OA Autism
Open Access

Review

Diagnosis Advancements

The background genetic effect of the genes underlying the broad autism phenotype as a unifying feature in gene × gene and gene × environment causal mechanisms in autism

RA Jensen*

Abstract

Introduction

This model examines the role of proposed broader autism phenotype candidate genes and unfavourable pre-, peri- and neonatal factors and environmental hazards associated with risk for early disruption of brain development, organisation of neural circuitry and increased risk for autism. A number of designated autism susceptibility genes may be more robustly characterised as broader autism phenotype candidate genes. This review proposes five broader autism phenotype candidate genes (*SLC6A4, COMT, CNTNAP2, MET, FOXP2*) for further review. Phenotypes result from the expression of an organism's genes as well as the influence of environmental factors and the interactions between the two. Broader autism phenotype candidate genes are pleotropic and include common heritable polymorphisms associated with general population risk for variable genotype–phenotype expressions that are frequently seen in autism, unaffected family members and in the general population. The general population broader autism phenotype candidate genes and genotype–phenotype expressions include social cognition and personality features, immune deficiencies, fine and gross motor incoordination, developmental language impairment, eating disorders, depression, anxiety and panic disorders, sensory processing impairments, obsessive compulsive behaviours, diabetes, gastrointestinal disorders, irritable bowel syndrome and repetitive behaviours that cluster within affected and unaffected family members and that are continuously and variably distributed throughout the general population. The independent broader autism phenotype component part is always reliant on other gene mutations inherited and/or *de novo*, environmental risk factors and epigenetic events acting alone or in concert that are involved in the transition to strictly defined autism. The general population risk for autism in developmentally compromised or at-risk individuals associated with a specific pre-, peri- or neonatal insult is calculated at about 7%. This review discusses the background genetic effect of the genes underlying the broad autism phenotype as a unifying feature in gene × gene and gene × environment causal mechanisms in autism.

Conclusion

Identifying unfavourable pre-, peri- and neonatal risk factors and environmental hazards associated with the severe developmental disorders (autism, intellectual disability, attention deficit hyperactivity disorder and schizophrenia) should be a high priority that might lead to more effective prevention strategies for these debilitating developmental conditions.

*Corresponding author
Email: rajensen088@aol.com

6100 N. Brookline Ave, #27, Oklahoma City, OK 73112, USA

Introduction

Autism is behaviourally defined by the Diagnostic and Statistical Manual, Fourth Edition, Text Revision[1] and involves a constellation of behavioural symptoms related to social cognition personality features, delayed, absent or unusual communication styles and stereotypical or obsessional and repetitive behaviours that fall under the umbrella category of the pervasive developmental disorders (PDD). The three major sub-categories are autistic disorder, PDD–Not Otherwise Specified and Asperger syndrome. In this review all sub-categories within the PDD's are referred to as autism. Individuals diagnosed with autism and their unaffected family members may share many subtle qualitative similarities in social-cognitive personality features, language, sensory processing and repetitive behaviours that are thought to mirror some aspects of autism features but that are not associated with a debilitating neurodevelopmental condition. The broader autism phenotype (BAP) and associated features are continuously and variably distributed throughout the general population[2,3].

An emerging consensus suggests that the broad spectrum of developmental disorders, including autism, may involve an early, long-lasting disruption of brain development that interferes with pre-programmed neuronal migration and is disruptive of normal synaptic connectivity. Neuropathological and imaging studies have consistently reported microscopic and macroscopic structural anomalies in the brain in autism[4,5]. Genetic and environmental influences have been invoked but autism

FOR CITATION PURPOSES: *Jensen RA*. The background genetic effect of the genes underlying the broad autism phenotype as a unifying feature in gene x gene and gene x environment causal mechanisms in autism. OA Autism 2013 May 01;1(2):11.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Autism
Open Access

Review

aetiology has proven to be elusive[6]. Heterogeneity and non-specificity in genetic, phenotypic, neuropathological, neuroimaging and environmental studies have emerged as a significant obstacle in advancing the understanding of the biological complexity and mechanisms underlying autism aetiology[7,8].

Two competing conceptual models for autism aetiology have been in place for decades. One model views autism aetiology primarily as a heritable genetic condition and the competing model views autism as primarily involving environmentally-induced structural anomalies in the brain. Both models associate autism with atypical brain development, however no single rare large genetic deletion or duplication, common genetic variant, unfavourable pre-, peri- or neonatal event or environmental hazard is predictive of autism. Autism is likely to involve multiple risk factors of small effect that in aggregate increases total risk in any individual case[9–11].

Rutter[12] has proposed a two-hit model and the existence of BAP candidate genes:

"In other words, what is required for autism 'proper' to develop are the susceptibility genes and some other risk factor that could be either genetic or environmental in origin. The implication, if it is a two hit process is that the genes underlying the broader autism phenotype may not be exactly the same as those involved in the transition to the handicapping disorder."

The long-lasting disruption of early brain development is involved in the transition to a broad spectrum of diverse neurodevelopmental conditions including autism, ADHD, schizophrenia and intellectual disability (primary mechanism). The common heritable genetic polymorphisms underlying the BAP component part (secondary mechanism) is a background genetic effect that when present is determinative of a developmental trajectory towards an autism diagnosis. In early childhood during the long-lasting rapid disruption of brain development and organisation of brain circuitry occurs, an array of BAP genotype–phenotype expressions may interactively manifest themselves at the extremes in strictly diagnosed autism. The aim of this review was to discuss the background genetic effect of the genes underlying BAP as a unifying feature in gene × gene and gene × environment causal mechanisms in autism.

The BAP candidate genes

An increasing number of autism candidate genes have been proposed and common heritable gene polymorphisms that are distributed throughout the general population may be more robustly characterised as BAP candidate genes. BAP candidate genes harbour within them subunits of genetic variants associated with autism risk. BAP candidate genes are pleotropic. Phenotypes result from the expression of an organism's genes as well as the influence of environmental factors and the interactions between the two. BAP candidate genes should include regions that harbour common genetic variants associated with general population risk for variable genotype–phenotypic expressions. General population genotype–phenotype expressions in BAP genes include unique social cognition and personality type features, immune deficiencies, fine and gross motor incoordination, developmental language impairment, eating disorders, depression, anxiety and panic disorders, bipolar disorder, sensory processing impairments, obsessive compulsive behaviours, diabetes, gastrointestinal disorders, irritable bowel syndrome and repetitive behaviours that cluster within strictly diagnosed autism, unaffected first-degree relatives in the families and in the general population.

The common genetic variants in the BAP candidate genes are heritable and very common in the general population. For example, the *MET* (7q31) gene region harbours a polymorphism, the MET promoter variant rs1858830 allele 'C', which is present in 47% of the general population and is associated with immune function, gastrointestinal repair, neuronal growth and development[13]. One of the first autism candidate genes proposed is the serotonin transporter gene *SLC64A* (5-HTT), which maps to chromosome 17q[11,12]. Multiple studies have implicated common genetic polymorphisms within the *COMT* gene (22q11) region as an autism candidate gene. One of the earliest target-rich regions containing autism candidate genes was mapped to chromosome 7 and include *MET* (7q31), *CNTNAP2* (7q35) and *FOXP2* (7q35). Extreme genotype–phenotype expressions in the BAP genes that harbour common polymorphisms may involve gene by environment or epigenetic mechanisms given how widely these polymorphisms are distributed throughout the general population. General population genotype–phenotype expressions in BAP proposed candidate genes are listed in Table 1.

In early childhood during the rapid and long-lasting disruption of early brain development, severe symptoms begin to emerge and an array of independent BAP component parts may be variably expressed at the extremes in strictly diagnosed autism. The BAP candidate genes all involve common polymorphisms associated with general population risk for obsessive compulsive disorder. In strictly diagnosed autism in early childhood, severe obsessive compulsive disorder-like symptoms may emerge including repetitively checking things, counting things, hoarding behaviours, lining up objects and amassing collections of objects. When these behaviours are disrupted severe anxiety and panic attacks are commonly observed[42]. Sensory impairments are seen and

FOR CITATION PURPOSES: *Jensen RA*. The background genetic effect of the genes underlying the broad autism phenotype as a unifying feature in gene x gene and gene x environment causal mechanisms in autism. OA Autism 2013 May 01;1(2):11.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Autism
Open Access

Review

Table 1 BAP candidate genes: genotype–phenotype expressions		
22q11 *COMT*	Self reported schizotypy traits	Avramopoulos et al.[14]
22q11 *COMT*	Anxiety and depression	Hettama et al.[15]
22q11 *COMT*	Obsessive compulsive disorder	Liu et al.[16]
22q11 *COMT*	Immune deficiencies	McLean-Tooke et al.[17]
22q11 *COMT*	Panic disorder	Domschke et al.[18]
22q11 *COMT*	Sensorimotor gating	Stark et al.[19]
22q11 *COMT*	Olfactory disorder	Sobin[20]
22q11 *COMT*	Hearing impairments	Zarrchi et al.[21]
17q11–12 *SLC6A4*	Anti-social personality disorder	Garcia et al.[22]
17q11–12 *SLC6A4*	Depression	Brummett et al.[23]
17q11–12 *SLC6A4*	Depression and bulimia	Mata & Gotlib[24]
17q11–12 *SLC6A4*	Borderline personality disorder	Hankin et al.[25]
17q11–12 *SLC6A4*	First episode depression	Bukh et al.[26]
17q11–12 *SLC6A4*	Obsessive compulsive disorder	Denys et al.[27]
17Q11–12 *SLC6A4*	Irritable bowel syndrome	Wang et al.[28]
17q11–12 *SLC6A4*	Rigid compulsive behaviours	Sutcliffe et al.[29]
17q11–12 *SLC6A4*	Thermal pain thresholds	Lindsted[30]
7q31 *MET*	Immune function and gastrointestinal repair	Randolph-Gips & Srinivasan[13]
7q31 *MET*	Bipolar disorder	Palo et al.[31]
7q31 *MET*	Obsessive compulsive disorder	Sakuri et al.[32]
7q31 *MET*	Tourette's syndrome (Tics)	Patel et al.[33]
7q31 *MET*	Tourette's syndrome: depression, anxiety, phobic disorder, hostility and aggression	Robertson[34]
7q35 *CNTNAP2 FOXP2*	Developmental language disorder	Lennon et al.[35]
7q35 *CNTNAP2 FOXP2*	Obsessive compulsive disorder	Verkerk et al.[36]
7q35 *CNTNAP2 FOXP2*	Variability in spoken language	Alarcon et al.[37]
7q35 *CNTNAP2 FOXP2*	Diabetic nephropathy	Conway et al.[38]
7q35 *CNTNAP2 FOXP2*	Auto-immune synaptic disorders	Serratrice G & Serratirice J[39]
7q35 *CNTNAP2 FOXP2*	Dyslexia	Peter et al.[40]
7q35 *CNTNAP2 FOXP2*	Selective mutism and social-anxiety related traits	Stein et al.[41]

may include unusual responses to touch, light, sound, heat and pain[43]. Idiosyncratic feeding behaviours are frequently observed perhaps related to general population risk for eating disorders[24]. Medical complications such as severe constipation, gastrointestinal problems, irritable bowel syndrome and immune deficiencies occur more frequently than general population norms. Impairments in gross and fine motor skills are a commonplace[44].

The phenomenon of transient echolalia appears to be universal in verbal young children diagnosed with autism[45]. Echolalia has been seen in other conditions that feature aberrant neuronal circuitry including patients with Alzheimer disease, brain tumour and stroke[46–48].

General population prevalence of the BAP and at the extremes

The BAP social cognition features concept by child psychiatry has its origins in Leo Kanner's[42] 1943 classic article 'Autistic Disturbance of Affective Contact'. He described the parents as follows:

"One other fact stands out prominently. In the whole group, there are very few really warm hearted fathers and mothers. For the most part, the parents, grandparents and collaterals are persons strongly preoccupied with abstractions of a scientific, literary, or artistic nature, and limited in genuine interest in people."

A number of groups have measured the general population prevalence of BAP social cognition, communication and repetitive traits by devising a check list of questionnaires including the Childhood Asperger Syndrome Test, the Autism Spectrum Questionnaire and the Social Reciprocity Scale. These checklists do not contain any biological symptoms that may cluster in affected and unaffected family members and in the general population that may also be associated with increased risk for disruption of early brain development.

Genetic epidemiology has measured the prevalence of BAP traits in the general population by recruiting thousands of volunteer samples often taken from twin registries with research questionnaires to be completed by parents or teachers or by self report. The studies have consistently reported that the prevalence of BAP traits are moderately to highly heritable and extend very broadly throughout the general population. Hoekstra et al.[49] measured the BAP using Autism-Spectrum Quotient scores from volunteers recruited

FOR CITATION PURPOSES: *Jensen RA*. The background genetic effect of the genes underlying the broad autism phenotype as a unifying feature in gene x gene and gene x environment causal mechanisms in autism. OA Autism 2013 May 01;1(2):11.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Autism
Open Access

from a twin registry and found the BAP to be highly heritable and continuously distributed showing substantial variability throughout the general population. Constantino & Todd[50] found sub-clinical autistic-like traits by parent-scored measures in the Social Responsiveness Scale to be highly to moderately heritable and also widely distributed throughout the general population. Ronald et al.[51] reported high heritability for extreme BAP traits and BAP traits as measured on a continuum. Preti et al.[52] reported on the self-administered Empathy Quotient test, thought to measure the prevalence of a putative BAP trait, empathy, taken by undergraduate students. A score below 30 represents the cut-off that best differentiates the presence of this putative BAP trait from controls. Of the 374 students (males = 118, females = 256) completing the test, 18 scored below the cut-off of 30 (males = 11.9%, females = 2.9%). About 20% of unaffected siblings have a history of language delay far greater than the 7.4% of general population children with a history of language delay[53,54]. Ronald et al.[55] selected the top 5% highest BAP scorers and reported high heritability that showed modest phenotypic and genetic overlap between three measures: social impairments, communication impairments and restricted repetitive and interests. Happe and colleagues[56] reported that "Around 10% of all children showed only social impairment, only communicative difficulties or only rigid and repetitive interests and behaviour, and these problems appeared to be at a level of severity comparable to that found in children with diagnosed autism in our sample."

The Rutter hypothesis was demonstrated in a gene × gene (G × G) causal mechanism, Down syndrome with autism, featuring the interplay between a *de novo* genetic mutation and a background BAP genetic effect that follows a developmental trajectory to an autism diagnosis. Ghaziuddin[57,58] compared a group of Down syndrome individuals and their first-degree relatives (parents and siblings) with or without a diagnosis of autism. In Down syndrome with autism there was an excess of first-degree relatives who met the description of BAP features compared to first-degree relatives in Down syndrome without autism who did not. The Down syndrome mutation and autism was not present in first-degree relatives, parents and siblings, and the genes underlying the BAP component part are independent of and are a background genetic effect secondary to the disruption of early brain development in Down syndrome and the transition to autism as predicted by the Rutter hypothesis.

Unfavourable pre-, peri- and neonatal factors in autism: gene × environment (G × E) causal mechanism

Several design methodologies examining obstetrical and environmental hazards associated with autism risk have been in place for decades. The most common design method is selecting autism diagnosed only individuals and largely unaffected sibling, neurotypical and/or national statistic controls. This method has produced consistent evidence that unfavourable events in the pre-, peri- and neonatal period may or may not be associated with autism risk. The data have been difficult to analyse as the factors representing possible risk for autism are not specific to autism and may represent various forms of pathological processes and developmental problems. No single unfavourable factor or unifying feature stands out as representing high autism risk[8].

A second less frequently used design method was serendipitously introduced by Chess[59] in her 1971 seminal article 'Autism in Children with Congenital Rubella'. In the aftermath of the last rubella epidemic that took place in 1960s in the US, 243 children diagnosed with congenital rubella syndrome were placed under her care at the New York University Medical Centre. Of the 243 children, a psychiatric diagnosis of autism was reported in 10 children and a psychiatric diagnosis of atypical autism in a further eight children which represented 7.4% of the total group, consistent with cut-off estimates for high-scoring BAP social cognition trait prevalence in the general population. A comprehensive detailed description of the behavioural disturbances in two of the boys under Chess's care diagnosed with autism was presented. The behavioural disturbances observed were indistinguishable from the very detailed behavioural disturbances of the 11 children described by Kanner[42].

The estimates for the prevalence of autism risk represented by the BAP highest scorers by various cut-offs in the general population of between 5% and 10% have been reported by Plomin's group. The cut-offs can be applied to the variable diagnostic outcomes within studies based on the Chess design method. The design selects all individuals identified with a specific unfavourable pre-, peri- or neonatal event and reports the prevalence of autism within the group. The Rutter hypothesis would expect striking heterogeneity in outcomes and that the prevalence of autism within the studies would be consistent with and test the reliability of the general population autism risk estimates based on high BAP scoring cut-off ranges. Exclusionary criteria are studies with less than 20 participants, retrospective studies based on parental recall, studies that compared autism diagnosed samples only with various control groups and studies that used autism screening tools only (Table 2).

Discussion

Of the 17 studies listed only one, infantile spasms, was an outlier for autism risk with a 30%

FOR CITATION PURPOSES: *Jensen RA*. The background genetic effect of the genes underlying the broad autism phenotype as a unifying feature in gene x gene and gene x environment causal mechanisms in autism. OA Autism 2013 May 01;1(2):11.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Autism
Open Access

Table 2 Autism prevalence identified with specific pre-, peri- and neonatal unfavourable factors in the general population

Description	ASD (%)	Total diagnosed ASD	Total in group	Study design	Author (s)
Congenital Rubella syndrome	7.4	18	243	Clinic	Chess[59]
Thalidomide embryopathy	4.0	4	100	Clinic	Stromland et al.[60]
Valproate acid syndrome	8.9	5	56	Clinic	Rasalam et al.[61]
Fetal alcohol syndrome	8.3	2	24	Clinic	Aronson et al.[62]
Unprovoked neonatal seizures	7.1	6	84	Population	Saemundsen et al.[63]
Infantile spasms	30.0	6	20	Population	Saemundsen et al.[64]
Newborn encephalopathy	5.0	12	239	Population	Badawi et al.[65]
Premature birth	7.3	16	219	Population	Johnson et al.[66]
Perinatal cocaine syndrome	11.4	8	70	Clinic	Davis et al.[67]
Post institutional autistic syndrome*	9.8	22	224	Clinic	Rutter et al.[68] Hoksbergen et al.[69]
Severe paediatric constipation	8.4	10	118	Clinic	Pang & Croaker[70]
Neonatal arterial switch surgery	6.1	4	65	Clinic	Neufeld et al.[71]
Congenital diaphragmatic hernia	7.3	3	41	Clinic	Danzer et al.[72]
Renal disease/ diabetes	5.6	3	53	Clinic	Loirat et al.[73]
Low birth weight	4.9	31	623	Population	Pinto-Martin et al.[74]
Cerebral palsy	8.1	39	476	Population	Kirby et al.[75]
Totals	6.8	189	2745		

*, pooled results of two post institutional autistic syndrome papers

prevalence (6/20). The results of 16 of the 17 studies were predicted by the estimates of autism risk associated with a specific pre-, peri- or neonatal unfavourable factor in the general population of developmentally compromised or at-risk individuals of around 7% (the highest BAP scorers) and by the Rutter hypothesis.

Six of the syndromes listed (Table 2) have such a hugely massive environmental effect that preventative measures can or have been put in place. Prevention measures are in place for congenital rubella syndrome and thalidomide embryopathy with the development of an effective rubella vaccine and the ban on the use of thalidomide in obstetrics. Foetal alcohol syndrome, valproate acid syndrome, perinatal cocaine exposure syndrome and post institutional autistic syndrome are all preventable syndromes with a massive environmental effect and high autism risk.

The prevalence of autism in many genetically determined syndromes is frequently much greater than the approximate 7% that the Rutter hypothesis would predict. Moss and Howlin[76] have presented good evidence that in the genetically determined syndromes autism symptoms are associated with intellectual disability and cautioned against over interpreting the superficial similarities between autism and the behavioural phenotypes seen in most genetically determined syndromes. The authors also found that many genetically determined syndromes have their own unique pattern of superficial autism symptoms.

Twin studies in autism where one or both twins met diagnostic criteria for strictly defined or broadly defined autism have produced monozygotic twin concordance rates as high as 92% in broadly defined autism. Studies of general population twins have reported high BAP concordance rates and heritability estimates in general population twins, dependent on arbitrary cut-offs. Classical twin study design heritability estimates cannot control for the high rates of *de novo* mutations in autism therefore autism twin study heritability estimates are inflated. Common gene polymorphisms in candidate BAP genes are inherited therefore BAP concordance rates and heritability estimates may be more informative with respect to heritability estimates and general population autism risk. The implication within this model is that what the twin studies are reflecting may not be the heritability of autism at all but rather the concordance rate and heritability estimates of the independent BAP component part. The independent BAP component part can be characterised as the 'missing heritability' in autism[77].

FOR CITATION PURPOSES: *Jensen RA*. The background genetic effect of the genes underlying the broad autism phenotype as a unifying feature in gene x gene and gene x environment causal mechanisms in autism. OA Autism 2013 May 01;1(2):11.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Autism
Open Access

Conclusion

The background BAP component part is a unifying feature that can be observed in G × G and G × E causal mechanisms that distinguishes autism cases from non-autism cases. Identifying unfavourable pre-, peri- and neonatal risk factors and environmental hazards associated with the severe developmental disorders (autism, intellectual disability, ADHD and schizophrenia) should be a high priority that might lead to more effective prevention strategies for these debilitating developmental conditions.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-Text Revision. Washington, DC: American Psychiatric Association; 2000.
2. Constantino JN, Todd RD. Intergenerational transmission of subthreshold autistic traits in the general population. Biol Psychiatry. 2005 Mar;57(6):655–60.
3. Losh M, Adolphs R, Poe MD, Couture S, Penn D, Baranek GT, et al. Neuropsychological profile of autism and the broad autism phenotype. Arch Gen Psychiatry. 2009 May;66(5):518–26.
4. Bauman ML, Kemper TL. Neuroanatomic observations of the brain in autism: a review and future directions. Int J Dev Neurosci. 2005 Apr–May;23(2-3):183–7.
5. Toal F, Murphy DG, Murphy KC. Autistic-spectrum disorders: lessons from neuroimaging. Br J Psychiatry. 2005 Nov;187:395–7.
6. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics. 2004 May;113(5):e472–86.
7. Abrahams BS, Geshwind DH. Advances in autism genetics: on the threshold of a new neurobiology. Nat Rev Genet. 2008 May;9(5):341–55.
8. Juul-Dam N, Townsend J, Courchesne E. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. Pediatrics. 2001 Apr;107(4):e63.
9. Bijlsma EK, Gijsbers AC, Schuurs-Hoeijmakers JH, van Haeringen A, Fransen van de Putte DE, Anderlid BM, et al. Extending the phenotype of recurrent rearrangements of 16p11.2: deletions in mentally retarded patients without autism and in normal individuals. Eur J Med Genet. 2009 Mar–Jun;52(2-3):77–87.
10. Stein D, Weizman A, Ring A, Barak Y. Obstetric problems in individuals diagnosed with autism and in healthy controls. Compr Psychiatry. 2006 Jan–Feb; 47(1):69–75.
11. Wermter AK, Kamp-Becker I, Strauch K, Schulte-Korne G, Remschmidt H. No evidence for involvement of genetic variants in the X-linked neuroligin genes NLGN3 and NLGN4X in probands with autism spectrum disorder on high functioning level. Am J Med Genet B Neuropsychiatr Genet. 2008 Jun;147B(4):535–7.
12. Rutter M. Genes and behavior: nature-nurture interplay explained. Wiley-Blackwell; New York 2006.p139.
13. Randolph-Gips M, Srinivasan P. Modeling autism: a systems biology approach. J Clin Bioinforma. 2012 Oct;2(1):17.
14. Avramopoulos D, Stefanis NC, Hantoumi I, Smyrnis N, Evodokimidis I, Stefanis CN. Higher scores of self reported schizotypy in healthy young males carrying the COMT high activity allele. Mol Psychiatry. 2002;7(7):706–11.
15. Hettama JM, An SS, Bukszar J, van den Oord EJ, Neale MC, Kendler KS, et al. Catechol-O-methyltransferase contributes to genetic susceptibility shared among anxiety spectrum phenotypes. Biol Psychiatry. 2008 Aug;64(4): 302–10.
16. Liu S, Liu Y, Wang H, Zhou R, Zong J, Li C, et al. Association of catechol-O-methyl transferase (COMT) gene -287A/G polymorphism with susceptibility to obsessive-compulsive disorder in Chinese Han population. Am J Med Genet B Neuropsychiatr Genet. 2011 Jun;156B(4):393–400.
17. McLean-Tooke A, Spickett GP, Gennery AR. Immunodeficiency and autoimmunity in 22q11.2 deletion syndrome. Scan J Immunol. 2007 Jul; 66(1):1–7.
18. Domschke K, Ohrmann P, Braun M, Suslow T, Bauer J, Hohoff C, et al. Influence of the catechol-O-methyltransferase val158met genotype on amygdala and prefrontal cortex emotional processing in panic disorder. Psychiatry Res. 2008 May;163(1):13–20.
19. Stark KL, Burt RA, Gogos JA, Karayiorgou M. Analysis of prepulse inhibition in mouse lines overexpressing 22q11.2 orthologues. Int J Neuropsychopharmacol. 2009 Aug;12(7):983–9.
20. Sobin C, Kiley-Brabeck K, Dale K, Monk SH, Khuri L, Karayiorgou M. Olfactory disorder in children with 22q11 deletion syndrome. Pediatrics. 2006 Sep;118(3):e697–703.
21. Zarrchi O, Attias J, Raveh E, Basel-Vanagaite L, Saporta L, Gothelf D. A comparative study of hearing loss in two microdeletion syndromes: velocardiofacial (22q11.2 deletion) and Williams (7q11.23 deletion) syndromes. J Pediatr. 2011 Feb;158(2):301–6.
22. Garcia LF, Aluja A, Fibla J, Cuevas L, Garcia O. Incremental effect for antisocial personality disorder genetic risk combining 5-HTTLPR and 5-HTTVNTR polymorphisms. Psychiatry Res. 2010 May;177 (1-2):161–6.
23. Brummett BH, Boyle SH, Siegler IC, Kuhn CM, Ashley-Koch A, Jonassaint CR, et al. Effects of environmental stress and gender on associations among symptoms of depression and the serotonin transporter gene linked polymorphic region (5-HTTLPR). Behav Genet. 2008 Jan;38(1):34–43.
24. Mata J, Gotlib IH. 5-HTTLPR moderates the relation between changes in depressive and bulimic symptoms in adolescent girls: a longitudinal study. J Eat Disord. 2011 Jul;44(5):383–8.
25. Hankin BL, Barrocas AL, Jenness J, Oppenheimer CW, Badanes LS, Abela JR, et al. Association between 5-HTTLPR and Borderline Personality Disorder Traits among Youth. Front Psychiatry. 2011 Mar;2:6.
26. Bukh JD, Bock C, Vinberg M, Werge T, Gether U, Vedel Kessing L. Interaction between genetic polymorphisms and stressful life events in first episode depression. J Affect Disord. 2009 Dec;119(1-3):107–15.
27. Denys D, Van Nieuwerburgh F, Deforce D, Westenberg HG. Association between serotonergic candidate genes and specific phenotypes of obsessive compulsive disorder. J Affect Disord. 2006 Mar;91(1):39–44.
28. Wang BM, Wang YM, Zhang WM, Zhang QY, Liu WR. [Serotonin transporter gene polymorphism in irritable bowel syndrome]. Zhoqhua Ke Za Zhi. 2004 Jun;43(6):439–41.
29. Sutcliffe JS, Delahanty RJ, Prasad HC, McCauley JL, Han Q, Jiang L, et al. Allelic heterogeneity at the serotonin

FOR CITATION PURPOSES: *Jensen RA*. The background genetic effect of the genes underlying the broad autism phenotype as a unifying feature in gene x gene and gene x environment causal mechanisms in autism. OA Autism 2013 May 01;1(2):11.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Autism
Open Access

Review

transporter locus (SLC6A4) confers susceptibility to autism and rigid-compulsive behaviors. Am J Hum Genet. 2005 Aug;77(2):265–79.
30. Lindstedt F, Lonsdorf TB, Schalling M, Kosek E, Ingvar M. Perception of thermal pain and the thermal grill illusion is associated with polymorphisms in the serotonin transporter gene. PloS One. 2011 Mar;6(3):e17752.
31. Palo OM, Soronen P, Silander K, Varilo T, Tuononen K, Kieseppa T, et al. Identification of susceptibility loci at 7q31 and 9p13 for bipolar disorder in an isolated population. Am J Med Genet B Neuropsychiatr Genet. 2010 Apr;153B(3):723–35.
32. Sakurai T, Ramoz N, Reichert JG, Corwin TE, Kryzak L, Smith CJ, et al. Association analysis of the NrCAM gene in autism and in subsets of families with severe obsessive-compulsive or self-stimulatory behaviors. Psychiatr Genet. 2006 Dec;16(6):251–7.
33. Patel C, Cooper-Charles L, McMullan DJ, Walker JM, Davison V, Morton J. Translocation breakpoint at 7q31 associated with tics: further evidence for IMMP2L as a candidate gene for Tourette syndrome. Eur J Hum Genet. 2011 Jun;19(6):634–9.
34. Robertson MM. The Gilles de la Tourette syndrome and obsessional disorder. Int Clin Psychopharmacol. 1991 Dec;6(Suppl 3):69–82.
35. Lennon PA, Cooper ML, Peiffer DA, Gunderson KL, Patel A, Peters S, et al. Deletion of 7q31.1 supports involvement of FOXP2 in language impairment: clinical report and review. Am J Med Genet A. 2007 Apr;143A(8):791–8.
36. Verkerk AJ, Mathews CA, Joosse M, Eussen BH, Heutink P, Oostra BA, et al. CNTNAP2 is disrupted in a family with Gilles de la Tourette syndrome and obsessive compulsive disorder. Genomics. 2003 Jul;82(1):1–9.
37. Alarcon M, Yonan AL, Gilliam TC, Cantor RM, Geschwind D. Quantitative genome scan and ordered-subsets analysis of autism endophenotypes support language QTL's. Mol Psychiatry. 2005 Aug;10(8):747–57.
38. Conway BR, Maxwell AP, Savage DA, Patterson CC, Doran PP, Murphy M, et al. Association between variation in the actin-binding gene caldesmon and diabetic nephropathy in type 1 diabetes. Diabetes. 2004 Apr;53(4):1162–5.
39. Serratrice G, Serratrice J. Continuous muscle activity, Morvan's syndrome and limbic encephalitis: ionic or non ionic disorders? Acta Myol. 2011 Jun; 30(1):32–3.
40. Peter B, Raskind WH, Matsushita M, Lisowski M, Vu T, Berninger VW, et al. Replication of CNTNAP2 association with nonword repetition and support for FOXP2 association with timed reading and motor activities in a dyslexia family sample. J Neurodev Disord. 2011 Mar;3(1):39–49.
41. Stein MB, Yang BZ, Charive DA, Hitchcock CA, Sung SC, Shipon-Blum E, et al. A common genetic variant in the neurexin superfamily member CNTNAP2 is associated with increased risk for selective mutism and social anxiety-related traits. Biol Psychiatry. 2011 May; 69(9):825–31.
42. Kanner L. Autistic disturbances of affective contact. Nervous Child 2. 1943; 217–250.
43. Gerrard S, Rugg G. Sensory impairments and autism: a re-examination of causal modelling. J Autism Dev Disord. 2009 Oct;39(10):1449–63.
44. Maski KP, Jeste SS, Spence SJ. Common neurological co-morbidities in autism spectrum disorders. Curr Opin Pediatr. 2011 Dec;23(6):609–15.
45. Grossi D, Marcone R, Cinquegrana T, Galluci M. On the differential nature of induced and incidental echolalia in autism. J Intellect Disabil Res. 2013 Oct;57(10):903–12.
46. Da Cruz FM. Verbal repetitions and echolalia in Alzheimer's discourse. Clin Linguist Phon. 2010 Nov;24(11): 848–58.
47. Endo K, Suzuki K, Yamadori A, Kumabe T, Seki K, Fujii T. [A case of crossed aphasia with echolalia after the resection of tumor in the right medial frontal lobe]. No To Shinkei. 2001 Mar; 53(3):287–92.
48. Mendez MF. Prominent echolalia from isolation of the speech area. J Neuropsychiatry Clin Neurosci. 2002 Summer;14(3):356–7.
49. Hoekstra RA, Bartels M, Verweij CJ, Boomsma DI. Heritability of autistic traits in the general population. Arch Pediatr Adolesc Med. 2007 Apr;161(4):372–7.
50. Constantino JN, Todd RD. Autistic traits in the general population: a twin study. Arch Gen Psychiatry. 2003 May; 60(5):524–30.
51. Ronald A, Happe F, Price TS, Baron-Cohen S, Plomin R. Phenotypic and genetic overlap between autistic traits at the extremes of the general population. J Am Acad Child Adolesc Psychiatry. 2006 Oct;45(10):1206–14.
52. Preti A, Vellante M, Baron-Cohen S, Zucca G, Petretto DR, Masala C. The Empathy Quotient: a cross-cultural comparison of the Italian version. Cogn Neuropsychiatry. 2011 Jan;16(1):50–70.
53. Constantino JN, Zhang Y, Frazier T, Abbacchi M, Law P. Sibling recurrence and the genetic epidemiology of autism. Am J Psychiatry. 2010 Nov;167(11):1349–56.
54. Tomblin JB, Records NL, Buckwalter P, Zhang X, Smith E, O'Brien M. Prevalence of specific language impairment in kindergarten children. J Speech Lang Hear Res. 1997 Dec;40(6):1245–60.
55. Ronald A, Happe F, Bolton P, Butcher LM, Price TS, Wheelwright S, et al. Genetic heterogeneity between the three components of the autism spectrum: a twin study. J Am Acad Child Adolesc Psychiatry. 2006 Jun;45(6):691–9.
56. Happe F, Ronald A, Plomin R. Time to give up on a single explanation for autism. Nat Neurosci. 2006 Oct;9(10):1218–20.
57. Ghaziuddin M. Autism in Down's syndrome: family history correlates. J Intellect Disabil Res. 1997 Feb;(Pt1):87–91.
58. Ghaziuddin M. Autism in Down's syndrome: a family history. J Intellect Disabil Res. 2000 Oct;44(Pt 5):562–6.
59. Chess S. Autism in children with congenital rubella. J Autism Child Schizophr. 1971 Jan–Mar;1(1):33–47.
60. Stromland K, Nordin V, Miller M, Akerstrom B, Gillberg C. Autism in thalidomide embryopathy: a population study. Dev Med Child Neurol. 1994 Apr;36(4):351–6.
61. Rasalam AD, Hailey H, Williams JH, Moore SJ, Turnpenny PD, Lloyd DJ, et al. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. Dev Med Child Neurol. 2005 Aug;47(8):551–5.
62. Aronson M, Hagberg B, Gillberg C. Attention deficits and autistic spectrum problems in children exposed to alcohol during gestation: a follow-up study. Dev Med Child Neurol. 1997 Sep;39(9): 583–7.
63. Saemundsen E, Ludvigsson P, Rafnsson V. Autism spectrum disorders in children with a history of infantile spasms: a population-based study. Child Neurol. 2007 Sep;22(9):1102–7.

FOR CITATION PURPOSES: *Jensen RA*. The background genetic effect of the genes underlying the broad autism phenotype as a unifying feature in gene x gene and gene x environment causal mechanisms in autism. OA Autism 2013 May 01;1(2):11.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Autism
Open Access

Review

64. Saemundsen E, Ludvigsson P, Hilmarsdotter I, Rafnsson V. Autism spectrum disorders in children with seizures in the first year of life: a population-based study. Epilepsia. 2007 Sep;48(9):1724–30.
65. Badawi N, Dixon G, Felix IF, Keogh JM, Petterson B, Stanley FJ, et al. Autism following a history of newborn encephalopathy: more than a coincidence? Dev Med Child Neurol. 2006 Feb;48(2):85–9.
66. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Autism spectrum disorders in extremely preterm children. J Pediatr. 2010 Apr;156(4): 525–31.
67. Davis E, Fennoy, I, Laraque, D, Kanem N, Brown G, Mitchell J. Autism and developmental abnormalities in children with perinatal cocaine exposure. J Natl Med Assoc. 1992 April;84(4):315–9.
68. Rutter M, Kreppner J, Croft C, Murin M, Colvert E, Beckett C, et al. Early adolescent outcomes of institutionally deprived and non-deprived adoptees. III. Quasi-autism. J Child Psychol Psychiatry. 2007 Dec;48(12):1200–7.
69. Hoksbergen R, ter Laak J, Rijk K, van Dijkum C, Stoutjesdijk. Post-institutional autistic syndrome in Romanian adoptees. J Autism Dev Disord. 2005 Oct;35(5):615–23.
70. Pang KH, Croaker GD. Constipation in children with autism and autistic spectrum disorder. Pediatr Surg Int. 2011 Apr;27(4):353–8.
71. Neufeld RE, Clark BG, Robertson CM, Moddemann DM, Dinu IA, Joffe AR, et al. Five-year neurocognitive and health outcomes after the neonatal arterial switch operation. J Thorac Cardiovasc Surg. 2008 Dec;136(6):1413–21, 1421. e1–1421.e2.
72. Danzer E, Gerdes M, Bernbaum J, D'Agostini J, Bebbington MW, Siegle J, et al. Neurodevelopmental outcome of infants with congenital diaphragmatic hernia prospectively enrolled in an interdisciplinary follow-up program. J Pediatr Surg. 2010 Sep;45(9):1759–66.
73. Loirat C, Bellanne-Chantelot C, Husson I, Deschenes G, Guigonis V, Chabane N. Autism in three patients with cystic or hyperechogenic kidneys and chromosome 17q12 deletion. Nephrol Dial Transplant. 2010 Oct; 25(10):3430–3.
74. Pinto-Martin JA, Levy SE, Feldman JF, Lorenz JM, Paneth N, Whitaker AH. Prevalence of autism spectrum disorder in adolescents born weighing <2000 grams. Pediatrics. 2011 Nov;128(5):883–91.
75. Kirby RS, Wingate MS, Van Naarden Braun K, Doernberg NS, Arneson CL, Benedict RE, et al. Prevalence and functioning of children with cerebral palsy in four areas of the United States in 2006: a report from the Autism and Developmental Disabilities Monitoring Network. Res Dev Disabil. 2011 Mar–Apr;32(2):462–9.
76. Moss J, Howlin P. Autism spectrum disorders in genetic syndromes: implications for diagnosis, intervention and understanding the wider autism spectrum disorder population. J Intellect Disabil Res. 2009 Oct;53(10):852–73.
77. Ronald A, Hoekstra RA. Autism spectrum disorders and autistic traits: a decade of new twin studies. Am J Med Genet B Neuropsychiatr Genet. 2011 Apr;156B(3):255–74.

FOR CITATION PURPOSES: *Jensen RA*. The background genetic effect of the genes underlying the broad autism phenotype as a unifying feature in gene x gene and gene x environment causal mechanisms in autism. OA Autism 2013 May 01;1(2):11.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.