Chapter 18

Understanding the genetics of empathy and the autistic spectrum

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Understanding other minds is at the heart of social functioning. We constantly process a multitude of social cues across a range of sensory modalities, and respond to them. Empathy plays a central role in all such processes, and is defined as the capacity to understand the emotions and mental states of others, and respond to them with an appropriate emotion. There is considerable variation of empathy in the general population, and individuals with autism spectrum conditions (ASC) are largely represented at the low end of this distribution.

Recent years have seen significant advances in understanding the neurobiology of empathy and its individual differences (Chakrabarti & Baron-Cohen, 2006; Singer & Lamm, 2009). Independently, human molecular genetics has made enormous advances in the past decade, both in delineating the role of specific genes as well as making it possible to identify a large number of sequence variations (e.g. polymorphisms) in the whole human genome at once. This is not to discount the important role that experience and learning plays in the development of empathy, but this chapter focuses narrowly on the role of genes (Baron-Cohen, 2011; Bowlby, 1969). It is therefore timely to take a multilevel perspective in the study of empathy that spans from genes to cognition. In this chapter, we provide a brief overview of genetic approaches to study empathy and other trait measures of ASC. We then describe a recent study from our group, using dimensional phenotypic measures of empathy and autistic traits. Finally, we discuss some initial studies that relate genetic variation to "intermediate phenotypes" (also known as endophenotypes) relevant to autism and empathy.

Empathy and its heritability

Empathy is not a unitary construct, and most theoretical accounts suggest the existence of at least two factors, which are cognitive empathy (which includes "theory of mind") and affective empathy (which includes "emotional contagion"). A third component that includes prosocial behaviour has also been suggested (Chakrabarti & Baron-Cohen 2006; Preston & de Waal, 2002). The importance of this fractionation is apparent in identifying neurological dissociations between the different components of empathy. For example, it is suggested that people with psychopathic personality disorder may have intact cognitive empathy (hence being able to deceive others), but impaired affective empathy (hence being able to hurt others), whilst people with autism may show the opposite profile (hence finding the social world confusing because of their deficit in cognitive empathy, but not being over-represented among criminal offenders, having no wish to hurt others, suggesting their affective empathy may be intact; Baron-Cohen, 2011; Jones, Happé, Gilbert, Burnett, & Viding, 2010; Rogers, Viding, Blair, Frith, & Happé, 2006).

Before embarking on a discussion about the genetic underpinnings of empathy, it is essential to establish that an individual's genetic composition contributes to his/her levels of empathy. A standard approach to do this has been to test for heritability of "trait empathy" (i.e. stable individual differences in empathy) or other aspects of social behaviour by comparing monozygotic (MZ) and dizygotic (DZ) twins. Nearly all of these studies have shown a greater correlation of empathy measures in MZ compared with DZ twins, suggesting a partially genetic basis for trait empathy (Davis, Luce, & Kraus, 1994; Loehlin & Nichols, 1976; Matthews, Batson, Horn, & Rosenman, 1981). Measures have included the Questionnaire Measure of Emotional Empathy (QMEE) (Mehrabian & Epstein, 1972). (Rushton, Fulker, Neale, Nias, & Eysenck, 1986), in a large-scale twin study, and which suggested a high heritability estimate of 68% for emotional empathy. Other twin studies, particularly in children, have used behavioural observation paradigms of empathy in a laboratory situation. These involve simulating scripted situations (e.g. the experimenter tripping on a chair, or the mother of the child getting her finger caught while closing a suitcase), while video-recording the child's reactions. A study of 14- and 20-month-old twins using this paradigm confirmed a genetic contribution to empathic concern (Zahn-Waxler, Radke-Yarrow, Wagner, & Chapman, 1992). A more recent twin study on 409 twin pairs by the same group showed that genetic effects on the prosocial behaviour component of empathy (measured using video-recorded behaviour in a laboratory setting) increase with age, while shared environmental effects decrease with age (Knafo, Zahn-Waxler, Van Hulle, Robinson, & Rhee, 2008). In contrast, twin studies of cognitive empathy (measured using a theory of mind paradigm) have reported a greater genetic component in early compared with late childhood (Hughes, Jaffi, Happé, Taylor, Caspi, & Moffitt, 2005). In summary, there is considerable evidence for a moderate to high genetic contribution to each of the component processes of empathy, quantified using observational measures.

In adults, self-reported measures of empathy have been widely used as one of the key measures of social behaviour. A number of such trait and observational measures of social behaviour have been studied for genetic contributions (Ebstein, Israel, Chew, Zhong, & Knafo, 2010). Important among these are behavioural assays of face perception and emotion perception. Face recognition is associated with a strong genetic component (Wilmer et al., 2010). Recognition of emotions from the eye region of the face, as tested by the "Reading the Mind in the Eyes" Task (RMET), shows a strong degree of familiality (Baron-Cohen & Hammer, 1997; Losh & Piven, 2007;). Questionnaire measures of social functioning using the Social Responsivity Scale (SRS; Constantino & Todd, 2000, 2005; Sung, Dawson, Munson, Estes, Schellenberg, & Wijsman, 2005) and of autistic traits using the Autism Spectrum Quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) also reveal strong familiality (Bishop, Maybery, Maley, Wong, Hill, & Hallmayer, 2004; Wheelwright, Auyeung, Allison, & Baron-Cohen, 2010), as well as heritability in twin studies (Hoekstra, Bartels, Verweij, & Boomsma, 2007). These studies corroborate findings from the early twin studies in suggesting a genetic underpinning for empathy and social behaviour relevant to ASC.

Insights from autism genetics

ASC entail a disability in social and communication development, alongside unusually narrow interests ("obsessions") and repetitive behaviour (APA, 1987; ICD-10, 1994). ASC have a genetic basis, indicated by significantly higher concordance rates in MZ than in DZ twins, and with some heritability estimates of over 90% (Bailey, Le Couteur, GottesmanBolton, Simmonoff, Yuzda, et al., 1995; Folstein & Rutter, 1977). Over the last three decades, a number of strategies have been used to discover genes related to ASC. A common feature in most of these studies has been

the use of clinical diagnosis of ASC as a categorical phenotype. In these studies, people with a diagnosis of ASC are compared with a group of people without a clinical diagnosis, matched on a variety of measures. This approach has implicated multiple genes, along with environmental (Wagner, Reuhl, Cheh, McRae, & Halladay, 2006) and epigenetic factors (Crespi & Badcock, 2008; Nagarajan Patzel, Martin, Yasui, Swanberg, & Hertz-Picciotto, 2008; LaSalle & Yasui, 2009). Mixed evidence from genome-wide linkage studies of samples that do not differentiate between classic (low-functioning) autism and Asperger syndrome (AS) has found linkage peaks in nearly all chromosomes (Abrahams & Geschwind, 2008).

Genome wide association studies (GWAS) are a more recent development, and use oligonucleotide microarrays that allow for simultaneous genotyping of common polymorphisms from nearly all known human genes. The initial GWAS on autism, using the traditional case-control design, found significantly associated polymorphisms in genes located on multiple chromosomes (AGPC, 2007; Wang, Zhang, Ma, Bucan, Glessner, Abrahams, et al., 2009). Oligonucleotide microarrays enable the detection of single nucleotide variations (e.g. change from an A to a C). Advances in the last five years have allowed the detection of larger segments of DNA across the genome (usually 1000 bases or longer), which are present in multiple copies or are deleted altogether in certain individuals. These are referred to as copy-number variations (CNV), and are believed to arise as de-novo events during gametogenesis. Rare *de novo* copy number variations (CNV) can potentially account for up to 10–24% of cases in families have only one child with ASC (Jacquemont, Sanlaville, Redon, Raoul, Cormier-Daire, Lyonnet, et al., 2006; Pinto, Pagnamenta, Klei, Anney, Merico, Regan, et al., 2010; Sebat, Lakshmi, Malhotra, Troge, Lese-Martin, Walsh, et al., 2007). In summary, case-control genetic studies of ASC suggest that:

1. ASC is an oligogenic condition (i.e. it is unlikely that there will be a single gene whose malfunction will explain all features of this condition).
2. Both rare CNVs as well as common sequence variants (single nucleotide polymorphisms; SNPs) are associated with this condition (Arking, Cutler, Brune, Teslovich, West, Ikeda, et al., 2008; Corvin, Craddock, & Sullivan, 2010; Glessner, Wang, Cai, Korvatska, Kim, Wood, et al., 2009; Holt & Monaco, 2011; Pinto et al., 2010; Wang et al., 2009).

While genotyping common and rare sequence variants of the whole human genome has become a routine procedure over the last few years, most studies have continued to use the classic case-control design. This poses some potential problems, particularly for autism research. The heterogeneity within ASC is not captured in this design, as most of these studies group people with classic autism together with those on the broader spectrum (having a diagnosis of high functioning autism (HFA) or AS). This raises the possibility of potential confounds due to factors such as language delay, below average IQ (seen in classic autism, but not in AS) or co-occurring (a term we prefer to the more medical term "comorbid," for obvious reasons) conditions such as epilepsy and hyperactivity. In addition, a commonly used measure for verifying a current clinical diagnosis of autism (e.g. the Autism Diagnostic Observation Schedule (ADOS) (Lord, Rutter, Goode, Heemsbergen, Jordan, Mawhood, et al., 1989) is

1. optimized for diagnosing classic autism, and not AS/HFA;
2. does not include one key dimension of the autistic symptomatology (repetitive behaviour) in its final scoring algorithm, both of which could result in a biased sampling within the clinical cohorts.

In view of the heterogeneity within ASC, and given the existence of the "broader autism phenotype" (BAP) (Piven, Palmer, Jacobi, Childress, & Arndt, 1997) or subthreshold instances of ASC, an emerging consensus in autism phenotypic studies suggests that autistic traits are distributed on a continuum not just within clinic samples, but right across the general population. Behavioural genetic studies confirm this, suggesting that the etiology of autistic traits is similar in the general population as well as the extreme ends of the continuum (Robinson, Koenen, McCormick, Munir, Hallett, Happé, et al., 2011). The AQ is one such trait measure that captures the population variability in autistic traits in both social and repetitive behaviour domains (Baron-Cohen et al., 2001). Another self-report measure focusing specifically on empathy is the empathy quotient (EQ), a 40-item questionnaire that provides a continuous range of scores across the general population (Baron-Cohen & Wheelwright, 2004). These, and other similar trait measures such as the SRS (Constantino, Przybeck, Friesen, & Todd, 2000) provide a dimensional measure of the social functioning in the general population, and people with ASC tend to cluster toward the low end of the score distribution.

Bridging the genotype-phenotype gap in ASC using a dimensional and case-control approach

Interestingly, while most phenotypic studies of ASC (using questionnaires, computer-based tasks, and neuroimaging) have focused on the higher functioning end of the autistic spectrum, large-scale genetic studies have primarily tested the "lower-functioning" end, largely focusing on classic autism. This presents a disconnection between advances at the phenotypic and genotypic ends of the sequence from DNA to cognition. A small number of pioneering studies have attempted to bridge this disconnect by studying the dimensional phenotypes within ASC using linkage and association studies (Campbell, Warren, Sutcliffe, Lee, & Levitt, 2010; Conciatori, Stodgell, Hyman, O'Bara, Militerni, Bravaccio, et al., 2004; Losh, Sullivan, Trembath, & Piven, 2008). We attempted to bridge this disconnect by conducting two parallel candidate gene association studies, which we describe in the next section. The first is of empathy (measured using the EQ) and autistic traits (measured using the AQ) in the general population. The second is of Asperger syndrome, which is marked by social and behavioural impairments and unusually narrow interests, but is not associated with language or general cognitive delays during development.

A key feature of our studies was in the choice of multiple candidate genes from three groups of genes, defined by gene function. This approach has been used in other conditions (Pharoah, Tyrer, Dunning, Easton, & Ponder, 2007), but not in the study of ASC. Traditionally, genetic association studies of ASC have either studied one or a small number of candidate genes, or on the whole genome (Losh et al., 2008). We chose 68 candidate genes for these two experiments, derived from three functional categories:

1. Sex hormone-related genes;
2. Genes involved in neural development and connectivity;
3. Genes involved in social and emotional responsivity (see Table 18.1). We searched for common genetic variants (SNPs) on the assumption that autistic traits are continuously distributed in the general population so the genetic contributions to individual differences in empathy or autistic traits are likely to be normative variants rather than "disease"-causing mutations.

Each of the three functional categories derives from a clear neurocognitive theory of ASC, outlined next.

The fetal androgen theory suggests that genes involved in sex steroid synthesis and transport might be related to empathy and ASC (Baron-Cohen, Knickmeyer, & Belmonte, 2005; Auyeung et al., chapter 17 in this book). Much of the empirical basis of this theory derives from studies that have measured levels of fetal testosterone (FT), measured in amniotic fluid in the general population. FT levels correlate *negatively* with markers of social behaviour, such as eye-contact at 12 months old, vocabulary size at 24 months old (Lutchmaya, Baron-Cohen, & Raggatt, 2002), and social development at 4 years old (Knickmeyer, Baron-Cohen, Raggatt, & Taylor, 2005). FT correlates negatively with scores on the EQ and the RMET at 8 years old (Chapman, Baron- Cohen, Auyeung, Knickmeyer, Hackett, & Taylor, 2006). FT levels also correlate *positively* with narrow interests at 4 years old (Knickmeyer et al., 2005), SQ, AQ at 8 years old (Auyeung, Baron- Cohen, Chapman, Knickmeyer, Taylor, & Hackett, 2006; Auyeung, Baron-Cohen, Ashwin, Knickmeyer, Taylor, Hackett, et al., 2009), and autistic traits at as young as 18–30 months of age (Auyeung, Taylor, Hackett, & Baron-Cohen, 2010).

The neural connectivity theory, based on evidence from studies of rodent and human brains, suggest that the key abnormality in autism might be related to neural growth and connectivity (Belmonte, Cook Jnr, Anderson, Rubenstein, Greenough, Beckel-Mitchener, et al., 2004; Wass, 2011). ASC has a neurodevelopmental origin and an emerging body of genetic evidence suggests a crucial role for genes involved in neural growth, synaptic development and function (Bourgeron, 2009). At the phenotypic end, several studies show functional (Just, Cherkassky, Keller, & Minshew, 2004; Minshew & Williams, 2007; Shih, Shen, Öttl, Keehn, Gaffrey, & Müller, 2010; Villalobos, Mizuno, Dahl, Kemmotsu, & Müller, 2005; Welchew, 2005) and structural underconnectivity in the autistic brain (Barnea-Goraly, Kwon, Menon, Eliez, Lotspeich, & Reiss, 2004; Keller, Kana, & Just, 2007; Sahyoun, Belliveau, & Mody, 2010; Sundaram, Kumar, Makki, Behen, Chugani, & Chugani, 2008), which is also marked by abnormal growth patterns (Courchesne, Pierce, Schumann, Redcay, Buckwalter, Kennedy, et al., 2007; Courchesne, Campbell & Solso, 2011). We therefore hypothesized that variations in genes governing neural development and synaptic function could contribute to autistic traits.

Finally, the social-emotional responsivity theory suggests that the atypical social behaviour patterns in ASC might be related in part to genes known to modulate social behaviour in animals (Chakrabarti, Kent, Suckling, Bullmore, & Baron-Cohen, 2006; Dawson, Carver, Meltzoff, Panagiotides, McPartland, & Webb, 2002; Insel, O'Brien, & Leckman, 1999). These included genes involved in the oxytocin and vasopressin systems, as well as other neuropeptides involved in endogenous reward systems, such as opioids and cannabinoids. Some of these genes have been associated with autism in previous genetic studies, and these are shown in Table 18.1.

These 68 candidate genes were tested in two experiments. 216 SNPs with a minor allele frequency (MAF) ≥0.2 in the Caucasian population were chosen from these genes (full list of SNPs are available in (Chakrabarti, Dudbridge, Kent, Wheelwright, Hill-Cawthorne, Allison, et al., 2009)). This approach, of selecting multiple common SNPs per gene, has the advantage of checking for informative associations both directly and indirectly (Collins, Guyer, & Chakravarti, 1997). The median SNP density across all genes was one SNP per 14.1 kb. 125 of these SNPs have been genotyped in one or more populations in the HapMap database (Release 23a). All volunteers contributed mouth swabs for DNA extraction. These were anonymized and DNA was genotyped for the 216 SNPs using standard PCR-based assays (TaqMan® SNP genotyping assays, Applied Biosystems Inc., California, USA). The two experiments conducted were as follows:

1. *Experiment 1:* An association study for EQ and AQ was conducted on the population sample ($n = 349$) using non-parametric analysis of variance for each SNP. Chi-square statistics and

Table 18.1 List of all genes included in the association study, along with brief functional roles where known. Genes marked in bold indicate those previously linked to ASC through genetic linkage/association studies

Neural development and connectivity	
NGF, BDNF, NTF3, NTF5, NGFR, NTRK1, NTRK2, NTRK3, TAC1, IGF1, IGF2	Neuronal survival, differentiation and growth.
RAPGEF4	Growth and differentiation of neurons. Mutations associated with classic autism.
VGF	Upregulated directly by NGF and expressed in neuroendocrine cells.
VEGF	Promotes cell growth and migration, especially during angiogenesis and vasculogenesis, often observed during hypoxia. Modulated directly by PTEN.
ARNT2	Neural response to hypoxia
NLGN1, ***NLGN4X****, AGRIN*	Synapse formation and maintenance in CNS neurons. *NLGN4X* mutations have been linked to autism.
NRCAM	Neuronal adhesion and directional signalling during axonal cone growth.
EN-2(AUTS1)	Neuronal migration and cerebellar development. *EN-2* has been previously linked to ASCs in several studies.
HOXA1	Hindbrain patterning. Mixed evidence suggests a link with ASCs.
Social and emotional responsivity	
OXT, ***OXTR****,* ***AVPR1A****, AVPR1B*	Linked to social attachment behaviour in humans and other mammals. *AVPR1A* and *OXTR* have previously been associated with ASCs.
CNR1, OPRM1, TRPV1	Mediate endogenous reward circuits, in tandem with dopaminergic pathways. Implicated in underlying rewarding features of social interactions.
MAOB	Synaptic breakdown of dopamine and serotonin. Suggested links with social cognition.
WFS1	Mutations linked to affective disorders. Overexpressed in amygdala during fear response, though exact functional role is not known.
GABRB3*,* ***GABRG3****, GABRA6,* ***ABAT***	Mediate inhibitory (GABA-ergic) neurotransmission as well as play a role in early cortical development. *GABRA6* is expressed strongly in the cerebellum; *GABRB3, GABRG3, ABAT* have all been associated with ASCs.
VIPR1	Suggested involvement in neural pathways underlying pheromone processing. Mutations associated with social behavioural abnormalities in mice. Its endogenous ligand (VIP) shows an overexpression in neonatal children with autism.
Sex hormone biosynthesis, metabolism and transport	
DHCR7	Metabolism of cholesterol: precursor for sex hormones (mutations associated with near-universal presence of ASC)

(Continued)

Table 18.1 *(Continued)*

Neural development and connectivity	
CYP1A1, CYP1B1, CYP3A, CYP7A1, CYP11A, CYP11B1, CYP17A1, CYP19A1, CYP21A2, POR	Synthesis of sex hormones such as progesterone, estrogen, cortisol, aldosterone and testosterone. *CYP21A2* and *POR* mutations associated with CAH.
HSD11B1, HSD17B2, HSD17B3, HSD17B4	Local regulation of sex steroids.
STS, SULT2A1, SRD5A1, SRD5A2	Steroid hormone metabolism
SHBG, SCP2, TSPO, SLC25A12, SLC25A13	Intracellular transport of sex steroids as well as their important precursors and/or metabolites. Mixed evidence suggests an association of *SLC25A12* with classic autism.
AR	Intracellular receptor for testosterone
ESR1, ESR2	Receptors for estrogen
CGA, CGRPR, LHB, LHRHR, LHCGR, FSHB	Regulation of reproductive functions.

asymptotic *p*-values (two-tailed) were generated from this test. A sex-specific analysis was conducted for all X-linked genes.

2. *Experiment 2:* A case-control association study of AS was conducted on all cases of AS (n = 174) and a subset of the population sample (n = 155). The controls were selected to be sex-matched with the cases, whilst having an AQ score <25. An AQ <25 cut-off was employed to exclude a small number of individuals who scored high on AQ even though they did not have a formal diagnosis. For each SNP, a Cochrane-Armitage chi-square statistic (1 d.f.) was calculated to test the null hypothesis that the different alleles have the same distribution in cases and controls. Asymptotic *P*-values (two-tailed) were calculated.

To control for multiple testing of SNPs within genes as well as for multiple phenotypes, permutation testing was conducted using UNPHASED (Dudbridge, 2008) for Experiment 1, and using PLINK (Purcell, Neale, Todd-Brown, Thomas, Ferreira, Bender, et al., 2007) for Experiment 2. Since each candidate gene was individually selected on the basis of a priori hypothesis, independent of other genes, permutation tests were performed separately for each gene. In each permutation, the phenotypes were randomly reassigned among participants, keeping the genotypes fixed to preserve their correlation structure. The multiple phenotypes for each subject were permuted together so as to preserve the correlation structure among phenotypes. Each SNP was then tested for association to each permuted phenotype and the minimum *P*-value recorded. The permutation was repeated 1000 times and the corrected *P*-value was the estimated proportion of permutations in which the minimum *P*-value was less than or equal to the minimum *P*-value seen in the original data. When the Family Wise Error Rate (FWER)- corrected *P*-value is significant, we may infer that at least one SNP in the gene is associated and that there is gene-wise significance. This gene-wise p-value thus reflects the p-value of the most significant SNP after FWER correction.

In Experiment 1, autistic traits and/or empathy (measured on AQ and/or EQ) were nominally associated at $P <= 0.05$ with SNPs from 19 genes. In Experiment 2, SNPs from 14 genes were nominally associated at $P <= 0.05$ with AS. Across both experiments, six genes showed nominal

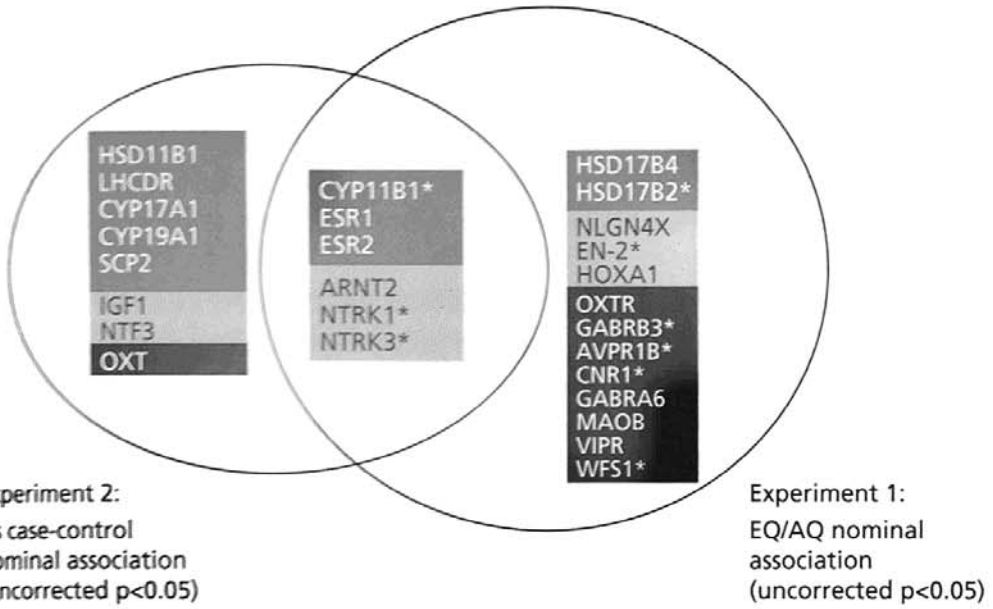

Figure 18.1 Genes showing nominal association with (1) AS case-control analysis, (2) autistic trait measures (AQ, EQ) in the population sample. Intersections summarize genes that show a nominal association in both experiments. Gene functional groups are colour coded: gray (sex hormone-related), light gray (neural connectivity related) and dark gray (social-emotional responsivity related). Genes in bold indicate replications of associations reported in earlier studies. * Indicates a nominally significant association with EQ. See also Plate 11.

significance at $P < = 0.05$. (See Figure 18.1 for a distribution of all nominally significant genes across the two experiments).

Eight genes in Experiment 1 and 5 genes in Experiment 2, showed gene-wise significance after 1000 permutations across all phenotypes. Two genes (*CYP11B1* and *NTRK1*) survived FWER correction in both the experiments, and are therefore strong candidates for future replication studies. Genes in all three functional groups were found to be significantly associated both with empathy and/or autistic traits, as well as with a diagnosis of AS. This provides further support for the non-unitary nature of autistic traits and AS (Happé, Ronald, & Plomin, 2006).

In the sex steroid group, the estrogen receptor beta (*ESR2*) was associated significantly in both experiments. Particularly, the C allele in rs1271572 and rs1152582 was associated with higher AQ in the typical population, and were also found to be more frequent in cases than in controls. *ESR2* codes for the main estrogen receptor expressed in the brain. In the fetal brain testosterone is aromatized to estradiol and exerts its effects on neural development through acting on these receptors, and mediating selective cell survival. It promotes the defeminization of the developing male brain in mice (Kudwa, Bodo, Gustafsson, & Rissman, 2005). Estrogen is thought to mediate social interaction in rodents, and this is supported by the presence of estrogen receptors in areas of the brain involved in emotion and affective behaviour, such as the amygdala and the hippocampus.

CYP17A1 catalyses the production of dehydroepiandrosterone (DHEA, a precursor of testosterone), as well as androstenedione (a precursor of estradiol). Higher levels of androstenedione were found in males and females with ASC in a recent study on an independent sample (Ruta, Ingudomnukul, Taylor, Chakrabarti, & Baron-Cohen, 2011). Polymorphisms in *CYP17A1* have been associated with PCOS in women (Park, Lee, Ramakrishna, Cha, & Baek, 2008), a condition known to be elevated in ASC (Ingudomnukul, Baron-Cohen, Wheelwright, & Knickmeyer, 2007). *CYP11B1* is cellularly localized in the mitochondria and converts11-deoxycortisol to cortisol.

Polymorphisms in this gene and the *CYP11A* gene are associated with congenital adrenal hyperplasia (CAH; Kuribayashi, Nomoto, Massa, Oostdijk, Wit, Wolffenbuttel, et al., 2005) in which FT is elevated. CAH is associated with higher AQ than in the general population (Knickmeyer, Baron-Cohen, Fane, Wheelwright, Mathews, Conway, et al., 2006). Together, these results implicate genes involved in the synthesis and metabolism of sex steroids in the aetiology of autistic traits, empathy, and AS, and provides some of the first genetic evidence in support of the role of sex-steroids in ASC and related trait measures.

In the neurodevelopmental group, four genes (*HOXA1*, *NLGN4X*, *NTRK1*, and *ARNT2*) survived FWER correction. rs10951154 in *HOXA1* has been previously associated with head size in ASC, as well as with head growth rate (Muscarella, Guarnieri, Sacco, Militerni, Bravaccio, Trillo, et al., 2007). We found that the G-allele carriers had more autistic traits than the *AA* homozygotes. This is consistent with the finding that the G allele has been found to be associated with larger head size and greater head growth rate (Muscarella et al., 2007). rs12836764 in the *NLGN4X* UTR was significantly associated with both EQ and AQ in females. This supports earlier findings implicating this gene in autism (Jamain, Quach, Betancur, Råstam, Colineaux, Gillberg, et al., 2003). A large-scale association study of autism found a significant association with neurexins (AGPC, 2007) that interact with neuroligins in mediating glutamatergic synaptogenesis. Among the molecules related to neurotrophin function, a strong association was seen in *NTRK1* with empathy (in Experiment 1), and with AS (in Experiment 2). *NTRK1* is situated within a peak (1q21–2) reported in the first ever linkage study of AS (Ylisaukko-oja, Nieminen-von Wendt, Kempas, Sarenius, Varilo, von Wendt, et al., 2004) and thus provides an independent validation. Nerve growth factor (NGF), signaling through TrkA (the protein product of *NTRK1*), mediates most neurotrophic action of NGF (Sofroniew, Howe, & Mobley, 2001). A primary role of the TrkA in the developing brain is in determining the fate and growth of neurites, in whether they become axons or dendrites (Da Silva, Hasegawa, Miyagi, Dotti, & Abad-Rodriguez, 2005). Additionally, two SNPs in the *ARNT2* gene were found to be associated in both the experiments. This gene is involved both in the development of the neuroendocrine cells in the hypothalamus (Michaud, DeRossi, May, Holdener, & Fan, 2000), as well as in the neural response to hypoxia (Maltepe, Keith, Arsham, Brorson, & Simon, 2000). These findings point to a key role played by these neurodevelopmental genes in the development of empathy and autistic traits.

In the social-emotional responsivity group, four genes (*MAOB*, *GABRB3*, *WFS1*, *OXT*) were found to be significant after FWER correction. *MAOB* was significantly associated in females only, and this is consistent with the earlier studies showing the importance of this locus in social cognition, both in humans and mouse models (Good, Lawrence, Simon-Thomas, Price, Ashburner, Friston, et al., 2003; Grimsby, Toth, Chen, Kumazawa, Klaidman, Adams, et al., 1997). The rationale for testing GABA-related genes came from the fact that social behaviour has been linked to GABA-ergic activity in the CNS (File & Seth, 2003), and that GABA receptors play a crucial role early in cortical development through their effect on neuronal migration, as well as on development of excitatory and inhibitory synapses. In this sense, GABA-related genes could have been placed in both the neurodevelopmental group of candidate genes too. We found *GABRB3* was significantly associated with empathy (EQ) in the typical sample, thus corroborating a role of this locus (15q11-q13) in autism (Ashley-Koch, Mei, Jaworski, Ma, Ritchie, Menold, et al., 2006; Buxbaum, Silverman, Smith, Greenberg, Kilfarski, Reichart, et al., 2002). Gabrb3 knockout mice have been shown to demonstrate low social and exploratory behaviour as well as smaller cerebellar vermal volumes, pointing to a potential animal model for autism (DeLorey, Sahbaie, Hashemi, Homanics, & Clark, 2007).

Another significant association in this functional group of genes was the Wolframin (*WFS1*) gene. Wolframin is strongly expressed in the amygdala, especially in response to fear-inducing

stimuli (Koks, Planken, Luuk, & Vasar, 2002). The amygdala is one of the key brain regions where functional and structural abnormalities have been consistently found in ASC (Baron-Cohen, Ring, Bullmore, Wheelwright, S., Ashwin, & Williams, 2000). 2 SNPs in *WFS1* showed a strong association with both AQ and EQ. One of these, rs734312, is a non-synonymous coding SNP and belongs to a haplotype that shows an increased risk for affective disorders (Koido, Kõks, Nikopensius, Maron, Altmäe, Heinaste, et al., 2004). Finally, three genes from the oxytocin-vasopressin system (*OXTR*, *OXT*, and *AVPR1B*) were found to be nominally associated with ASC and/or with AQ and EQ. These genes have suggestive links with autism (Insel et al., 1999; Jacob, Brune, Carter, Leventhal, Lord, & Cook Jr, et al., 2007; Tops et al., 2011; Wermter, Kamp-Becker, Hesse, Schulte-Körne, Strauch, K., & Remschmidt, 2009; Wu Jia, Ruan, Liu, Guo, Shuang, et al., 2005; Wu et al., 2012) and with social behaviour in animal models. Of these, *OXT* survived a FWER correction in Experiment 2. Oxytocin is of particular interest, given the recent reports of oxytocin levels being low in autism, and treatment effects of both intranasal and intravenous administration of oxytocin (Hollander, Novotny, Hanratty, Yaffe, DeCaria, Aronowitz, et al., 2003). Oxytocin levels are also correlated with empathy and prosocial measures, such as the Eyes Test (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007) and trust in neuroeconomics (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). This provides partial support for the involvement of the oxytocin-vasopressin system in autistic traits. Together, these results support the idea that genes implicated in social and emotional responsivity contribute to individual differences in traits related to ASC.

In summary, in the two studies described above, we identified 9 candidate genes, some of which are associated with autistic traits in the general population and/or AS. These genes fall into the three functional categories related to sex-steroid synthesis and metabolism, neural development and connectivity, and social-emotional responsivity, providing some support for three theories of autism. It is essential that these are replicated in independent samples, and validated through molecular genetic techniques such as gene expression measurement. Importantly, these associations should be validated against other relevant endophenotypes.

Endophenotypes and future directions

Endophenotypes are defined as measurable intermediate phenotypes that are generally closer to the action of the gene and thus exhibit higher genetic signal-to-noise ratios (Gottesman & Gould, 2003). A range of endophenotypic measures have been suggested for empathy and autistic behaviour, and social cognition and emotion processing ranks highly among these (Losh & Piven, 2007). In our study described above, we did a preliminary test of two such endophenotypic measures (the "Reading the Mind in the Eyes" Test, and the Embedded Figures Test) for cross-validation of our trait association results, in a small subset of the general population sample. This found a nominal association in seven genes with these measures that overlapped with the significantly associated genes in either/both of the two main experiments (Chakrabarti et al., 2009). While this analysis was preliminary, and under-powered, this provides a framework for future studies. Additional endophenotypes that have been put forward to study social behaviour in humans involve the use of neuroimaging Hariri, Drabant, Munoz, Kolachana, Mattay, Egan, et al. (2005); Hariri, Mattay, Tessitore, Kolachana, Fera, Goldman, et al. (2002), showed that variability in serotonin transporter (*SLC6A4*) genotype modulates amygdala response to fear faces. Using the same paradigm Meyer-Lindenberg, Kolachana, Gold, Olsh, Nicodemus, Mattay, et al. (2008) showed that polymorphisms in the arginine vasopressin receptor 1A (*AVPR1A*) gene (previously linked to autism) are related to the amygdala response to faces displaying fear or anger. Work from our and other groups has shown that variations in the cannabinoid receptor (*CNR1*) gene modulate striatal response to

happy faces (Chakrabarti & Baron-Cohen, 2006; Domschke, Dannlowski, Ohrmann, Lawford, Bauer, Kugel, et al., 2008). While the studies above rely on a more bottom-up response to emotion (since the task involves passive viewing of facial expressions, or doing a matching task), a recent imaging genetic study reported the genetic variation underlying cognitive component of empathy (Walter, Schnell, Erk, Arnold, Kirsch, Esslinger, et al., 2010). Future research should further characterize such endophenotypes in ASC in combination with ideal candidate genes. In this regard, a range of robust endophenotypes pertaining to autism and empathy have been put forward, both at the behavioural and neural levels (Lombardo, Baron-Cohen, Belmonte, & Chakrabarti, 2011; Losh, Adolphs, Poe, Couture, Penn, Baranek, et al., 2009).

The emerging picture that dimensional endophenotypes, rather than categorical diagnostic entities are useful targets for future genetic research is also reflected by the recent move to incorporate more dimensional measures in the new version of the DSM (DSM-5). This approach raises the issue of specificity, i.e. the endophenotypes may not be specific to certain categorical diagnostic entities. There is considerable evidence to suggest similarities in the social cognitive impairments between ASC and schizophrenia (Couture, Penn, Losh, Adolphs, Hurley, & Piven, 2010; King & Lord, 2011). Indeed, the polymorphism associated with differences in neural response in a ToM task was first reported from a GWA study of schizophrenia (Walter et al., 2010). The lack of disease-specificity of endophenotypic measures is mirrored by a similar overlap across diagnostic entities seen in genetic studies (Burbach & van der Zwaag, 2009; Guilmatre, Dubourg, Mosca, Legallic, Goldenberg, Drouin-Garraud, et al., 2009). The proposed future direction is therefore one where specific genetic loci will be characterized with their role in well-defined endophenotypes. One such genetic loci that has been well characterized is 7q11. Deletions in this locus are associated with Williams-Beuren Syndrome (where individuals are highly social), and duplications have been associated with ASC (Sanders, Hus, Luo, Murtha, Moreno-De-Luca, Chu, et al., 2011).

In closing, in this chapter we have presented a brief overview of genetics approaches to study empathy and autism. We have then discussed two recent genetic association experiments from our lab, one on autistic traits and empathy, and one on Asperger Syndrome. Finally, we have suggested potential avenues for future research, particularly using cross-validation through relevant endophenotypes. This combination of a functional hypothesis-driven search for candidate genes, alongside the development of fine-tuned quantitative phenotypic measures of brain and behaviour, will slowly bridge the gap between genes to cognition in the study of empathy and autism.

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