turned inwards. Additionally, the C allele was associated with decreased aggressive behaviour inhibition (Giegling et al. 2006).

The Serotonin Receptor 2B Gene (5-HTR2B)

The serotonin receptor 5-HTR2B is a G protein-coupled receptor coded for by a gene located at chromosome 2 (2q36.3–q37.1) and expressed, among others, in the brain (Bonaventure et al. 2002). Its function is currently under investigation, although presynaptic 5-HTR2B receptors were shown to regulate serotonin reuptake (Launay et al. 2006) and were also implicated in mesolimbic dopaminergic activity modulation (Auclair et al. 2010).

There is a functional stop codon (C20T, Q20*), most probably limited to the Finnish population, causing RNA decay and 5-HTR2B expression blockage. In a study of a Finnish population of violent criminal offenders, Q20* carriers showed no cognitive deficits and committed crimes mediated by high impulsivity levels (Bevilacqua et al. 2010).

The Serotonin Receptor 2C Gene (5-HTR2C)

The serotonin receptor 5-HTR2C is again a G protein-coupled receptor, implicated among others in mood, anxiety and reproductive behaviour regulation. The receptor is coded for by a gene located at X chromosome (Xq23). There is a SNP (rs6318) in the gene's coding region, C68G, leading to an amino acid substitution (cysteine is substituted by serine at codon 23, Cys23Ser).

Although one study indicated an association between the serine variant and trait impulsiveness in males displaying repeatedly self-harming behaviour (Evans et al. 2000), another study of suicide completers belonging to two different ethnicities, German and Slavic, did not reveal any association between the C68G SNP and suicidal behaviour (Stefulj et al. 2004a). Absence of an association between the C68G polymorphism and suicidal behaviour was confirmed by a recent meta-analysis of seven studies (2297 suicidal cases versus 3431 healthy controls) (Clayden et al. 2012).

Lastly, a study of a German population of suicide attempters and healthy controls, as well as of Italian patients diagnosed with a mood disorder, did not reveal an association between the C68G polymorphism and different personality traits (Serretti et al. 2009) (Table 9.4).

9.2.1.4 Tryptophan Hydroxylase 1 Gene (TPH1)

The TPH1 Gene Polymorphisms

Tryptophan hydroxylase, TPH, is an enzyme that regulates serotonin availability by catalysing the rate-limiting step in serotonin biosynthesis. The isoform 1, TPH1, is coded for by TPH1 gene, located at chromosome 11 (11p15.1), and is expressed in a variety of tissues. Still, there are contradictory results regarding its expression in the brain (Zill et al. 2007; Gutknecht et al. 2009).

There is a SNP (rs1800532) in intron 7, A218C. The 218A allele is also referred to as "upper"/U allele and constitutes the minor allele, while the 218C is also referred to as "lower"/L allele. Originally, the A218C SNP was not shown to alter TPH1 amino acid sequence (Nielsen et al. 1997). Later, and based on a post-mortem study of suicide victims and healthy controls, 218A allele was considered the high activity allele, since it was associated with significantly higher TPH1 immunoreactivity. Still, the A218C polymorphism was not shown to affect only TPH1 production but 5-HTR2A receptor regulation as well, since the 218A allele was associated with decreased 5-HTR2A receptor density. (Ono et al. 2002).

Another SNP (rs1799913) in intron 7 is the A779C transversion. Accordingly, the allele 779A is referred to as U allele and was related to lower CSF 5-HIAA levels in healthy males (Jonsson et al. 1997), while the allele 779C is referred to as L allele. The A779C SNP, which was also not shown to alter TPH1 amino acid sequence (Nielsen et al. 1997), is in almost complete LD with the A218C SNP in Caucasian populations (alleles 218C and 779C are in phase).

The A218C Polymorphism and Behaviour/Personality

Altogether, studies of the A218C SNP in relation to suicidal behaviour led to great discrepancy both in Caucasian, as well as in Asian populations (Rujescu et al. 2003b). The 218A allele was associated with suicidal behaviour within the context of affective (Mann et al. 1997; Souery et al. 2001) and other psychiatric disorders (Abbar et al. 2001), although the latter finding was not confirmed in Caucasian suicide completers of French-Canadian origin (Turecki et al. 2001), in a family-based study of Israeli adolescent suicide attempters diagnosed with different psychiatric

disorders (Zalsman et al. 2001) as well as in a German population of suicide attempters diagnosed with different psychiatric disorders (Rujescu et al. 2003b). On the contrary and based on a post-mortem study of Croatia/Southern Slavic suicide victims, it was the lower activity 218C allele that was associated with suicidal behaviour, especially in combination with the lower ten repeat allele of STin2 (SLC6A4 gene) polymorphism (Jernej et al. 2004).

A meta-analysis of seven studies of Caucasian populations only (898 suicidal cases versus 1179 healthy controls) revealed an association between the 218A allele and suicide-related behaviours (Rujescu et al. 2003b). A subsequent study restricted again to Caucasian populations meta-analysed data from seven studies (860 suicidal cases versus 1279 healthy controls), confirming the association between the 218A allele and suicidal behaviour (Bellivier et al. 2004). A more recent meta-analysis of 21 studies (4829 suicidal cases versus 7945 healthy controls) confirmed partly previous outcomes, since results indicated that the 218A allele was associated only with suicide attempt, and not with completed suicide (Clayden et al. 2012).

Furthermore, homozygosity for the 218A allele was associated with higher aggression and more intense tendency towards unprovoked anger in males (Manuck et al. 1999), as well as with higher levels of proactive aggression (Hennig et al. 2005). The 218A allele was also associated with trait anger, state anger and anger temperament in a German population (Rujescu et al. 2002).

The A779C Polymorphism and Behaviour/Personality

Although evidence was provided for an association between the 779C allele and non-impulsive suicide attempts (Nielsen et al. 1998), results regarding the implication of both A779C and A218C polymorphisms in the manifestation of suicidal behaviour were altogether rather controversial. A meta-analysis of 15 studies (1290 suicide attempters/completers versus 2295 healthy control subjects) investigating the A779C and/or the A218C polymorphism in relation to suicidal behaviour revealed no significant associations. The same meta-analysis searched for an association between the two TPH1 SNPs and suicidal behaviour only in patients with psychiatric diagnoses (9 studies; 625 suicide attempters versus 1475 non-attempters), confirming absence of any association between the SNPs and suicidal behaviour (Lalovic and Turecki 2002). Previous results were confirmed by a meta-analysis of 13 studies (1272 suicide attempters, 1727 non-suicide attempters, all participants were diagnosed with a psychiatric disorder), which did not find any association between the A779C/A218C polymorphisms and suicidal behaviour (Saetre et al. 2010).

Contradictory results were provided by a subsequent meta-analysis of 34 studies (3922 suicidal cases versus 6700 healthy controls), which reported a strong overall association, regardless of alleles, between the TPH1 A779C/A218C polymorphisms and suicidal behaviour. The same meta-analysis revealed though no association between the promoter A-6526G SNP (rs4537731) and suicidal behaviour (Li and He 2006). Lastly, a more recent meta-analysis of eight studies (1512 suicidal cases versus 3408 healthy controls) found again no association between the A779C polymorphism and suicidal behaviour (Clayden et al. 2012).

Homozygosity for the 779C allele was associated with low CSF 5-HIAA levels in a Finnish population of impulsive alcoholic violent offenders (Nielsen et al. 1994), as well as with impulsive aggression in males diagnosed with personality disorders (New et al. 1998). Lastly, the 779A allele was associated with trait anger, state anger and anger temperament in a German population (Rujescu et al. 2002) (Table 9.5).

9.2.1.5 Tryptophan Hydroxylase 2 Gene (TPH2)

The tryptophan hydroxylase isoform 2, TPH2, is expressed in brain serotonergic neurons. The enzyme is encoded by a gene located at chromosome 12 (12q21.1) (Zill et al. 2007). There is a TPH2 gene SNP, C1473G, which has been studied only in animal models. Homozygosity for the G allele in mouse strains was associated with reduced TPH2 activity and lower 5-HT levels (Zhang et al. 2004b). On the contrary, mice homozygous for the C allele showed higher TPH2 activity, which was associated in turn with higher levels of inter-male aggression (Kulikov et al. 2005).

Although TPH2 SNPs have been studied in relation with psychiatric disorders (Walitza et al. 2005; Zhang et al. 2005), further investigation is required regarding their association with aggressive behaviour in humans (Zhang et al. 2006).

9.2.2 Dopaminergic System

The dopaminergic system is involved, among others, in motor control, motivation, emotional stability, reward and cognition. Thus, impulsive, compulsive or addictive behaviours could be related to dopaminergic gene dysregulation.

There is evidence for the implication of dopamine in the manifestation of aggression (de Almeida et al. 2005), since antipsychotic drugs display anti-aggressive effects (Groleger 2007). It has been suggested that dopamine is implicated in the initiation of aggressive behaviour, whereas serotonin in its termination (Olivier and van Oorschot 2005). On the contrary, novelty and sensation seeking were associated with lower dopamine system activity (Cloninger 1986). The Table 9.6 presents meta-analyses of studies investigating dopaminergic genes in relation with behaviour and personality.

9.2.2.1 Dopamine Receptor Genes

The Dopamine 2 Receptor Gene (DRD2)

Dopamine's function is mediated by dopamine receptors, among which the dopamine 2 receptor, D2R, also known as the "antipsychotic dopamine receptor", since it constitutes the main target receptor of all antipsychotic drugs.

The D2R receptor is encoded by the DRD2 gene, located at chromosome 11 (11q22–q23). There is a DRD2 gene TaqI restriction fragment length polymorphism (RFLP), giving rise to alleles A1 and A2 (Grandy et al. 1989). Its functional significance has not been fully elucidated yet. Different studies reported an association

Table 9.6 Dopaminergic gene polymorphisms and personality/behaviour

Gene (chromosome location)	Encoded protein	Polymorphisms	Alleles	Behavioural phenotype	Meta-analyses
DRD4 (11p15.5)	Dopamine 4 receptor	48 bp VNTR	S: short alleles, 2R-5R L: long alleles, 6R-10R	Novelty seeking	Meta-analysis of 20 studies (3907 individuals) Results: no association (Kluger et al. 2002)
					1. Meta-analysis of 14 studies (21 separate samples; 2720 individuals) Results: no association between 7R allele and novelty seeking 2. Meta-analysis of ten studies (12 separate samples; 1719 individuals) grouping all long alleles together Results: association between long alleles and novelty seeking (Schinka et al. 2002)
				Novelty seeking Extraversion Trait impulsivity	Meta-analysis of 36 independent non-clinical adult samples (around 5600 individuals); included studies had grouped 48 bp VNTR into short and long alleles Results: no association between long alleles and personality traits, even when European samples were analysed separately (Munafo et al. 2008)
		rs1800955: C-521T SNP	C T	Novelty seeking	Meta-analysis of four studies (677 individuals) Results: association between C/C genotype and novelty seeking (Schinka et al. 2002)
				Novelty seeking Extraversion Trait impulsivity	Meta-analysis of 11 independent non-clinical adult samples (around 1600 individuals) Results: association between C/T and T/T genotype and novelty seeking, as well as trait impulsivity (T allele carriers displayed lower novelty seeking and trait impulsivity levels). No association with extraversion (Munafo et al. 2008)

(continued)

Table 9.6 (continued)

Gene (chromosome location)	Encoded protein	Polymorphisms	Alleles	Behavioural phenotype	Meta-analyses
COMT (22q11.21)	Catechol-o-methyltransferase	rs4680: G472A SNP (Val158Met)	COMT-L: corresponds to methionine and is associated with low enzyme activity COMT-H: corresponds to valine and is associated with high enzyme activity	Suicidal behaviour	Meta-analysis of 6 studies (519 suicide attempters and completers versus 933 healthy controls) Results: association between COMT-L allele and suicidal behaviour (Kia-Keating et al. 2007)
					Meta-analysis of ten studies (1324 suicidal cases versus 1415 healthy controls) Results: no association (Calati et al. 2011)
					Meta-analysis of 12 studies (2723 suicidal cases versus 1886 healthy controls) Results: no association, even when Caucasians and suicide attempters were analysed separately (Tovilla-Zarate et al. 2011)
					Meta-analysis of nine studies (3226 suicidal cases versus 3055 healthy controls) Results: no association (Clayden et al. 2012)
				Aggressive/violent behaviour	Meta-analysis of 15 studies (2370 schizophrenia patients) Results: presence of at least one COMT-L allele increased risk for manifestation of violent behaviour in male schizophrenia patients by around 50% (Singh et al. 2012)

between the A1 allele and reduced D2 receptor activity in different brain areas (Noble et al. 1997), an association between the A1 allele and decreased receptor density (Pohjalainen et al. 1998) as well as an association between the A1 allele and increased dopamine synthesis, perhaps due to decreased D2R receptor expression (Laakso et al. 2005).

A study of more than 2500 adolescents and young adults showed that contrary to the homozygous A1/A1 and A2/A2 genotype, the heterozygous A1/A2 genotype was associated with serious and violent delinquency only in males (Guo et al. 2007). These findings were discussed within the context of "heterosis". Based on this phenomenon, it is heterozygous rather than homozygous individuals manifesting a trait to a greater or lesser extend (Comings and MacMurray 2000). Elsewhere, the A1 genotype (A1/A1 homozygosity or A1/A2 heterozygosity) was related to aggressive-violent behaviour (Chen et al. 2005).

The Dopamine 4 Receptor Gene (DRD4)

The dopamine receptor 4, D4R, is a D2R-like receptor coded for by the DRD4 gene at chromosome 11 (11p15.5). There is a VNTR in exon III, namely, a 48 bp sequence repeated two (2R) to ten (10R) times. Different alleles vary in regard to number of repeats, nucleotide sequence and variant order, leading to different receptor products containing 32–160 amino acids at the corresponding position. Allele frequencies vary greatly between different populations. It was shown that the 4R allele is the most commonly found, together with the 7R and the 2R allele, while alleles 3R, 5R, 6R and 8R are rare. Alleles up to 5R are considered "short", while the rest, including the 7R allele, "long" (Lichter et al. 1993; Chang et al. 1996; Ding et al. 2002). The 7R allele was associated with decreased in vitro gene expression and receptor binding compared with short alleles (Asghari et al. 1994; Asghari et al. 1995).

There is another DRD4 gene polymorphism, namely, a C-521T SNP (rs1800955) in the promoter region, which is in LD with 48 bp VNTR. This SNP was shown to affect gene's transcription, since the T allele was associated with up to 40% lower transcription levels compared with the C allele (Ronai et al. 2001).

Lastly, there is a tandem 120 bp duplication located 1.2 kb upstream from the initiation codon, giving rise to the long (L) and the short (S) allele. It was shown that the S allele was associated with increased transcriptional activity compared with the L allele (D'Souza et al. 2004).

The DRD4 48 bp VNTR and Personality

A study of the DRD4 48 bp VNTR and its association with novelty seeking in a non-clinical Israeli population reported that 7R allele carriers scored significantly higher in novelty seeking (Ebstein et al. 1996).

Another study supported an association between the 48 bp VNTR and novelty seeking in a sample of white Americans, mainly male (95%, mostly male siblings). Instead of examining the 7R allele as previously described, participants were subgrouped into long or short allele carriers, and it was shown that long allele carriers displayed higher levels of trait novelty seeking (Benjamin et al. 1996). The same

association was replicated in another healthy female population, recruited from Japan (Ono et al. 1997), as well as in other Asian (Tomitaka et al. 1999; Lee et al. 2003a) and German (Strobel et al. 1999) populations.

Still, there were studies that were not able to confirm aforementioned results (Baron 1998; Lusher et al. 2001). Contradictory findings were also reported, supporting an association between the 5R allele and high novelty seeking in healthy Japanese individuals (Tsuchimine et al. 2009), an association between the short 2R and 5R alleles and high novelty seeking in a Finnish population (Ekelund et al. 1999) as well as no associations at all in a non-clinical Korean (Kim et al. 2006b) and different Japanese populations (Mitsuyasu et al. 2001; Tochigi et al. 2006).

A former meta-analysis of 20 studies (3907 individuals) applied two different meta-analytic methods. The results did not confirm an association between the 48 bp VNTR and novelty seeking (Kluger et al. 2002). Another meta-analysis published shortly after the previous one reviewed data from 14 studies (21 separate samples, 2720 individuals) and revealed no association between the long 7R allele and novelty seeking. The same study meta-analysed data from ten studies (12 separate samples, 1719 individuals) grouping all long alleles together. In this case, results revealed a significant association between long repeat alleles and high novelty seeking (Schinka et al. 2002). Lastly, a more recent meta-analysis included data from 36 independent non-clinical adult samples (around 5600 individuals). The studies included in this meta-analysis had grouped 48 bp VNTR into short and long alleles and investigated them in relation with novelty seeking, extraversion and trait impulsivity. The results showed absence of an association between long alleles and aforementioned traits, even when samples of European origin were analysed separately. Furthermore, this analysis revealed significant heterogeneity between employed studies (Munafo et al. 2008).

In another study of a mixed population consisting of young men recruited from Harvard University, the 7R allele was proven a significant predictor of sensation seeking, including thrill and adventure seeking (Campbell et al. 2010). Similarly, in a Russian study, 7R allele carriers had higher thrill seeking elements, delinquency and short temper. Still, this was observed only in males, while when social parameters (parental monitoring of youths, exposure to violence) were taken into account, the interaction between thrill seeking and the 7R allele, as well as the gender effect, were no longer significant (Dmitrieva et al. 2011).

Lastly, a study of a Japanese population revealed an association between the 2R-4R short alleles and higher neuroticism levels, including anxiety, depression and vulnerability (Tochigi et al. 2006).

The DRD4 C-521T SNP/120 bp Duplication and Personality

A meta-analysis of four studies (677 individuals) confirmed an association between the C-521T SNP C/C genotype and high novelty seeking (Schinka et al. 2002), a finding that was confirmed by a recent meta-analysis of 11 independent non-clinical adult samples (around 1600 individuals), which reported a significant association between the C-521T SNP and novelty seeking, as well as impulsivity. Namely, T allele carriers (C/T or T/T genotype) displayed lower levels of aforementioned

traits, while the C-521T SNP accounted for 2% of the phenotypic variance. Still, the latter polymorphism was not related to extraversion (Munafo et al. 2008).

Lastly, a study of the tandem 120 bp duplication in regard to novelty seeking was performed in four different clinical samples, one diagnosed with bipolar disorder, one with alcohol dependence and two with depression. Combined data revealed an association with novelty seeking. Specifically, individuals genotyped as S/S scored higher in novelty seeking, including impulsivity, extravagance and disorderliness. Still, due to the fact that the S allele is rare, one could assume that it would not contribute greatly to population variance (Rogers et al. 2004) (Table 9.6).

9.2.2.2 Dopamine Transporter Gene (SLC6A3)

The SLC6A3 Gene Polymorphism

The dopamine transporter 1, DAT1, is a protein regulating dopamine synaptic levels by limiting dopamine receptor activation and facilitating neuronal dopamine reuptake.

This protein is coded for by the gene "Solute Carrier Family 6, member 3" (SLC6A3), located at chromosome 5 (5p15.3). Several DAT1 gene polymorphisms have been described. Among these, there is a 40 bp VNTR most commonly repeated nine (DAT1*9R) and ten (DAT1*10R) times. Less abundant alleles include 3, 7 and 11 repeats (Vandenbergh et al. 1992). There is evidence that this polymorphism may be functional, altering gene expression (Fuke et al. 2001). Although it was found that healthy DAT1*10R/10R genotype carriers showed lower striatal transporter binding (Jacobsen et al. 2000) and DAT1*9R allele carriers increased striatal dopamine transporter availability (van Dyck et al. 2005), contradictory findings were also reported (Heinz et al. 2000).

The DAT1 40 bp VNTR and Behaviour

Contrary to the DAT1*9R/9R genotype, the DAT1*10R/10R and the DAT1*10R/9R genotypes were associated with serious and violent delinquency in males (Guo et al. 2007), as well as with aggressive-violent behaviour (Chen et al. 2005). Still, not all studies were able to confirm an association between the DAT1 genotype and violent behaviour (Reif et al. 2007).

Lastly, DAT1 gene, together with other dopamine-related genes, was implicated in the aetiology of ADHD, which is characterised by impulsive behaviour (Khan and Faraone 2006).

9.2.2.3 Dopamine Beta-Hydroxylase Gene (DBH)

Dopamine beta-hydroxylase, DBH, is an enzyme involved in norepinephrine synthesis by catalysing dopamine hydroxylation. Previous studies showed that low plasma norepinephrine levels were associated with antisocial behaviour (Rogeness et al. 1982; Gabel et al. 1995).

The DBH gene is located at chromosome 9 (9q34.2). There is a C1021T SNP, accounting for about 35–52% of the variance of DBH plasma levels. A German study reported an association between the C1021T SNP and personality traits.

Patients diagnosed with more than two personality disorders and genotyped as T/T displayed higher neuroticism levels, as well as higher levels of neuroticism's facet "anger hostility". The same individuals displayed higher novelty seeking levels, as well as higher levels of novelty seeking's facets "impulsiveness" and "disorderliness" (Hess et al. 2009).

9.2.2.4 Catechol-O-Methyltransferase Gene (COMT)

The COMT Gene Polymorphism

Catechol-o-methyltransferase (COMT) is an enzyme catalysing catecholamine methylation. This o-methylation constitutes a major degrading pathway of catecholamine neurotransmitters dopamine, epinephrine and norepinephrine. Brain COMT activity regulates active dopamine and norepinephrine amounts.

The gene coding for COMT is located at chromosome 22 (22q11.21). There is a functional SNP in exon 4 (rs4680, G472A transition), resulting in an amino acid change, i.e. valine is substituted by methionine at codon 158 of membrane-bound COMT (Met158Val) and at codon 108 of soluble COMT (Met108Val). The G472A polymorphism was shown to decrease enzyme thermostability and therefore activity three- to fourfold. Specifically, genetically polymorphic COMT enzyme activity may be low (COMT-LL, corresponding to Met/Met genotype), intermediate (COMT-LH, corresponding to Met/Val genotype) or high (COMT-HH, corresponding to Val/Val genotype). Altogether, carriers of the more active form of the enzyme display less dopamine for neurotransmission (Lachman et al. 1996; Stahl 2003).

The G472A Polymorphism and Behaviour/Personality

The COMT-LL genotype was associated with violent suicide attempts (e.g. hanging, shooting, etc.) but not with non-violent (e.g. drug overdose, gas suffocation, etc.) in a German psychiatric population, independent of diagnosis, compared with healthy controls. Additionally, the latter study found a correlation between the COMT genotype and state anger assessed by the State-Trait Anger Expression Inventory. Specifically, the COMT-HH genotype was related to inward anger expression (higher scores in "Anger-In") while the COMT-LL genotype with outward anger expression (higher scores in "Anger-Out") (Rujescu et al. 2003a). Still, an association between the G472A polymorphism and suicidal behaviour was not confirmed in another mixed (mainly Caucasian) (Russ et al. 2000) and in a Mexican population (Tovilla-Zarate et al. 2011).

Altogether, a meta-analysis of six studies (519 suicide attempters and completers versus 933 healthy controls) revealed a significant association between the COMT-L allele and suicidal behaviour, which was not affected by age or ethnicity. Several studies reported though a gender effect on the association between the G472A polymorphism and suicidal behaviour, reporting COMT-L allele to be more abundant in male compared to female suicidal cases. In accordance, aforementioned meta-analytic results were shown to be affected by the proportion of females to males in both suicidal cases and healthy controls, a gender effect that requires further investigation (Kia-Keating et al. 2007). On the contrary, a subsequent meta-analysis of ten

studies (1324 suicidal cases versus 1415 healthy controls) considering both allele frequency and genotype did not report an association between the G472A polymorphism and suicidal behaviour. The meta-analysis of three among ten studies, which compared suicide attempters versus non-suicide attempters diagnosed with the same psychiatric disorders (mood disorders and schizophrenia), showed again lack of any association (Calati et al. 2011). A following meta-analysis of 12 studies (2723 suicidal cases versus 1886 healthy controls) did not find any association between the risk COMT-L allele and suicidal behaviour, even when Caucasians and suicide attempters were analysed separately (Tovilla-Zarate et al. 2011). Lastly, a meta-analysis of nine studies (3226 suicidal cases versus 3055 healthy controls) confirmed lack of an association between the G472A polymorphism and suicidal behaviour (Clayden et al. 2012).

In regard to aggressive behaviour, one study of unselected women showed that COMT-LL carriers displayed lower levels of physical aggression compared with COMT-HH carriers (Kulikova et al. 2008). Altogether, although there was discrepancy in study findings, the G472A polymorphism (in particular COMT-HH genotype) may be associated with aggressive traits [for review see Calati et al. (2011)].

There was one meta-analysis that included 15 studies of the G472A polymorphism in relation with violent behaviour within the context of schizophrenia (2370 schizophrenia patients). Based on results, the presence of at least one COMT-L allele increased risk for violent behaviour in male schizophrenia patients by around 50%. No association was found in females or when data from male and female patients was pooled together (Singh et al. 2012).

Other studies focused on the relation between the COMT genotype and personality traits. There were reports of an association between the COMT-HH genotype and high levels of extraversion, the COMT-HH genotype and the "exploratory excitement" component of novelty seeking in healthy individuals (Reuter and Hennig 2005) as well as the COMT-HH genotype and novelty seeking in a non-clinical female Chinese population (Tsai et al. 2004b). In accordance with previous findings, a study of a non-clinical German population revealed an association between the G472A polymorphism and sensation seeking in females. Specifically, female subjects genotyped as COMT-HH showed higher levels of sensation seeking, including disinhibition, boredom susceptibility and thrill and adventure seeking, compared with subjects genotyped as COMT-LH and COMT-LL (Lang et al. 2007).

Since harm avoidance was correlated inversely with novelty and sensation seeking (McCourt et al. 1993), aforementioned results were not supported by a study of a Korean population, reporting a different association between the COMT genotype and harm avoidance again only in females. Specifically, females carrying the COMT-LL genotype showed the lowest harm avoidance levels, whereas the COMT-LH genotype was associated with intermediate and the COMT-HH with higher harm avoidance levels (Kim et al. 2006c). Lastly, there was some evidence for an association between the COMT-LL genotype and neuroticism in females, which was drawn though from a study employing a selected population (high or low scorers) (Eley et al. 2003).

Altogether, the COMT G472A polymorphism was shown to exhibit a sexually dimorphic effect, relating to personality traits only in females. A plausible explanation could be the correlation between the COMT-HH genotype and low oestrogen levels, which were in turn associated with lower thrill and adventure seeking levels in healthy females (Balada et al. 1993). Still, the latter observation is again not in accordance with previously presented studies [for review of the G472A polymorphism studies in relation to personality traits, see Calati et al. (2011)] (Table 9.6).

9.2.3 Genes Involved in Sexual Behaviour

9.2.3.1 Arginine Vasopressin Receptor 1A Gene (AVPR1A)

Arginine vasopressin (AVP), also called "antidiuretic hormone" (ADH), is a hormone regulating body water retain. Recent evidence suggested though that AVP may be also implicated in social, sexual and reproductive behaviour (Insel 2010).

The arginine vasopressin receptor 1 gene, AVPR1A, is located at chromosome 12 (12q14.2), and its polymorphisms have been studied in relation with reproductive behavioural motifs in other mammals (Young 2002). One study extended research of AVPR1A polymorphisms in humans. A large population consisting of 2085 males and females was genotyped at two different gene loci, c.-5518 AVPR1A (TC)x(TG)y and c.-2481 AVPR1A (AGAT)7_16. Alleles were grouped as short, medium and long for each polymorphism, giving rise to six possible genotypes: short/short, short/medium, short/long, medium/medium, medium/long and long/long. It was observed that males genotyped as long/long AVPR1A (TC)x(TG)y and females genotyped as long/long AVPR1A (AGAT)7_16 showed an increased probability of beginning sexual intercourse at an earlier age, i.e. before the age of 15 (Prichard et al. 2007b).

9.2.3.2 Oxytocin Receptor Gene (OXTR)

Oxytocin is a protein involved in attachment processes, such as social, familiar and maternal bonding, as well as in sexual reproduction. Its function is mediated by oxytocin receptor, OXTR, encoded by a gene located at chromosome 3 (3p25.3).

A large population consisting of 2085 males and females was genotyped at gene locus 1170*712 OXTR (CA)10_15. Alleles were grouped as short and long, giving rise to three genotypes: short/short, short/long and long/long. Based on results, it was more probable for females genotyped as long/long not to use oral contraceptives and to have children at a younger age (Prichard et al. 2007b).

9.2.4 Other Genes

9.2.4.1 Nitric Oxide Synthase Gene (NOS1)

Nitric oxide, NO, is an abundant neurotransmitter in emotion-regulating brain areas. The neuronal nitric oxide synthase, NOS-I, is coded for by NOS1 gene, located at chromosome 12 (12q24.3). The NOS1 is a complex gene, containing multiple

protein-coding exons, as well as a variable region with multiple first exons (Zhang et al. 2004a).

There is a highly polymorphic CA dinucleotide repeat (180–210 repeats) within the promoter region (exon 1f), termed NOS1 Ex1f VNTR. Alleles containing 180–196 repeats were defined as short/S and were associated with decreased gene expression, while alleles containing 198–210 repeats were defined as long/L and were associated with maximal gene expression. The NOS1 Ex1f VNTR polymorphism was also shown to dysregulate many other different genes (Reif et al. 2009).

A study of more than 3200 probands (mixed population consisting of healthy controls, patients diagnosed with personality disorder or ADHD, suicide attempters and criminal offenders) reported that the S alleles were associated with psychiatric disorders manifesting impulsive behaviour as a common phenotype, such as ADHD and cluster B personality disorders. Additionally, S alleles were associated with suicidal and aggressive/criminal behaviour, phenotypes relating to impulsivity (Reif et al. 2009).

Still, the implication of NOS1 Ex1f VNTR in the manifestation of impulsiveness warrants further research. The same, above-mentioned, research group assessed impulsiveness and empathy in a male population consisting of criminal offenders with a history of a psychiatric disorder but without acute psychopathology. Previous results were not fully replicated, while there were also contradictory outcomes, since it was heterozygous S/L individuals displaying the highest impulsivity levels, a phenomenon previously described as "heterosis". On the other hand, homozygous S/S carriers displayed the lowest impulsiveness levels and the highest empathy levels. Conflicting results were attributed to behavioural phenotypes and measures being related but not identical, as well as to employment of a different study population, in the latter case with high psychiatric comorbidity (Retz et al. 2010). Another explanation for outcome diversity could be the fact that environmental factors may moderate the effect of gene polymorphisms on behavioural phenotype. In an effort to clear the issue, the same research group conducted a longitudinal study of children (mean age 15 years) followed up as adults (mean age 18 years). Based on study outcomes, a hypothesis was formed. Short alleles were considered risk alleles for trait adaptive impulsivity, i.e. fast decision-making and excitement seeking, while the S/S risk genotype was associated with behavioural measures of impulsivity. These findings applied for male participants. On the other hand, maladaptive impulsivity, i.e. disinhibition and thoughtlessness, was associated again with the S/S risk genotype, though only in participants with a history of stressful life events, specifically increased perceived maternal rejection and beliefs that parents showed lack of love, appreciation and care towards them. Altogether, environmental stressful events could mediate the phenotypic outcome of the risk S/S genotype, turning adaptive impulsivity into dysfunctional (Reif et al. 2011).

9.2.4.2 Androgen Receptor Gene (AR)

The androgen receptors mediate testosterone's (i.e. hormone implicated in the development of primary male sexual characteristics) and dihydrotestosterone's (i.e. hormone regulating secondary male characteristics) function. The androgen

receptor gene, AR, is located at X chromosome (Xq12) and presents with a triallelic polymorphism [GCA locus or AR_(CAG)n], giving rise to short, medium and long alleles. Caucasian males homozygous for the medium allele showed more severe antisocial traits. However, it should be noted that this association was rather weak (Prichard et al. 2007a).

9.2.4.3 Nuclear Receptor 4A2 Gene (NR4A2)

Nuclear receptor subfamily four group A member 2, NR4A2, is a protein possibly functioning as a transcription factor involved in dopamine neuron development (Sacchetti et al. 2001). It is encoded by a gene located at chromosome 2 (2q24.1). There was some evidence for an association between the long/long NR4A2 (AC) genotype and antisocial traits in females, a finding that requires though further verification (Prichard et al. 2007a).

9.2.4.4 Transcription Factor AP-2 Beta Gene (TFAP2B)

Transcription factor AP-2 beta, TFAP2B, is a protein acting both as a transcriptional activator and repressor, mediating monoaminergic neuron development and regulating gene expression. The corresponding gene is located at chromosome 6 (6p12.3). There are two polymorphisms in strong LD, TFAP2B (AACA) and TFAP2B (TC) (Prichard and Easteal 2006).

The TFAP2B (CAAA) polymorphism, an intron 2 tetranucleotide repeat (CAAA), repeated four or five times, was associated with different personality traits, such as somatic anxiety and indirect aggression (Damberg et al. 2000). In another study, the short/long genotype of TFAP2B (TC locus) was associated with antisocial traits in females (Prichard et al. 2007a).

9.2.4.5 FK506 Binding Protein 5 Gene (FKBP5)

FK506 binding protein 5, FKBP5, is a heat shock protein 90 co-chaperone, regulating the activity of glucocorticoid receptors and as a result the hypothalamic-pituitary-adrenal axis. The corresponding gene, located at chromosome 6 (6p21.31), has been studied in regard to dysregulated stress response in affective and anxiety disorders (Gillespie et al. 2009).

There are four FKBP5 gene SNPs (rs3800373, rs9296158, rs1360780 and rs9470080) in strong LD, giving rise to six haplotypes. Among these, haplotypes H1 and H2 are considered functional. Three possible diplotypes may be formed, derived from the combination of these two functional haplotypes, H1/H1, H1/H2 and H2/H2.

Study of the aforementioned FKBP5 gene SNPs in a population of substance-dependent African-Americans revealed an association between H1/H1 diplotype and suicidal behaviour, though only in participants with a history of childhood trauma (Roy et al. 2010), while another study reported that the less common H2/H2 diplotype was associated with increased risk for aggressive-violent behaviour in male prisoners with a background of physical abuse (Bevilacqua et al. 2012).

9.2.4.6 Brain-Derived Neurotrophic Factor Gene (BDNF)

Brain-derived neurotrophic factor, BDNF, is a member of the neurotrophin superfamily, a nervous system growth factor implicated in neuronal differentiation, growth, survival and death, affecting multiple neurotransmitter systems, among which the serotonergic and the dopaminergic. It is encoded by a gene located at chromosome 11 (11p14.1). There is a functional SNP (rs6265), G196A, resulting in an amino acid substitution (valine is substituted by methionine at codon 66, Val66Met). The more common G allele codes for valine, while the A allele codes for methionine. An in vitro study indicated that the G196A polymorphism was functional, since the A/A genotype was associated with decreased BDNF neuronal secretion (Egan et al. 2003).

The first meta-analysis of 12 studies (1202 suicidal patients diagnosed with psychiatric disorders versus 1699 non-suicidal patients diagnosed with the same psychiatric disorders and 451 healthy controls) investigating the relation between the G196A polymorphism and suicidal behaviour showed that the low-functioning A allele constituted a risk allele. The association between the A allele and suicidal behaviour was more significant in Asian populations (Chinese, Japanese, Korean) as well as when suicide attempters were compared with non-suicide attempters diagnosed with the same psychiatric disorders (eight studies) (Zai et al. 2012). Contrary to previous findings, a subsequent meta-analysis of seven studies (1700 suicidal cases versus 2584 healthy controls) did not reveal a significant association between the G196A polymorphism and suicidal behaviour (Clayden et al. 2012).

A study of a non-clinical German population focused on the association between the G196A polymorphism and different personality traits. Based on results, the BDNF genotype explained 1.9% of the variance of trait anxiety. Specifically, trait anxiety was significantly higher in G/G carriers (Lang et al. 2005).

In another study, the G allele was associated with increased neuroticism levels, explaining 4% of the genetic variance. Specifically, and in regard to six neuroticism facets, the association was confirmed between the G allele and increased anxiety, depression, self-consciousness and vulnerability (Sen et al. 2003). Similarly, G/G genotype carriers within a German population showed higher neuroticism levels compared with G/A and A/A carriers. It should be noted though that the latter findings failed to reach statistical significance (Lang et al. 2005). Another study of a healthy Japanese population reported an association between the A/A genotype and extraversion, though only in females (Itoh et al. 2004), while a recent genome-wide association study confirmed the association between the G196A polymorphism and extraversion (Terracciano et al. 2010).

On the other hand, a study of a healthy female Chinese population failed to confirm any association between the G196A polymorphism and different personality traits (novelty seeking, harm avoidance, reward dependence and persistence) (Tsai et al. 2004a).

Altogether, a meta-analysis of four studies (non-clinical population consisting of 607 individuals) investigated the relation between the G196A polymorphism and harm avoidance. Results showed that the A/A genotype was associated with a

trend towards higher harm avoidance. The same meta-analysis investigated the association between the G196A polymorphism and neuroticism pooling five studies (non-clinical population consisting of 1633 individuals). According to the results, the G/G genotype was associated with higher neuroticism levels (Frustaci et al. 2008).

Lastly, a study of a non-clinical Korean population investigated both COMT G472A polymorphism and BDNF G196A polymorphism in relation to sensation seeking and reported no significant associations when the two polymorphisms were considered separately. On the contrary, focus on the combined effect of COMT and BDNF polymorphisms on sensation seeking revealed a significant association with only one sensation seeking facet. Specifically, among female homozygous or heterozygous COMT-L carriers, female BDNF G/G carriers displayed higher boredom susceptibility levels (Kang et al. 2010) (Table 9.7).

9.2.4.7 Nerve Growth Factor Gene (NGF)

The nerve growth factor, NGF, is a neurotrophic factor involved in neuronal growth and survival of basal forebrain cholinergic neurons. Although the NGF complex consists of α, β and γ subunits, it is the β subunits exhibiting NGF stimulating function.

The NGF gene is located at chromosome 1 (1p13.2). There is a non-synonymous C104T SNP (rs6330) giving rise to the more common C allele coding for alanine and the T allele coding for valine. This amino acid substitution (alanine is substituted by valine at codon 35, Ala35Val) may affect NGF secretion (Syed et al. 2007).

A study of a non-clinical German population revealed a gender-specific effect of the C104T polymorphism on state-trait anxiety levels. Specifically, females genotyped as C/C showed increased anxiety levels compared with heterozygous carriers. Contrary to females, males genotyped as C/C displayed lower anxiety levels compared with heterozygous carriers. Still, results were not significant in both females and males, when homozygous C/C were compared with homozygous T/T individuals (Lang et al. 2008).

9.2.4.8 Cholinergic Receptor Nicotinic Alpha 4 Subunit Gene (CHRNA4)

The cholinergic system is involved in neural plasticity and associated with learning. The nicotinic acetylcholine receptors constitute a receptor family, whose members are formed by diverse combinations of five different subunits (α1–α10 and β2–β4). The neuronal receptor α4β2 is the main receptor found in mammalian brain (Gotti et al. 2009). The α4 subunit is encoded by the CHRNA4 gene, located at chromosome 20 (20q13.2–13.3). There is a synonymous SNP (rs1044396) in exon five, a C to T transition, giving rise to two alleles. Although the SNP does not cause any amino acid change, there is evidence that it affects receptor sensitivity (Eggert et al. 2015).

Table 9.7 Brain-derived neurotrophic factor gene polymorphism and behaviour

Gene (chromosome location)	Encoded protein	Polymorphism	Alleles	Behavioural phenotype	Meta-analyses
BDNF (11p14.1)	Brain-derived neurotrophic factor	rs6265: G196A SNP (Val66Met)	G: the more common coding for valine A: coding for methionine; A/A genotype was associated with decreased BDNF neuronal secretion	Suicidal behaviour	Meta-analysis of 12 studies (1202 suicidal patients diagnosed with a psychiatric disorder versus 1699 non-suicidal patients diagnosed with the same psychiatric disorders and 451 healthy controls) Results: association between A allele and suicidal behaviour, which was even more significant in Asian populations (Chinese, Japanese, Korean), as well as when suicide attempters were compared with non-suicide attempters diagnosed with the same psychiatric disorders (Zai et al. 2012)
					Meta-analysis of seven studies (1700 suicidal cases versus 2584 healthy controls) Results: no association (Clayden et al. 2012)

In a study of a non-clinical sample, contrary to T allele carriers, C/C carriers displayed higher levels of negative emotionality, specifically anxiety and emotional instability, in combination with more intense harm avoidance and behavioural inhibition (Markett et al. 2011). A German study of a large population (1673 subjects) obtained from a German multicentre study of nicotine dependence genetics confirmed aforementioned results, reporting an association between the C allele and higher harm avoidance, as well as increased neuroticism levels (Bey et al. 2016).

Lastly, a study of maltreated children showed that the rs1044396 polymorphism moderated the effects of maltreatment on childhood personality outcome. Children carrying the T/T genotype displayed higher neuroticism levels when they had a background of childhood maltreatment. Contrary to maltreated, non-maltreated children carrying the T/T genotype displayed lower neuroticism levels and higher levels of openness to experience (Grazioplene et al. 2013).

9.3 Conclusions

9.3.1 Discrepancy in Study Outcomes

Association studies within the research field of behavioural genetics have provided in several cases controversial or inconsistent results. There are different issues in regard to study design, leading to outcome discrepancy and difficulties in interpreting findings. Inadequate study strategies may lead to false-positive, probably on chance, or false-negative results. Several factors should be taken into consideration when studying genetic background of behaviour and personality:

1. *Ethnicity*: studies of diverse ethnic groups, showing different allele variant frequency, should pay considerable effort in sample selection so as to avoid bias (Li and He 2007). For instance, research outcomes of MAOA, one of the most studied genes in relation to aggression, were characterised by both discrepancy and inconsistency, partly due to different MAOA allele frequency in diverse ethnic groups (Lea and Chambers 2007). Furthermore, it should be noted that the risk MAOA-L allele is not uncommon, occurring in 40% of the population (Brunner et al. 1993a, b; Hunter 2010).

   Additionally, different allele frequencies between cases and healthy controls in case-control study designs may also confound results. For instance, the frequency of the 5-HTTLPR S allele was shown to be significantly different between Caucasian and Asian healthy controls. In this sense, family-based designs could provide a more appropriate study approach (Lin and Tsai 2004).

   Lastly, the discovery of population-specific mutations associating with behavioural characteristics emphasises the importance of exact description of study populations' genetic background (Brunner et al. 1993a, b; Kelsoe 2010; Zai et al. 2012).

2. *Demographics*: in case of genes with a sexually dimorphic effect, such as the COMT gene, or X-linked genes, such as the MAOA gene, several studies recruited selected samples in regard to sex, possibly limiting results to these particular populations (Manuck et al. 2000; Tsai et al. 2004b; Kulikova et al. 2008). Specifically, MAOA-H/MAOA-L heterozygosity is only present in females, while males are always homozygous, due to the presence of one X chromosome. Since MAOA expression in heterozygous cases has not been fully elucidated yet, many studies excluded all females or included strictly female homozygous allele carriers (Kim-Cohen et al. 2006; Alia-Klein et al. 2008; Derringer et al. 2010; Ficks and Waldman 2014). Furthermore, only a few researchers have provided data on allele frequency in males and females separately, hindering analysis of a plausible gender effect on study outcomes (Lin and Tsai 2004).

   Age is another important variable, specifically in research of gene polymorphisms and personality traits. For instance, novelty seeking diminishes with age, as most personality traits do. In order to avoid bias, recruited individuals should be preferably under the age of 45 (Lusher et al. 2001; Lang et al. 2005). Furthermore, socio-economic or cultural differences may also affect study outcomes in regard to personality traits (Campbell et al. 2010; Kang et al. 2010).
3. *Methodological issues*: studies employing large populations may be at risk of finding false associations, while studies of small populations may fail in revealing statistically significant results. Furthermore, contrary to studies of unselected populations, studies employing selected samples may lead to overestimation of a genetic association, since they focus only on the extremes of normal distribution (Munafo et al. 2008).

   Different definition of a behavioural phenotype may also result in inconsistent findings across studies. For instance, it should be noted that self-report measures of aggression may reflect trait aggression, without reflecting aggressive acts. Additionally, most behaviours and personality traits constitute a continuum that may be defined by a different genetic background. For instance, animal studies suggested that trait aggression may be positively associated with serotonergic activity, whereas impulsive/violent state aggression may be negatively associated with serotonergic activity (Olivier and van Oorschot 2005). Another example is the behavioural spectrum of suicidal behaviour, ranging from death wish to completed suicide. Within this spectrum, suicide attempt constitutes also a broad phenotype, including failed suicide (strong intent of dying, usually careful planning, lethal/violent suicide methods) and suicide gesture (less intent of dying, usually a reaction to acute interpersonal conflicts, less lethal/non-violent suicide methods) (Mann 1998). In this sense, genetic background of severe/violent suicidal behaviour may be different from genetic background in cases of milder/non-violent suicidal manifestations (Lin and Tsai 2004). Accordingly, suicide completers may constitute a distinct group from suicide attempters (Clayden et al. 2012). Lastly, diversity in assessment tools, employed for measuring a specific behaviour or a personality trait, was also shown to moderate results (Schinka et al. 2004). Altogether, each study should describe clearly the

behaviour being studied in a particular population, by defining assessment tools and what these measure.

4. *Common pathophysiology*: the possibility of a common pathophysiology underlying extreme manifestation of a specific behaviour and psychiatric disorders should not be overlooked. For instance, alcohol dependence and anorexia/bulimia nervosa are examples of psychiatric disorders characterised by impulsive behaviour. Both disorders were associated with the G-1438A 5-HT2A polymorphism. Additionally, there was evidence that the COMT gene may be a risk gene for schizophrenia. Based on a meta-analysis, presence of at least one COMT-L allele (G472A polymorphism) increased risk for violent behaviour in male schizophrenia patients by around 50% (Williams et al. 2007; Singh et al. 2012).

   Similarly, suicidal behaviour has been mostly studied within the context of different psychiatric disorders, e.g. affective, schizophrenia spectrum, personality and substance use disorders, since 90–95% of suicidal individuals are diagnosed with at least one psychiatric disorder (Gonzalez-Castro et al. 2013a, b). Research has provided evidence for a genetic component for most psychiatric disorders that usually involves the serotonergic and the dopaminergic system. Therefore, it cannot be excluded that risk genes for impulsive, aggressive or suicidal behaviour overlap with susceptibility genes for psychiatric disorders, confounding results. Others suggested that serotonergic system dysfunction may predispose to both suicidal behaviour and psychiatric disorders. In such a case, only psychiatric patients carrying a particular risk allele would manifest suicidal behaviour (Lin and Tsai 2004). Still, although suicidal behaviour has been associated with both TPH1 (Courtet et al. 2005) and SLC6A4 gene (Li and He 2007) independent of psychiatric diagnosis, others failed to confirm this association, claiming that psychiatric history is a major confounding factor. The latter assumption was based on the fact that genetic associations were not confirmed when suicidal versus non-suicidal psychiatric patients were compared (Saetre et al. 2010).

   Altogether, due to comorbidity between specific behaviours, e.g. suicidal and aggressive behaviour, and psychiatric disorders, case-control analyses carry mental health status as a confounding factor. Thus, differentiating the genetic component of a behaviour from the genetic component of a psychiatric disorder may prove a difficult challenge (Schild et al. 2013).

5. *Common comorbidity*: common comorbidity between psychiatric disorders suggests that a certain biological substrate may be shared. Thus, elucidating genetics of a behavioural phenotype present within the context of different diagnostic categories may prove difficult, since the genetic contribution to the behavioural phenotype may be masked by the genetic contributor to comorbid psychiatric disorders.

6. *Environmental factors*: study results have not always supported the association between a gene polymorphism and a particular behaviour or personality trait, such as in case of the MAOA-uVNTR polymorphism and aggressive/antisocial behaviour (Jacob et al. 2005; Huizinga et al. 2006; Widom and Brzustowicz 2006). This may be partly attributed to the fact that the effects of the MAOA

gene polymorphism on the manifestation of aggressive/antisocial behaviour were shown to be moderated by environmental factors, specifically childhood maltreatment (Caspi et al. et al. 2002; Hart and Marmorstein 2009; Derringer et al. 2010). Therefore, studies investigating gene effects without considering history of stressful environmental factors may not be able to reveal an association between a gene polymorphism and a particular behaviour.

7. *Allele grouping:* in case of the DRD4 48 bp VNTR, most studies grouped alleles into short (up to 5) and long (6, 7, 8) repeats. Still, the 7R allele is evolutionary younger than the common 4R allele and has increased in frequency due to positive selection. Thus, it may not be so simply related to other long alleles. Additionally, the 7R allele is extremely rare in Asians; thus it could not possibly contribute to the manifestation of novelty seeking (Kluger et al. 2002).

In regard to the TPH1 gene polymorphisms, diverse A218C and A779C polymorphism alleles have been associated with the manifestation of suicidal behaviour. Therefore it cannot be excluded that the "causative" risk allele is another one, until now unknown, which is not in strong LD with the TPH1 genetic variants implicated so far in suicidal behaviour. As a result, the TPH1 genetic variant associated with suicidal behaviour may depend on the original haplotype carrying the unknown risk allele (Lalovic and Turecki 2002).

Furthermore, several SNPs are not functional and may be in strong LD with other "causative" polymorphisms, located perhaps at different chromosomes. Additionally, a single polymorphism probably accounts for a small proportion of the variance, contributing minorly to the manifestation of a behaviour or expression of a personality trait. Thus, a haplotype approach could be more elucidating (Kluger et al. 2002). For instance, a study of suicide completers investigated the association between three different TPH1 SNPs (A218C; promoter region A-6526G; promoter region G-5806T) and the more extreme manifestation of suicidal behaviour. These three SNPs were in strong LD and were not found to be related to suicidal behaviour when they were analysed separately. On the contrary, when haplotype analysis was conducted, considering all three SNPs simultaneously, the haplotype -6526G-5806T-218C was more abundant in violent suicide completers compared with healthy controls. Based on results, haplotype analysis provided increased statistical power for the identification of a risk locus. Furthermore, although the A218C SNP alone does not seem to be functional, the risk haplotype could affect protein binding (Turecki et al. 2001).

9.3.2 Meta-analyses

Individual studies may lack sufficient statistical power to detect small gene effects. As a result, meta-analyses have been extensively applied in the field of behavioural genetics to investigate a global effect with a greater statistical power, based on studies using smaller sample sizes. Meta-analyses are additionally used to search for sources of heterogeneity between different studies, excluding studies with

significant contribution to the magnitude of an association. Although they were proven a useful tool for quantitative summarisation of heterogeneous and/or small sample size studies, meta-analyses are prone to false-positive results due to publication bias (Anguelova et al. 2003). Publication bias is attributed to the fact that studies reporting positive associations are more likely to get published compared with studies reporting negative outcomes (Bellivier et al. 2004). Inclusion of less negative studies, as well as unpublished negative studies, may lead to meta-analyses' undersampling. Thus, studies reporting non-significant associations are equally important as studies with positive findings, in order to avoid overestimation of an association (Munafo et al. 2008). For instance, there was a meta-analysis of the TPH1 A218C polymorphism in relation to suicidal behaviour that pooled data from only one study reporting a positive and six studies reporting a negative association. Overall results revealed a positive association (Bellivier et al. 2004). The one research field that does not seem to be affected by publication bias is genetics of suicidal behaviour (Anguelova et al. 2003).

Still, there were cases of similar meta-analyses, reporting contradictory results, such as in the case of the association between the BDNF G196A polymorphism and suicidal behaviour (Clayden et al. 2012; Zai et al. 2012). Contradictory results may be explained by factors similar to the ones causing heterogeneity between individual studies:

1. *Ethnicity*: pooling samples from different ethnicities is a source of heterogeneity. For instance, genetic distinct populations, such as the Ashkenazi population, were shown to be a significant source of heterogeneity in meta-analyses (Bellivier et al. 2004). Therefore, there were meta-analyses that took ethnicity into consideration, pooling data from studies of Caucasian populations only (Rujescu et al. 2003b; Bellivier et al. 2004).
2. *Methodological issues*: diversity in assessment tools of behaviour and personality was shown to moderate results (Schinka et al. 2004). Therefore, meta-analyses should include studies applying the same measuring tools. For instance, a meta-analysis of the DRD4 48 bp VNTR in relation to novelty seeking based on studies assessing novelty seeking explicitly by Cloninger's TPQ questionnaire (Kluger et al. 2002) revealed different outcomes from a meta-analysis pooling studies independent of assessment scales (Schinka et al. 2002). Lastly, different meta-analytic methods may also contribute to contradictory findings. There were meta-analyses applying fixed effects model, which assumes the same true genetic effects, while other meta-analyses used the random effects model, which assumes normally distributed effects. The latter model may be more advantageous, considering and parameterising in between study variability (Lin and Tsai 2004).
3. *Non-homogeneous phenotypes*: as previously mentioned, human behaviour and personality constitute a spectrum. For instance, suicidal behaviour includes both non-violent and violent suicide. Pooling all suicidal cases together may be a reason why there were negative results among meta-analyses pooling suicide attempters and completers together, instead of analysing them separately (Lalovic and Turecki 2002; Kia-Keating et al. 2007). Contrary to suicidal behav-

iour, another meta-analysis did not prove broad definition of antisocial behaviour to be a cause of heterogeneity among studies (Ficks and Waldman 2014).

4. *Different psychiatric history*: a meta-analysis clearly showed that psychiatric diagnosis (mixed psychiatric populations or psychiatric populations with unclear diagnosis) is a significant source of heterogeneity (Wang et al. 2015). For instance, inclusion of suicidal bipolar patients was shown to moderate meta-analytic results, while inclusion of suicidal patients with different psychiatric diagnoses was not (Bellivier et al. 2004). Altogether, psychiatric history may contribute to outcome diversity, at least in case of genetic studies of suicidal behaviour (Tovilla-Zarate et al. 2011).
5. *Environmental factors*: since behavioural and personality outcome is not affected by genetic factors alone, moderating effects of environmental factors should be taken into consideration. Meta-analyses of studies of gene-environment interactions probably constitute a crucial step towards drawing more certain conclusions (Taylor and Kim-Cohen 2007; Ficks and Waldman 2014).

9.3.3 Closing Remarks

Psychopathology may be viewed as the extreme manifestation of behaviours and personality traits normally distributed in a population. A future aim of behavioural genetics is prediction of the probability that an individual with a specific genetic variation will manifest impulsive, suicidal, aggressive or antisocial/criminal behaviour, behaviours often expressed within the context of different psychiatric disorders. Accordingly, elucidation of the genetics of personality could contribute to early diagnosis and intervention in case of personality disorders (Mulder et al. 1999). Lastly, a wedge issue in regard to behavioural genetics would be adducing evidence of genotypic data explaining aggressive/violent behaviour in legal trials of criminal defendants (Bernet et al. 2007). Genetic studies of criminal behaviour raised severe legal issues. In 2009, a court in Italy lightened the sentence of a man convicted for murder by 1 year, based on scientific evidence linking his violent behaviour to "abnormal genes". Others suggested though tougher sentences in cases of evidence linking criminal behaviour with genetic background, arguing that a genetically determined behaviour will probably be repeated and cannot be treated.

Still, research is a long way before contributing to aforementioned goals. To date, reported associations between gene polymorphisms and behavioural/personality outcomes were proven relatively weak. Furthermore, the influential effect of different study inclusion on meta-analytic outcomes underlines discontinuity in results (Schild et al. 2013; Vassos et al. 2014). Associating a single gene polymorphism with behaviours and personality traits was proven a non-accomplishable task until now. Both human behaviour and personality are of complex origin, the result of genes interacting with each other, as well as with environmental factors. Additionally, behaviour and personality traits manifest themselves in a continuum. Complex phenotypes lying on a continuum are most probably attributed to polygenic inheritance.

Altogether, studies of the association between specific alleles and behaviours/personality traits have mostly contributed to exclude the theory of a single gene's major contribution. "Missing heritability" has been attributed to variants, possibly rare variants with greater effects, which have not been discovered yet, or to gene-gene interactions (Manolio et al. 2009; Zuk et al. 2012). Since a research approach focusing on separate risk alleles was proven unfruitful, genome-wide association studies of large populations (thousands) assaying multiple SNPs could constitute a more effective approach for the identification of candidate genes (Schild et al. 2013; Vassos et al. 2014).

Lastly, behavioural genetics alone are in danger of failing in contributing substantially to effective drug treatment. A certain "risk" allele may not always correspond with high or low protein activity. As a result, the mechanism mediating the effects of a risk genotype remains in several cases unknown. Thus, supplementary studies, enlightening the effects of gene polymorphisms on pathophysiology and focusing on epigenetic regulation, are required.

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