Psych 3102 Introduction to Behavior Genetics

Lecture 22

Childhood psychopathologies

(Developmental psychopathology)

Prevalence of DSM-IV developmental disorders

- pervasive developmental disorders eg autistic disorder
- attention-deficit & disruptive behavior disorders eg ADHD, conduct disorder
- anxiety disorders
- mood disorders

Population sample, children 8-15 years nationwide, unselected

12% met 12-month criteria for at least one disorder

14% of those children met criteria for 2 or more disorders

only 50% had sort treatment Merikangas et al, 2010

Median age of onset = 11 for anxiety, impulse-control disorders

= 30 for depression

50% of all lifetime cases start by age 14

Autistic disorder

DSMIV

- mental disorder diagnosed within the first 3 years of life

- defined as a severe neurodevelopmental disorder characterised by ALL of following:
  1. gross impairment in social interaction
  2. impairments in verbal and non-verbal communication
  3. restricted repetitive and stereotypical behaviors

- typically no period of normal development

- moderate retardation in 75% of cases IQ 35-50

more variable:

hyperactivity, under- or over-sensitivity to sensory stimuli, impulsivity, aggression, self-injury

- only small % go on to live independently as adults

Autism spectrum disorders

Autistic disorder
Asperger syndrome
Pervasive developmental disorder

} DSMIV

- will be replaced with single category ‘Autism spectrum disorder’ in DSMV (2013)
- will recognize numerous phenotypic dimensions which overlap with those found in other conditions and the **general population**
- currently only negative aspects emphasized
- positive: strong persistent interests, attention to detail, unusual memory, fascination with systems & patterns, ability to concentrate for long periods of time
- Is autism just part of human diversity? Our inability to tolerate those perceived as different? Do we need more respect for cognitive differences?

“ Since when has it meant I have a disorder if I have less than optimal social skills, a lack of spontaneity, don’t make eye contact easily but otherwise function very well and am successful in life?”

Extreme heterogeneity

Functioning

very low → very high

MR (75%)	high IQ
NO speech (1 in 10)	articulate
NO interactions	social problems
ONLY stereotyped behavior	restricted interests
dependent on parents, even as adults (4 in 5)	successful adults
no regular job (9 in 10)	

Plus development over time can change where someone falls on this spectrum

Commonly used screening tools:

Childhood Autism Rating Scale (CARS)

- similar to DSMIV

excludes autism with known causes, only idiopathic

Autism Behavioral Checklist (ABC)

– does not exclude other developmental problems

includes those suffering from other known disorders

Known causes of autism spectrum symptoms

1-2% have Fragile X syndrome

1% have tuberous sclerosis

0.5% have Rett syndrome

other Mendelian conditions possible (eg NF1, Angelman/Prader Willi)

other known chromosomal copy number variants

25% ASD cases have known genetic cause

most have no known cause

Prevalence USA

DSMIV autistic disorder: 10 in 10,000 (0.1%)

autism spectrum disorders: 1 in 100 (1%)

4 : 1 boys:girls

Rising prevalence:

1966 UK 4-5 per 10,000 Autistic disorder

1992 US 19 per 10,000

2006 US 90 per 10,000 } Autism spectrum disorder

South Korea 1 in 38

- greater awareness
- wider diagnostic criteria
- more frequent diagnosis of children with MR as having ASD
- diagnosis at younger ages

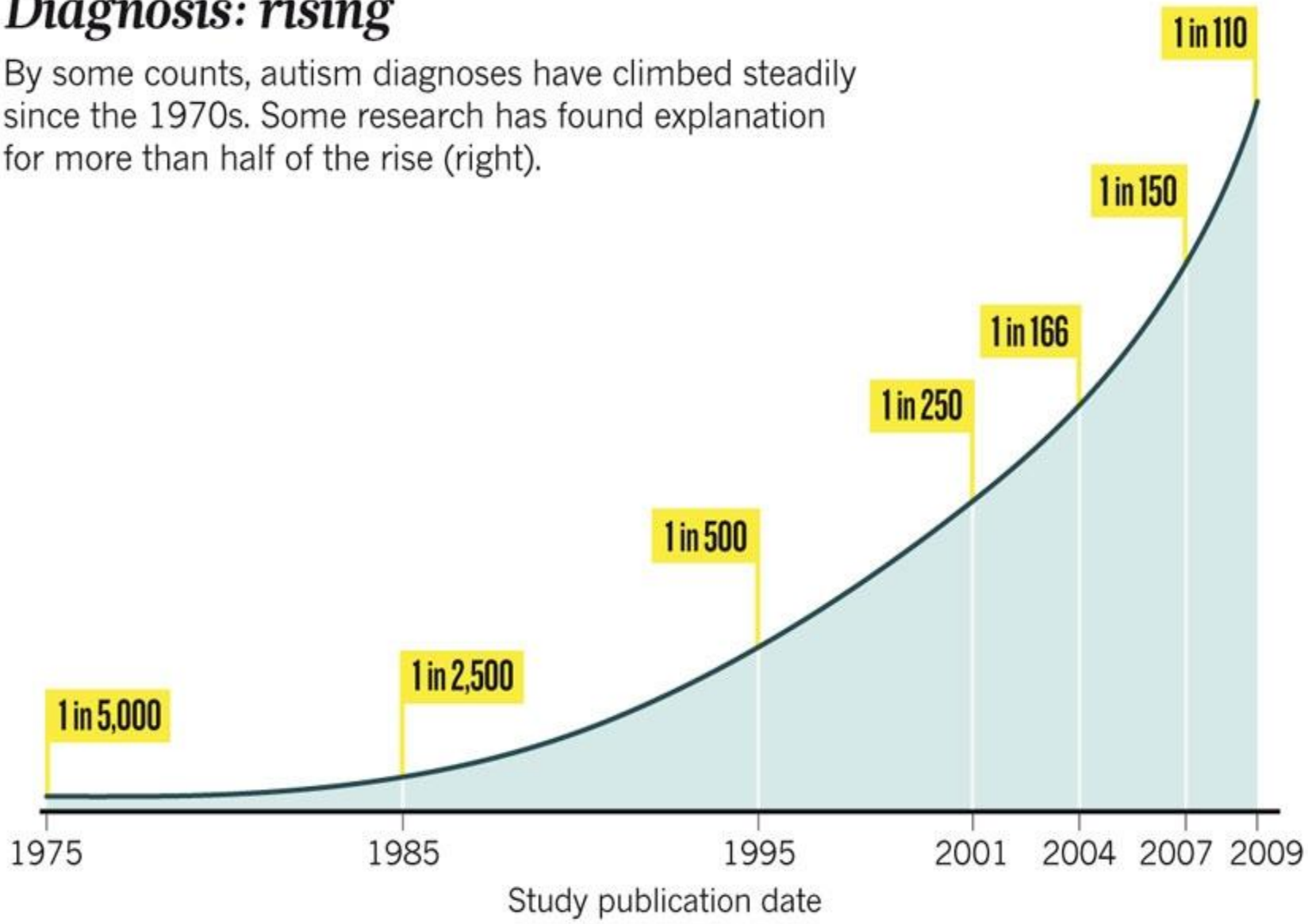
- dispute over whether there are new environmental causes
- has there even actually been an increase?

Sweden prevalence has been 1% since 1970's

Recent population survey of UK adults prevalence 9.8 per 1000

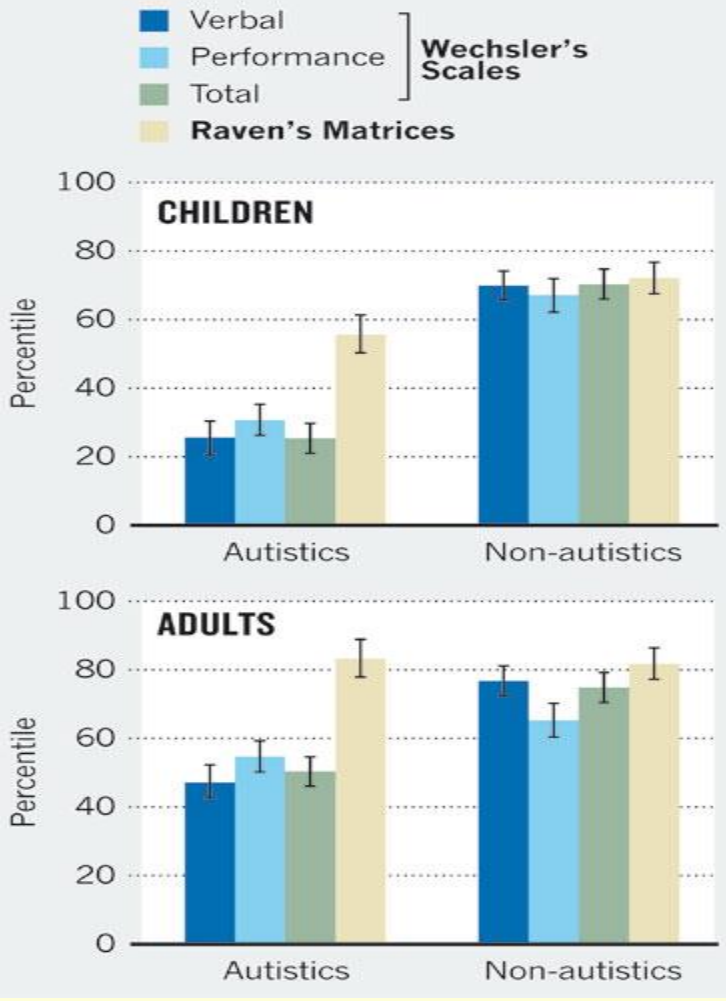
Diagnosis: rising

By some counts, autism diagnoses have climbed steadily since the 1970s. Some research has found explanation for more than half of the rise (right).



AUTISTIC INTELLIGENCE

Non-autistics typically perform equally well in tests of verbal and non-verbal intelligence. Autistics, however, score much higher in non-verbal tests, such as Raven's Matrices, than in verbal ones, such as Wechsler's Scales.



Twin and family studies

"It's not genetic because: no reported cases of autistic children having autistic parents , risk to siblings only 5%" (100xprevalence at the time)

- data from studies is consistent, indicate strong genetic component
- 80-90% ASD cases are familial

Concordances (Goldsmith, 2009)

Relationship	Recent studies	Cognitive/social deficit
MZ twins	69-79%	90%
DZ twins	19-42%	53%
unrelated	0.5%	0.3%
	tetrachoric correlations	
MZ twins	0.91	0.99
DZ/sibs	0.44	0.55

total population screening, systematic standardized methods of diagnosis, screening out of other conditions - ONLY idiopathic autism

- diagnosis of ASD in one twin produced increased risk for ADHD and learning disabilities in co-twin - does broadly-defined autism exist as a discrete disorder?

"

One of the most recent studies

Lichtenstein et al (2010) Am J Psychiatry

large sample size 7982 twin pairs

population sample (all 9-12 yr old twins , Sweden, 80% cooperation)

diagnosed by parent report in structured interview (high specificity, ~95%)

h^2 = 80%

autism spectrum 0.9% prevalence

1.3 boys : 0.4 girls

Comorbidities

(Scerff et al, 2011 Ronald et al, 2011 Lichtenstein et al, 2010)

- **ADHD** h^2 ~ 80% ~2% prevalence (2.5 boys, 1.0 girls)
  44% MZ comorbidity with ASD 15% DZ
- 75% with ASD also have ADHD symptoms
- genetic correlation : 0.5 - 0.87 (up to 75% shared variance, goes up w.age)
- phenotypic correlation: 0.48
  - autistic & ADHD trait scores (h^2 = .77 ASD,.84 ADHD)
  - IQ regressed out so not driving this

- **Developmental coordination disorder** h^2 = 70%
- genetic correlation .71 (50% shared variance)
- **Learning disorders** 34% comorbidity
- **Other psychiatric disorder** : 70% comorbidity with ASD

  2 or more extra disorders: >40% comorbidity

Molecular Psychiatry (2013) 18, 236–244

www.nature.com/mp

Open

ORIGINAL ARTICLE

Disorder-specific functional abnormalities during sustained attention in youth with Attention Deficit Hyperactivity Disorder (ADHD) and with Autism

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Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) are often comorbid and share behavioural-cognitive abnormalities in sustained attention. A key question is whether this shared cognitive phenotype is based on common or different underlying pathophysiologies. To elucidate this question, we compared 20 boys with ADHD to 20 age and IQ matched ASD and 20 healthy boys using functional magnetic resonance imaging (fMRI) during a parametrically modulated vigilance task with a progressively increasing load of sustained attention. ADHD and ASD boys had significantly reduced activation relative to controls in bilateral striato–thalamic regions, left dorsolateral prefrontal cortex (DLPFC) and superior parietal cortex. Both groups also displayed significantly increased precuneus activation relative to controls. Precuneus was negatively correlated with the DLPFC activation, and progressively more deactivated with increasing attention load in controls, but not patients, suggesting problems with deactivation of a task-related default mode network in both disorders. However, left DLPFC underactivation was significantly more pronounced in ADHD relative to ASD boys, which furthermore was associated with sustained performance measures that were only impaired in ADHD patients. ASD boys, on the other hand, had disorder-specific enhanced cerebellar activation relative to both ADHD and control boys, presumably reflecting compensation. The findings show that ADHD and ASD boys have both shared and disorder-specific abnormalities in brain function during sustained attention. Shared deficits were in fronto–striato–parietal activation and default mode suppression. Differences were a more severe DLPFC dysfunction in ADHD and a disorder-specific fronto–striato–cerebellar dysregulation in ASD.
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Keywords: ADHD; ASD; attention; dorsolateral prefrontal cortex; fMRI

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#MRC AIMS Consortium is a collaboration of autism research centres in the UK including the Institute of Psychiatry, London, The Autism Research Centre, University of Cambridge, and the Autism Research Group, University of Oxford. It is funded by the MRC UK and headed by the Department of Forensic and Developmental Sciences, Institute of Psychiatry. The Consortium members are in alphabetical order: Bailey AJ, Baron-Cohen S, Bolton PF, Bullmore ET, Carrington S, Chakrabarti B, Daly EM, Deoni SC, Ecker C, Happe F, Henty J, Jezzard P, Johnston P, Jones DK, Lombardo M, Madden A, Mullins D, Murphy CM, Murphy DG, Pasco G, Sadek S, Spain D, Steward R, Suckling J, Wheelwright S, Williams SC.
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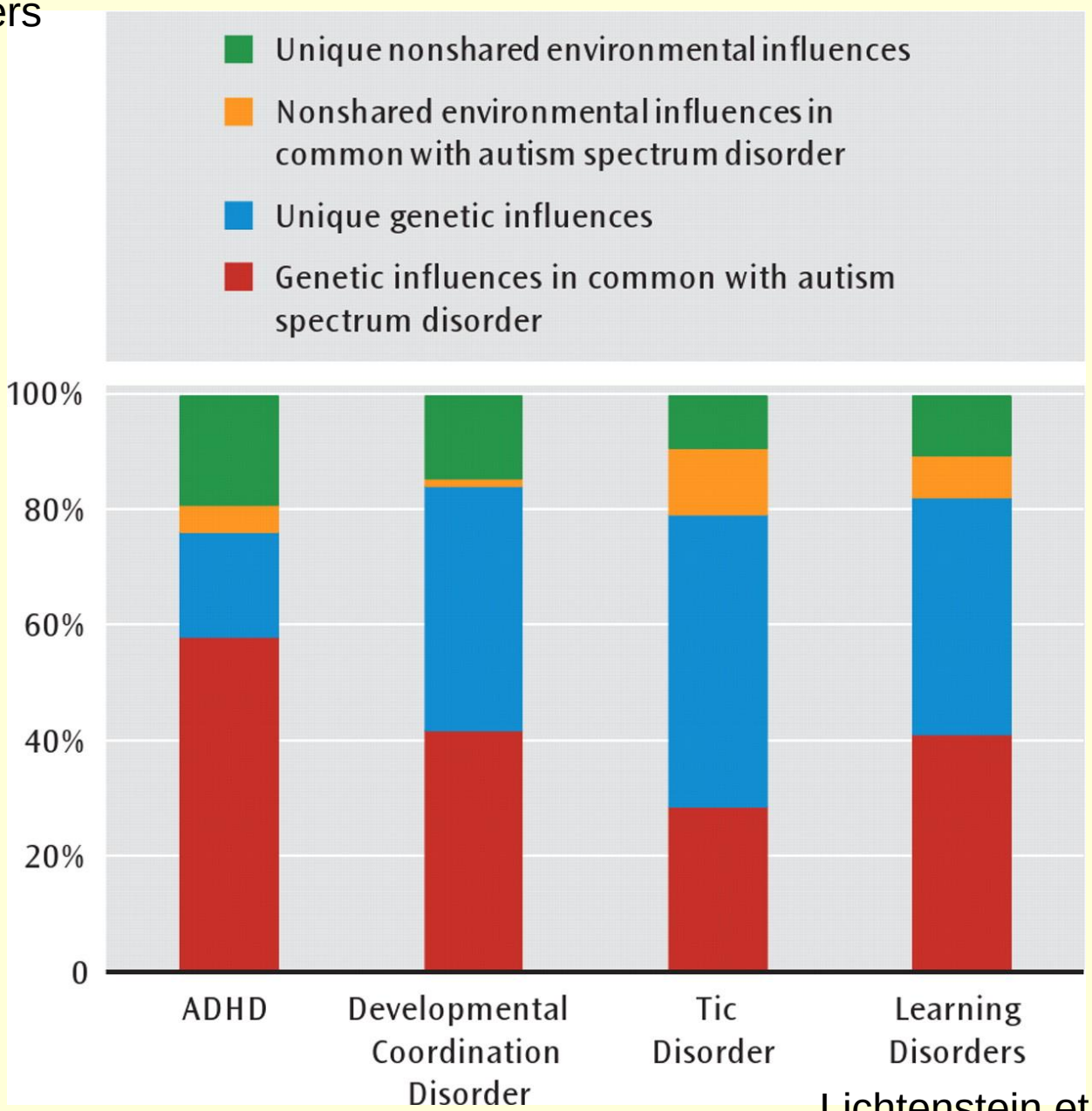
Introduction

Autism spectrum disorder (ASD) is characterised by abnormalities in social interaction, communication and stereotyped/repetitive behaviours (DSM-IV-TR; ICD-10).[1,2] About 30% of ASD patients have comorbid Attention Deficit Hyperactivity Disorder (ADHD),[3,4] characterised by age-inappropriate inattention, impulsiveness and hyperactivity (DSM IV).[1]

A shared behavioural/cognitive phenotype is inattention.[4,5] Sustained attention deficits are among the most consistent cognitive deficits in ADHD.[6,7] In ASD, there is evidence for similar impairment,[8–11] albeit with also negative findings.[12]

Sustained attention/vigilance is defined here as the ability to voluntarily maintain the focus of attention to infrequently occurring critical events,[13,14] as opposed to the definition of a decrement of vigilance/

Amount of variance in liability in ASD in common with other neuropsychiatric disorders



Lichtenstein et al (2010)

Conclusions

- caused by disruption of brain development
- autism is among the most heritable of psychiatric disorders
- heritability ~80%

- no evidence for shared environment
- very small non-shared environment component

  % phenocopies estimated to be very low (eg. maternal alcohol abuse , rubella in utero)

- complex, quantitative inheritance –many genes, interactions

  exome-wide sequencing confirms NO major loci for autism risk

- any environmental factors likely work by interacting with susceptible genotypes
- as with adult psychopathologies, underlying genetic liabilities do not map well onto current DSMIV categories

Kendler(2010) .. ‘ our genes seem not to have read the DSMIV nor do they particularly respect the diagnostic boundaries it established’

Letter to the Editor

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Autism recurrence in half siblings: strong support for genetic mechanisms of transmission in ASD

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Current estimates of the heritability of autism spectrum disorders (ASD) derived from existing clinical twin studies[1, 2, 3, 4] are potentially confounded by a number of factors, including low sample size, inconsistency in case definition and the role of *de novo* mutation (currently estimated to contribute to some 20% of cases), and the possibility that heritable causes of ASD in a twin could result in environmentally engendered affectation of a non-identical co-twin *in utero*, especially if mediated by humoral or immune mechanisms. To minimize these confounds, we compared autism recurrence in half siblings versus that in full siblings, using data (6 June 2011) from over five thousand families enrolled in the Interactive Autism Network (IAN), a national volunteer register for ASD, detailed characteristics of which have been previously described by our group.[5, 6] Recurrence rate among full siblings was observed to be approximately twice that among half siblings, providing strong evidence of genetic transmission of ASD.

The data included 5237 families with (a) an ASD-affected child and (b) at least one additional sibling. Among these, 619 included at least one maternal half-sibling, 55 included a paternal half-sibling and 4832 contained at least one full sibling of an ASD proband. A maximum of one full sibling and one maternal half sibling per family (selected at random in families in which more were available) were incorporated into the analysis. Sample characteristics are provided in Supplementary Table 1.

The recurrence rate was 0.052 for maternal half siblings (0.081 for males, 0.020 for females), 0.00 for the small number of paternal half siblings and 0.095 for full siblings (0.141 for males, 0.050 for females). There was no difference in the full sibling recurrence rate in families with additional half siblings (0.100) compared with those without. The full sib recurrence rate is in agreement with numerous prior studies of sibling recurrence for categorical ASD-affectation status among school-aged children using modern categorical case definitions.[5] In a logistic regression model adjusting for sibling type (full versus maternal half sibling), gender and difference in age between proband and sib, gender ($P<0.0001$) and sibling type ($P=0.004$) were highly statistically significant, with a calculated point estimate (for risk incurred by half sibling status in comparison to full sibling status) of 0.56, and a 95% confidence interval of 0.38–0.83.

Structural equation modeling generated robust heritability estimates of 50–70% over a broad range of assumptions for population prevalence (Figure 1 and Supplementary Table 2). For this analysis, we implemented the commonly used bivariate probit model, with the correlation in

Biological basis

– dysregulation of transcription and splicing of genes in brain
- altered cortical patterning, disrupted synaptic , neuronal signaling
- inflammation implicated – secondary to gene mutation effects?

EEG measures from infancy 80% accurate in predicting ASD?

eye-tracking measures of social preference 100% accurate from 14 months? but both only tested from at-risk populations so far

Treatments

NO effective drug treatments yet

mGluR5 antagonists being tested

mice – BDNF oral supplements being tested

only work if synaptic function effected

Behavioral interventions – small improvements

BTBR mice - model

no changes on cross-fostering so no post-natal maternal effects

rearing closely with social mice improves sociability

Neuropsychopharmacology (2011) 36, 2151–2152

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Commentary

Can Understanding Social Preferences in Rodents Lead to Novel Pharmacotherapies for Social Anxiety and Avoidance in Psychiatric Disorders?

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Neuropsychopharmacology (2011) **36,** 2151–2152; doi:10.1038/npp.2011.124

Social creatures, including us, are naturally drawn to social stimuli. We are more attracted to biological motion, faces, and other social cues than we are to trees, rocks, or other inanimate objects. Social interactions are critical for our well-being. However, individuals with autism spectrum disorder or schizophrenia display diminished interest in social stimuli and may be socially withdrawn. In addition, social phobias and social anxiety can have devastating impacts on the development of healthy social relationships. A study published in this issue by Lukas *et al* (2011) from Inga Neumann's group in Regensburg, Germany, used rats and mice to explore the role of the neuropeptide, oxytocin, on the preference for social stimuli and a form of social anxiety induced by social defeat. These preclinical studies in animals have important implications for developing novel pharmacotherapies for psychiatric disorders with muted social interest and elevated social withdrawal.

Oxytocin has had a prominent spotlight in biology for over a century (Burbach *et al*, 2006), and is now experiencing a renaissance in neuropsychopharmacology. In 1906, Sir Henry Dale found that the constituents in the pituitary potently stimulate uterine contractions, an activity that he dubbed as 'oxytocin,' from the Greek meaning 'quick birth'. Oxytocin also stimulates milk ejection during nursing, making it the quintessential maternal hormone. Oxytocin was the very first peptide to have its structure defined and synthesized, leading to a Nobel Prize in Chemistry for Vincent du Vigneaud in 1955.

The first evidence that oxytocin influences behavior came in the 1980s, when Cort Pedersen and colleagues reported that oxytocin induces the onset of maternal behavior in virgin rats (Pedersen and Prange, 1979), and Kendrick *et al* (1997) showed that oxytocin stimulates the mother–infant bond in sheep. A series of papers published in the 1990s using monogamous prairie voles as subjects showed that oxytocin also stimulates pair bonding (reviewed in Ross and Young, 2009). More recent studies in rats and mutant mice now suggest that oxytocin is more than just a maternal, or a bonding hormone, but it also enhances various aspects of social cognition and promotes social affiliation (Ross and Young, 2009). In these early years of oxytocin research few, if any, investigators were aware of the translational implications of their work.

However, today there are many studies, inspired by the basic biology elucidated in animal models, showing that intranasally delivered oxytocin enhances trust, empathy, and attention to social cues and various other aspects of social cognition (Bos *et al*, 2011). In fact, there is a remarkable congruence between the effects of oxytocin on social behavior in animals and social cognition in man. This congruence provides some level of confidence that pre-clinical studies in rodents can inform pharmacotherapies for social disorders in humans.

Lukas *et al* (2011) used rats and mice to demonstrate for the first time that endogenous oxytocin is involved in the preference for social stimuli over non-social stimuli. As expected, control rats and mice spent more time exploring a novel stimulus animal in a wire cage than in an empty wire cage. However, infusion of a selective oxytocin receptor antagonist prevents this preference. In a sense, they became socially aloof. Similar results were found if the rats were tested in their home cage and the stimulus rat was a freely moving juvenile.

The authors further showed that oxytocin infusion could overcome the social anxiety induced by social defeat, a rodent version of bullying. Male rats that have been defeated by another male continue to show a social preference as long as the stimulus animal is not the bully. But when presented with the bully male in a wire cage, the experimental male spends no more time exploring the wire cage with the bully than exploring an empty cage, presumably reflecting an experimentally induced social anxiety and social avoidance. However, an infusion of OT

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CNTNAP2 homozygous mouse knock-out, autism model

- contactin-associated protein-like 2
- recapitulates 3 core symptoms?

emit fewer ultrasonic vocalizations when separated from mother
spend less time interacting w. unfamiliar mice
do not show usual preference for another mouse over inanimate object

} abnormal social, communication behaviors

repetitive behavior – more time self-grooming & digging

stereotyped behavior - use more rigid behavioral strategies in water- & T-maze tests

hyperactive, develop stress-induced seizures – mirrors CNTNAP2 mutation syndrome in humans

gene product expressed in migratory zones of developing cortex in embryo – role in neuron development & migration

- knock-out mice show abnormal distribution of neurons in cortex, fewer GABAergic neurons, asynchronous firing
- Risperidone normalizes hyperactivity, stereotyped behaviors, but has NO effect on social , communication behaviors as in treated humans

Nature Reviews Neuroscience(2011), 12 Cell(2011), 147

NEURODEVELOPMENTAL DISORDERS

Mice that mirror autism

> "the finding that risperidone affects repetitive but not social behaviour suggests that new therapeutics for autism may involve different drugs for different symptoms."

Understanding the pathophysiology of autism, and ultimately the development of treatments for impairments associated with the condition, is greatly dependent on reliable animal models. As described in a paper published in *Cell*, mice lacking contactin-associated protein-like 2 (*Cntnap2*) recapitulate the three core symptoms of autism, two of which are normalized by treatment with the antipsychotic drug risperidone.

Autism is currently described as a syndrome characterized by a triad of symptoms: impaired communication, impaired social interaction, and repetitive behaviours and restricted interests. Several common and rare mutations have been associated with the disorder, including variants of the gene encoding CNTNAP2. Peñagarikano *et al.* set out to investigate how alterations in this protein might contribute to the pathophysiology of autism, in mice lacking *Cntnap2* (*Cntnap2*$^{-/-}$ mice).

The authors showed that juvenile *Cntnap2*$^{-/-}$ mice emitted fewer ultrasonic vocalizations in response to maternal separation and spent less time interacting with unfamiliar mice then did wild-type mice. As adults, *Cntnap2*$^{-/-}$ mice did not show the usual preference for another mouse over an inanimate object. These findings point to abnormal social behaviour and communication. The knockout mice also showed evidence of repetitive behaviour: they spent more time grooming and digging than wild-type littermates, and used more rigid behavioural strategies in a water maze test and in a T-maze test. In addition, *Cntnap2*$^{-/-}$ mice were hyperactive and developed stress-induced seizures after 6 months of age — an interesting finding considering that a human mutation in *CNTNAP2* is associated with a syndrome that includes both epilepsy and autism.

How might an absence of CNTNAP2 contribute to this phenotype? In the embryonic brain of wild-type mice, *Cntnap2* was preferentially expressed in migratory and post-migratory zones of the developing cortex and in regions that contain migrating interneurons, suggesting that CNTNAP2 may have a role in neuron development and migration. Indeed, 5-bromodeoxyuridine (BrdU) staining and immunohistochemistry experiments revealed an abnormal distribution of neurons in deep cortical layers in the brains of 1-week-old and adult *Cntnap2*$^{-/-}$ mice, and ectopic neurons in the corpus callosum from postnatal day 14 onwards — findings that are all indicative of deficits in the migration of cortical projection neurons in *Cntnap2*$^{-/-}$ animals.

A gene co-expression network analysis revealed that *Cntnap2*$^{-/-}$ is part of a module of functionally related genes, and these genes are more highly expressed in GABAergic than in glutamatergic neurons. The authors therefore also assessed how the absence of *Cntnap2* affected GABAergic interneurons and found that *Cntnap2*$^{-/-}$ mice have fewer interneurons — particularly parvalbumin-positive ones — in cortex, striatum and hippocampus.

Assessing the functional consequence of these alterations using two-photon calcium imaging, the authors showed that cortical neurons of *Cntnap2*$^{-/-}$ mice had a highly asynchronous firing pattern, unlike neurons from wild-type mice. As the average firing rate and amplitude did not differ between the two groups, the abnormal firing pattern was probably due to altered network properties.

Finally, the authors investigated whether the drug risperidone, which is used to alleviate hyperactivity, repetitive behaviour and self-injurious behaviour in people with autism, could reverse the behavioural abnormalities in *Cntnap2*$^{-/-}$ mice. The drug normalized the hyperactivity, excessive grooming and rigid behaviour in the T-maze test but had no effect on social interactions, resembling its effect in humans.

The results from this study are important in several respects. They inform us about possible roles of CNTNAP2 in neuronal development, suggest that neural asynchronization may be important in autism symptoms and indicate that *Cntnap2*$^{-/-}$ mice may be used as a model for autism. In addition, the finding that risperidone affects repetitive but not social behaviour suggests that new therapeutics for autism may involve different drugs for different symptoms.

Leonie Welberg

ORIGINAL RESEARCH PAPER Peñagarikano, O. *et al.* Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. *Cell* **147**, 235–246 (2011)
FURTHER READING Silverman, J. L., Yang, M., Lord, C. & Crawley, J. N. Behavioural phenotyping assays for mouse models of autism. *Nature Rev. Neurosci.* **11**, 490–502 (2010)

Neuropsychopharmacology (2011) 36, 2159–2168

www.neuropsychopharmacology.org

The Neuropeptide Oxytocin Facilitates Pro-Social Behavior and Prevents Social Avoidance in Rats and Mice

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Social avoidance and social phobia are core symptoms of various psychopathologies but their underlying etiology remains poorly understood. Therefore, this study aims to reveal pro-social effects of the neuropeptide oxytocin (OT), under both basal and stress-induced social avoidance conditions in rodents using a social preference paradigm. We initially show that intracerebroventricular (i.c.v.) application of an OT receptor antagonist (OTR-A) in naïve male rats (0.75 μg/5 μl), or mice (20 μg/2 μl), reduced social exploration of a novel con-specific indicative of attenuated social preference. Previous exposure of male rats to a single social defeat resulted in loss of their social preference and social avoidance, which could be restored by i.c.v. infusion of synthetic OT (0.1 μg/5 μl) 20 min before the social preference test. Although the amygdala has been implicated in both social and OT-mediated actions, bilateral OTR-A (0.1 μg/1 μl) or OT (0.01 μg/1 μl) administration into various subnuclei of the amygdala did not affect basal or stress-induced social preference behavior, respectively. Finally, we demonstrate the social specificity of these OT-mediated effects by showing that neither an arginine vasopressin V1a receptor antagonist (0.75 μg/5 μl, i.c.v.) nor the anxiogenic drug pentylenetetrazol (15 mg/kg, i.p.) altered social preference, with OTR-A not affecting non-social anxiety on the elevated plus-maze. Overall, the data indicate that the basal activity of the endogenous brain OT system is sufficient to promote natural occurring social preference in rodents while synthetic OT shows potential to reverse stress-induced social avoidance and might thus be of use for treating social phobia and social dysfunction in humans.
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Keywords: social preference; social interaction; social defeat; amygdala; vasopressin; anxiety

INTRODUCTION

Animal and human studies indicate a facilitatory role of the neuropeptide oxytocin (OT) in a broad variety of social interactions. Released within the brain (for reviews, see Landgraf and Neumann, 2004; Neumann, 2009), OT promotes various aspects of social behavior in both females and males related to reproduction, including the onset and fine-tuned maintenance of maternal behavior in lactation (Bosch *et al*, 2005; Kendrick, 2000; McCarthy, 1990; Pedersen *et al*, 1982; van Leengoed *et al*, 1987), receptive behavior of female rats (Schulze and Gorzalka, 1991; Witt and Insel, 1991), various aspects of sexual behavior in males (Argiolas and Melis, 2004), as well as pair bonding in female voles (Cho *et al*, 1999; Williams *et al*, 1994). Furthermore, chronic central OT administration increases social interactions of male with female rats (Witt *et al*, 1992). Also, OT has a role in social recognition in both male (Popik and van Ree, 1991) and female (Engelmann *et al*, 1998) rats, which has been confirmed in OT and OT receptor knockout mice, which display impaired social memory (Ferguson *et al*, 2000; Choleris *et al*, 2003; Takayanagi *et al*, 2005).

Intranasal OT administration has been shown to affect many aspects of human sociability ranging from social perception, increased gazing toward the eye region (Gamer *et al*, 2010; Guastella *et al*, 2008), and improved recognition of emotional facial expressions (Domes *et al*, 2007; Savaskan *et al*, 2008) to complex social behaviors like trust, social-risk taking, and empathy (Baumgartner *et al*, 2008; Hurlemann *et al*, 2010; Kosfeld *et al*, 2005). The amygdala, a brain region strongly involved in social perception and emotional processing, has been implicated as one of the key regions mediating neuronal actions of OT on social behaviors in humans (Baumgartner *et al*, 2008; Gamer *et al*, 2010; Hurlemann *et al*, 2010; Kirsch *et al*, 2005) as well as in rodents (Choleris *et al*, 2007; Ferguson *et al*, 2001; Lee *et al*, 2007).

In addition to these multiple effects on sociability, brain OT functions as an endogenous anxiolytic neuropeptide in females (Neumann *et al*, 2000b) and males (Waldherr and Neumann, 2007), and acute or chronic administration of synthetic OT reduces anxiety-related behavior in rodents (Blume *et al*, 2008; Ring *et al*, 2006; Slattery and Neumann, 2010; Windle *et al*, 1997). The anxiolytic effect of OT could be localized within both the amygdala of females (Bale *et al*, 2001; Neumann, 2002) and the hypothalamic paraventricular nucleus (PVN) of males (Blume *et al*, 2008). On the

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Specific genetic influences

- evidence for rare variation and common variants
- ~5 - 10% cases have one of large number of rare but fairly large copy number variants (CNVs)
- increased structural variation burden seen
- ASD is co-morbid, low penetrance feature of >100 single-gene Mendelian genetic syndromes (eg fragile X, Rett, tuberous sclerosis)
- highly polygenic (estimated 400-1000 genes)

- several candidate DNA regions from whole genome scans
- currently, 31 SNPs predict ASD in about ½ males, ¼ females

Different genetic influences may exist for the 3 types of autism symptoms (social, communications, restricted interests)

evidence from

cognitive and brain data [Happe, Ronald, Plomin, 2006]

genome wide association study [Ronald et al, 2011]

mouse models

Recent exon sequencing study (Neale et al, 2012, Nature)

- confirmed 3 genes previously associated in other studies as being very likely involved in risk for ASD

CHD8 chromodomain helicase DNA binding protein 8

- transcription repressor, binds β catenin, regulates Wnt signalling, vital role in early development

KATNAL2 hydrolase involved in microtubule organization

SCN2A sodium channel subunit, expressed in brain, previously associated with seizure disorders

Predicting diagnosis of ASD using gene pathway analysis (Skafidas et al Mol Psy, 2012) about 72% correct in prediction in control population test

Table 2. List of 15 most contributory (Table 2a) and 15 most protective (Table 2b) SNPs for ASD diagnosis in the CEU Cohort

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SNP	Weight lower (0.95)	Weight	Weight higher (0.95)	delta	Gene number	Gene symbol
(a) Risk SNPs and their weightings						
rs968122	1.5465	1.5555	1.5645	0.0090	27345	*KCNMB4*
rs876619	0.9476	1.2092	1.4708	0.2616	2775	*GNAO1*
rs11020772	0.8553	0.8641	0.8729	0.0088	2915	*GRM5*
rs9288685	0.5856	0.5998	0.6140	0.0142	3635	*INPP5D*
rs10193128	0.5836	0.5946	0.6056	0.0110	3635	*INPP5D*
rs7842798	0.5298	0.5386	0.5474	0.0088	114	*ADCY8*
rs3773540	0.5125	0.5208	0.5291	0.0083	55799	*CACNA2D3*
rs1818106	0.5002	0.5161	0.5320	0.0159	80310	*PDGFD*
rs2384061	0.4195	0.4306	0.4417	0.0111	109	*ADCY3*
rs12582971	0.3983	0.4295	0.4607	0.0312	5288	*PIK3C2G*
rs10409541	0.4067	0.4189	0.4311	0.0122	773	*CACNA1A*
rs2300497	0.3782	0.3889	0.3996	0.0107	801	*CALM1*
rs7562445	0.3741	0.3843	0.3945	0.0102	2066	*ERBB4*
rs7313997	0.3382	0.3567	0.3752	0.0185	5801	*PTPRR*
rs2239118	0.3348	0.3552	0.3756	0.0204	775	*CACNA1C*
(b) Protective SNPs and their weightings						
rs17629494	−0.5242	−0.5070	−0.4898	0.0172	5592	*PRKG1*
rs4648135	−0.5807	−0.5260	−0.4713	0.0547	4790	*NFKB1*
rs17643974	−0.5527	−0.5424	−0.5321	0.0103	1488	*CTBP2*
rs1243679	−0.5771	−0.5674	−0.5577	0.0097	341799	*OR6S1*
rs2240228	−0.5942	−0.5816	−0.5690	0.0126	26532	*OR10H3*
rs260808	−0.5938	−0.5836	−0.5734	0.0102	80310	*PDGFD*
rs4128941	−0.6166	−0.6082	−0.5998	0.0084	8313	*AXIN2*
rs769052	−0.6321	−0.6235	−0.6149	0.0086	7322	*UBE2D2*
rs984371	−0.7273	−0.7181	−0.7089	0.0092	219437	*OR5L1*
rs4308342	−1.0196	−0.8938	−0.7680	0.1258	1633	*DCK*
	−0.9400	−0.9172	−0.8944	0.0228	9630	*GNA14*

Table 1. Statistically significant pathways for the CEU and Han Chinese

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KEGG pathway	*Pathway name*	*CEU significance (P-values)*	*HAN significance (P-values)*
hsa04020	**Calcium signaling**	**5.0×10^{-7}**	**5.0×10^{-7}**
hsa04540	**Gap junction**	**5.0×10^{-7}**	**5.0×10^{-7}**
hsa04730	**Long-term depression**	**5.0×10^{-7}**	**5.0×10^{-7}**
hsa04070	**Phosphotidylinositol signaling**	**1.5×10^{-6}**	**5.0×10^{-7}**
hsa04720	**Long-term potentiation**	**2.5×10^{-6}**	**5.0×10^{-7}**
hsa00230	**Purine metabolism**	**1.0×10^{-5}**	**5.0×10^{-7}**
hsa04010	mitogen-activated kinase-like protein	**5.0×10^{-7}**	—
hsa04740	Olfactory transduction	**5.0×10^{-7}**	—
hsa04910	Insulin signaling pathway	**1.5×10^{-6}**	—
hsa04916	Melanogenesis	**2.0×10^{-6}**	—
hsa04310	Wnt signaling	**4.0×10^{-6}**	—
hsa04912	GnRH signaling	**4.5×10^{-6}**	—
hsa04120	Ubiquitin-mediated proteolysis	**7.0×10^{-6}**	—
hsa04080	Neuroactive ligand receptor	1.2×10^{-5}	**5.0×10^{-7}**
hsa04062	Chemokine signaling pathway	1.2×10^{-5}	**5.0×10^{-7}**
hsa04060	Cytokine–cytokine receptor	1.65×10^{-5}	**5.0×10^{-7}**
hsa04114	Oocyte meiosis	—	**5.0×10^{-7}**
hsa04360	Axon guidance	—	**5.0×10^{-7}**
hsa04510	Focal adhesion	—	**5.0×10^{-7}**
hsa04514	Cell adhesion molecules	—	**5.0×10^{-7}**
hsa04670	Leukocyte transendothelial migration	—	**5.0×10^{-7}**
hsa04144	Endocytosis	—	**2.0×10^{-6}**
hsa04742	Taste transduction	—	**2.0×10^{-6}**

Abbreviations: CEU, of Central (Western and Northern) European origin; HAN, of Han Chinese origin; KEGG, Kyoto Encyclopedia of Genes and Genomes ().

P-values in bold are statistically significant. The pathways highlighted in ‘bold’ denote pathways that have reached statistical significance in both populations.

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Multiplex Targeted Sequencing Identifies Recurrently Mutated Genes in Autism Spectrum Disorders
Brian J. O'Roak *et al.*
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ORIGINAL ARTICLE

QTL replication and targeted association highlight the nerve growth factor gene for nonverbal communication deficits in autism spectrum disorders

AT-H Lu[1,4], J Yoon[1,4], DH Geschwind[1,2,3] and RM Cantor[1,2]

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Autism Spectrum Disorder (ASD) has a heterogeneous etiology that is genetically complex. It is defined by deficits in communication and social skills and the presence of restricted and repetitive behaviors. Genetic analyses of heritable quantitative traits that correlate with ASD may reduce heterogeneity. With this in mind, deficits in nonverbal communication (NVC) were quantified based on items from the Autism Diagnostic Interview Revised. Our previous analysis of 228 families from the Autism Genetics Research Exchange (AGRE) repository reported 5 potential quantitative trait loci (QTL). Here we report an NVC QTL replication study in an independent sample of 213 AGRE families. One QTL was replicated ($P < 0.0004$). It was investigated using a targeted-association analysis of 476 haplotype blocks with 708 AGRE families using the Family Based Association Test (FBAT). Blocks in two QTL genes were associated with NVC with a *P*-value of 0.001. Three associated haplotype blocks were intronic to the Nerve Growth Factor (*NGF*) gene ($P = 0.001$, 0.001, 0.002), and one was intronic to *KCND3* ($P = 0.001$). Individual haplotypes within the associated blocks drove the associations (0.003, 0.0004 and 0.0002) for *NGF* and 0.0001 for *KCND3*. Using the same methods, these genes were tested for association with NVC in an independent sample of 1517 families from an Autism Genome Project (AGP). NVC was associated with a haplotype in an adjacent *NGF* block ($P = 0.0005$) and one 46 kb away from the associated block in *KCND3* (0.008). These analyses illustrate the value of QTL and targeted association studies for genetically complex disorders such as ASD. *NGF* is a promising risk gene for NVC deficits.
Molecular Psychiatry (2013) **18,** 226–235; doi:10.1038/mp.2011.155; published online 22 November 2011

Keywords: autism spectrum disorders; GWAS; nerve growth factor; nonverbal communication; QTL

Introduction

Autism spectrum disorders (ASDs) are a heterogeneous group of neurodevelopemental disorders defined by impairments in language and nonverbal communication, deficits in reciprocal social interactions and an excess of restricted and repetitive behaviors. The onset of developmental disabilities occurs before the age of 3 years and persists throughout life.[1,2] ASD prevalence estimates have been increasing, and it has recently been reported that approximately 9 children per 1000 are affected, as reported on the website of the Centers for Disease Control. ASD symptoms vary among individuals, and it is likely that this wide range in phenotypes along with inconsistent genetic results derive, at least partially, from a substantial amount of genetic heterogeneity.

Prior studies established that ASDs are heritable genetically complex disorders with associated quantitative traits exhibiting familiality. A recent twin study estimates the probandwise concordance rate for strict autism in male monozygotic twin pairs as 0.58, with a 95% confidence interval estimate of 0.42–0.74 and in male dizygotic twin pairs as 0.21, with a 95% confidence interval estimate of 0.09–0.43,[3] implicating a substantial heritability and an important role for environmental factors in Autism. Although, a monozygotic prenatal environment can make those pairs more concordant than dizygotic pairs, thereby inflating the heritability estimate, such an effect is unlikely to be large enough to preclude an important role for genes.

Research indicates that siblings and parents of affected children are more likely to show deficits in quantitative measures of social skills and their abilities to communicate,[4,5] providing evidence that some quantitative ASD traits are familial and likely to be heritable. Analyzing a single quantitative heritable ASD phenotype can provide a powerful

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Recurrent fusion in pediatric AMKL

James Downing and colleagues report the discovery of recurrent driver mutations in non-Down syndrome acute megakaryoblastic leukemia (non-DS-AMKL), including a *CBFA2T3-GLIS2* fusion present in 27% of pediatric cases (*Cancer Cell* 22, 683–697, 2012). The authors sequenced the transcriptomes of 14 pediatric AMKL cases and found 7 with a balanced inversion on chromosome 16 resulting in an in-frame fusion of *CBFA2T3* and *GLIS2*. Follow-up analyses in a larger set of pediatric and adult AMKL cases showed that this fusion was recurrent, restricted to pediatric cases and associated with unfavorable outcome. The authors also identified a *NUP98-KDM5A* fusion in 8% of pediatric cases, as well as recurrent mutations in *GATA1* and JAK kinase genes. To examine the biological effects of the *CBFA2T3-GLIS2* fusion, the authors transduced mouse hematopoietic cells with a retrovirus encoding *CBFA2T3-GLIS2* and found that the fusion conferred increased capacity for self-renewal, with evidence for differentiation along the megakaryocytic lineage. They further showed that these effects on self-renewal were likely mediated by upregulation of bone morphogenetic protein (BMP) signaling. These findings provide insights into the biology of AMKL and identify *CBFA2T3-GLIS2* as a new clinical marker with prognostic significance for pediatric patients with AMKL. *KV*

TREM2 and Alzheimer's disease

Two groups have independently identified a rare variant that is associated with susceptibility to late-onset Alzheimer's disease (LOAD), with an effect size similar to that of the ε4 risk allele of apolipoprotein E. Researchers in the Alzheimer Genetic Analysis Group (*N. Engl. J. Med.*, published online 14 November 2012; doi:10.1056/NEJMoa1211851) nominated *TREM2* as a promising candidate because homozygous loss-of-function *TREM2* mutations cause Nasu-Hakola disease, a rare recessive, early-onset form of dementia with leukoencephalopathy and bone cysts. They generated exome sequence data sets and identified a TREM2 missense variant, R47H, which associated with LOAD in cohorts from North America and Europe. Separately, researchers at deCODE Genetics (*N. Engl. J. Med.*, published online 14 November 2012; doi:10.1056/NEJMoa1211103) identified the R47H variant in an imputation-based genome-wide association study using the Icelandic population and replicated the association with LOAD in North American and European cohorts. TREM2 is an immune phagocytic receptor expressed in brain microglia. Assuming that the *TREM2* risk variants impair TREM2 function, these studies suggest that reduced function of TREM2 causes reduced phagocytic clearance of amyloid proteins or cellular debris and thus impairs a protective mechanism in the brain. *EN*

Migration from trees to graphs

Joseph Pickrell and Jonathan Pritchard report a new statistical model for demographic inference from genome-wide allele frequency data sets (*PLoS Genet*, 8, e1002967, 2012). Implemented in the freely available software TreeMix (http://treemix.googlecode.com/), their approach involves building a population tree, finding populations that show poor fit to the tree model and modeling migration events to improve the fit within a graph-based model. They tested their method in simulations as well as on a human data set including genome-wide data from 53 modern and 2 archaic populations. They inferred a maximum-likelihood tree from the human data set that recapitulates known population relationships and explains 98.8% of the variance in relatedness between populations. By sequentially adding the ten migration events that are most consistent with known events, they increased the explained variance to 99.8%. The authors also applied their approach to a canine genome-wide data set of 82 dog breeds or wild canids. They found that a significant amount of gene flow occurred between breeds during dog domestication and again demonstrate the ability to increase the explained variance in relatedness between dog breeds by sequentially adding migration events. For both humans and dogs, the authors infer many migration events, including previously known and new relationships between populations. *OB*

Written by Orli Bahcall, Pamela Feliciano, Emily Niemitz & Kyle Vogan

MED12 in cancer drug resistance

Targeted cancer drugs do not typically lead to long-term survival benefits owing to emergent drug resistance caused by secondary-site mutations in the targeted gene or mutations in genes downstream. René Bernards and colleagues report that suppression of *MED12* confers drug resistance to multiple targeted cancer drugs in multiple cancer cell lines (*Cell* 151, 937–950, 2012). The authors conducted an *in vitro* RNA interference (RNAi) screen targeting 8,000 genes. They found that *MED12* was the only gene whose suppression led to resistance to the ALK inhibitor crizotinib. They then performed an inverse screen with a short hairpin RNA (shRNA) library that covers all 518 human kinases to identify genes whose suppression would restore drug sensitivity. They found that suppression of *TGFBR2* resensitized $MED12^{KD}$ cells to crizotinib. Further experiments showed that treatment of multiple cancer cell lines with recombinant TGF-β conferred resistance to multiple targeted cancer drugs, as well as the widely used chemotherapy drug cisplatin. Finally, the authors tested the combination of a TGF-βR2 inhibitor with crizotinib in $MED12^{KD}$ cells and observed a synergistic inhibitory effect. The authors suggest that the combination of TGF-βR2 inhibitors with targeted tyrosine kinase inhibitors might be an effective therapy for tumors with elevated TGF-β signaling. *PF*

Autism candidate gene resequencing

Although much effort has been made in sequencing autism exomes, it has been difficult to robustly establish ASD (autism spectrum disorder) candidate genes as bona fide genetic risk factors, as only single mutations are typically observed. Now, Evan Eichler, Jay Shendure and colleagues report ultra-low-cost ASD candidate gene resequencing of 44 genes in 2,446 ASD probands (*Science*, published online 15 November 2012; doi:10.1126/science.1227764). This resequencing method uses a modified molecular inversion probe (MIP) strategy, such that reagent costs are less than $1 per gene per sample. Applying this method to ASD probands from the Simons Simplex Collection (SSC), the authors identified 27 *de novo* mutations in 16 genes, with 59% of the mutations predicted to be truncating or disruptive of splicing. Six of the genes (*CHD8*, *GRIN2B*, *DYRK1A*, *PTEN*, *TBR1* and *TBL1XR1*) have statistically significant evidence of mutation burden; five of these are contained within the β-catenin/chromatin-remodeling network. Altogether, approximately 1% (24/2,573) of ASD probands had a mutation in 1 of these 6 genes. Because the SSC was established for families with simplex ASD and these probands typically possess higher cognitive functioning levels than other ASD cohorts, it is not known how generalizable the mutation burdens of these six genes will be in idiopathic autism. *PF*

ADHD - attention-deficit hyperactivity disorder

Most predictive characteristics:

1. very restless, difficulty staying seated for long
2. squirmy, fidgety, impulsive
3. poor attention span

DSMIII-R single category

DSMIV 3 categories

ADHD I primarily inattentive

ADHD H/I primarily hyperactive/impulsive

ADHD C combined type

Prevalence: 9% at elementary school age

5 : 1 boys : girls

Adult ADHD

- ~30% of childhood cases persist into adulthood
- symptoms less prominent because
  - adaptive mechanisms develop
  - comorbid conditions modify or dominate clinical manifestations

Comorbidities

- substance abuse
- affective disorders
- personality disorders

} most common

- bipolar disorder

Distinctive personality profile

NEO hi neuroticism score, lo extroversion, openness,conscientiousness

TPQ high novelty seeking, harm avoidance

Family and adoption studies

Recent large US study: ADHD combined type

familial tendency: 25% first degree relative risk

5% prevalence

adoption studies: biological parent/offspring resemblance is much greater than adoptive parent/offspring

Twin studies

- consistent results even with different measurement methods and heterogeniety of phenotype

Concordances pooled findings across 20 twin studies

MZ = 51% DZ = 33% Prevalence = 5%

heritability ~ 76% no shared e Faraone et al, 2005

Meta-analysis across 21 studies heritability = 70% Burt, 2009

Using quantitative measure:
same sex, 13 year-old twins, hyperactivity ratings:

Rated by	Mother	Father	Teacher
MZ twins	0.68	0.48	0.62
DZ twins	-0.08	0.21	0.26

mother's ratings show contrast effects (a form of rater bias)
Parents - see home-related symptoms
- may not be able to compare their children to many others
teachers - see school-related symptoms
- are able to compare twins with many other children

School/home - some difference in symptoms, genetic effects, displayed

Conclusions from behavior genetic studies:

- clear genetic influence
- heritability ~70%
- heritability range = 50 – 90% depending on whether situation-specific, continues into adulthood
- non-additive gene effects
- little evidence for shared environment
- genetic overlap between inattentive & hyperactive symptoms

‘Environmental’ risk factors identified in some studies:

parental alcohol dependence, maternal smoking, maternal drinking during pregnancy, very low birth weight

Specific genetic influences

mouse model

knock-out of dopamine transporter (DAT) gene, chr 9

BDNF knock-out

} Show increased hyperactivity

humans

DAT1, DRD4, DRD5, 5HTT, HTR1B, SNAP25 – strong support

(SNAP25 – axon growth, synaptic plasticity)

8% of cases have familial CNV some involve CHRN*A7*

DIRAS2 - product thought to regulate neurogenesis, implicated in ADHD with comorbid disorders OR ranging 1.12 – 1.45

'Specific' ?

One rare CNV increases risk for ADHD, autism, sz, bipolar, intellectual disability

DISC1 gene implicated in sz, bipolar, MDD, autism

Some common underlying pathology likely involved in many disorders

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REVIEW ARTICLE

Candidate gene studies of ADHD: a meta-analytic review

Ian R. Gizer · Courtney Ficks · Irwin D. Waldman

Received: 20 May 2009 / Accepted: 27 May 2009 / Published online: 9 June 2009

Abstract Quantitative genetic studies (i.e., twin and adoption studies) suggest that genetic influences contribute substantially to the development of attention deficit hyperactivity disorder (ADHD). Over the past 15 years, considerable efforts have been made to identify genes involved in the etiology of this disorder resulting in a large and often conflicting literature of candidate gene associations for ADHD. The first aim of the present study was to conduct a comprehensive meta-analytic review of this literature to determine which candidate genes show consistent evidence of association with childhood ADHD across studies. The second aim was to test for heterogeneity across studies in the effect sizes for each candidate gene as its presence might suggest moderating variables that could explain inconsistent results. Significant associations were identified for several candidate genes including *DAT1, DRD4, DRD5, 5HTT, HTR1B,* and *SNAP25.* Further, significant heterogeneity was observed for the associations between ADHD and *DAT1, DRD4, DRD5, DBH, ADRA2A, 5HTT, TPH2, MAOA,* and *SNAP25,* suggesting that future studies should explore potential moderators of these associations (e.g., ADHD subtype diagnoses, gender, exposure to environmental risk factors). We conclude with a discussion of these findings in relation to emerging themes relevant to future studies of the genetics of ADHD.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by persistent and pervasive symptoms of inattention, hyperactivity, and impulsivity (American Psychiatric Association 2000). Approximately 3–7% of children are diagnosed with ADHD, making it one of the most prevalent childhood psychiatric disorders (American Psychiatric Association 2000). Twin and adoption studies of ADHD suggest that genetic influences contribute substantially to its etiology, with heritability estimates ranging from 60 to 90% (Waldman and Rhee 2002). Thus, molecular genetic studies attempting to identify the specific genes involved in the etiology of ADHD are being published at a rapid rate (Faraone and Khan 2006; Waldman and Gizer 2006).

Despite such efforts, the search for susceptibility genes for ADHD, like those for other complex traits (Ioannidis et al. 2001; Lohmueller et al. 2003), has yielded largely inconsistent results (Faraone et al. 2005; Waldman and Gizer 2006). For example, one of the first candidate gene studies of ADHD reported a significant association between the dopamine transporter gene (*DAT1*) and ADHD (Cook et al. 1995). This report was followed by studies attempting to replicate the original association that yielded approximately equal numbers of positive and negative results (Curran et al. 2001b; Swanson et al. 2000b; Todd et al. 2001a; Waldman et al. 1998). Notably, this pattern of results is not specific to candidate gene studies of ADHD, as similar findings have been reported for genetic association studies of most if not all complex traits that have been studied (Ioannidis 2003).

Adolescent conduct disorder (CD)

- general disregard for rights & property of others
- persistent pattern of rule-breaking & aggressive behaviors
  - destruction of property, theft
  - aggressive behavior fighting, bullying
  - disobedience, lying, deceit, running away from home
  - irresponsible, impulsive, self-destructive

Prevalence: 5 -20% boys > girls

rate varies across populations studied

CD is one of the most prevalent childhood disorders

most common reasons for psychiatric referral

strongest predictors of adult psychopathology

alcohol & drug dependence depression anxiety disorders

anti-social personality disorder

Not a new problem

From ‘A Winter’s Tale’ Shakespeare

“I would there was no age between ten and three and twenty, or that youth would sleep out the rest; for there is nothing in the between but getting wenches with child, wronging the ancientry, stealing, fighting”

Looking at variance components Older studies in text book

McGuffin (1985) juvenile delinquency

Twin concordances: MZ = 87% DZ = 72%

Twin correlations for quantitative measures:

	CBCL by mother	Rutter scale by mother
MZ boys	0.47	0.73
girls	0.56	0.70
DZ boys	0.40	0.50
girls	0.38	0.55
opposite sex	0.49	0.32

- modest/low genetic influence, heritability higher in girls on CBCL
- sex differences for Rutter scale ratings, higher heritabilities
- large non-shared and shared environment

CBCL Childhood Behavioral Checklist

More recent studies

example: Slutske et al (1997) J. Abnormal Psych

2682 twin pairs community-based sample DSMIII-R

Australian Twin Registry Male prevalence = 20%

Female prevalence = 3%

		n	Concordance	Tetrachoric r
Male	MZ	396	0.53	0.70
	DZ	231	0.37	0.37
Female	MZ	930	0.30	0.68
	DZ	533	0.18	0.48
Opposite sex		592	0.34	
- male proband			0.08	
- female proband			0.45	

- larger genetic influence heritability 40-66%
- shared environment < 30%
- sex differences in prevalence rates but not influences

Inconsistency in the literature on CD

Inconsistencies identified in study methodology:

- sample ascertainment clinical, court referrals, 'volunteers'
- age distribution pre- and post- adolescent, adult
- method of assessment self- or parent-administered questionnaire, interviews, official records
- heterogeneity aggressive/non-aggressive, early/late onset, with/without hyperactivity, persistent into adulthood and across situations? callous, non-empathetic?

Explaining the results:

Large environmental component - role of family emphasized

- ineffective and/or harsh parenting, poor supervision, lack of discipline, parental conflict, separation, divorce
- all identified as risk factors for CD
- but could these reflect parental psychopathology?

Peer influence

- previously identified as part of environmental influence
- but, more modest effect once prior level of proband's behavior taken into account by using longitudinal studies
- association with similar peers is mostly 'assortative friendship'
  rather than peer imitation/influence
- gene-environment correlation

Comorbidity with ADHD

CD probands 30-50% also have ADHD

ADHD probands 50% show CD/antisocial symptoms

latent trait analysis (latent class analysis)

– type of multivariate factor analysis capable of revealing common underlying influences for CD, ADHD

here = genetic influence

environmental influences separate CD from ADHD

DRD4 7-repeat(long) allele } associated with ADHD and comorbid CD

CHRN*A7*

Heritability has been found to be highest for CD that shows:

- early-onset (prior to adolescence, eg age 7)
- aggressive antisocial behavior
- hyperactivity, callousness, lack of empathy
- persistence into adulthood
- persistence across situations

Environmental risks highest for CD that shows:

- nonaggressive behavior
- less hyperactive, callous, unemotional behavior
- adolescent onset
- no persistence into adulthood

Genes for 'bad behavior'?

- mediation of gene influence is likely to be via personality attributes, cognitive style

tolerance of frustration impulse control need for stimulation

activity level level of empathy social cognitive skills

Example

Sociologist type of CD 'Delinquent behavior' (Harden et al, 2011)

delinquent behavior peaks at 16 then drops off (like CD)

corresponds to peak level of personality trait 'sensation-seeking' similar to novelty-seeking, distinct from impulsivity

impulsivity levels also still high at this age

Hypothesize sensation seeking drives delinquent behavior in those with high levels of impulsivity (start car, no brakes)

As levels of sensation seeking and impulsivity drop off towards adulthood, so does tendency towards delinquent behavior – accounts for lower prevalence with increasing age – gene influence changes over time

Those with high levels of delinquent behavior in later life show higher h^2

sensation seeking trait variation mostly due to additive genes, no shared e

+ evidence that same genes drive delinquency

Born to be wild

Enjoy taking risks? Blame your parents. CU researchers say your appetite for high-risk activities may rest in your DNA.

BY LISA MARSHALL

You know the type. He drives too fast, eschews helmets and seatbelts, delights in things the rest of us find terrifying and views the threat of harm or punishment as a dare, not a danger.

If properly directed, such thrill-seeking teens can make for great downhill mountain bikers, or Wall Street day-traders in adulthood. But in some cases, their affinity for risk can lead them into risky sex, drug addiction and other self-destructive behaviors, studies show.