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The Genetic Basis of Phenotypic Diversity: Autism as an Extreme Tail of a Complex Dimensional Trait

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1. Introduction

Autism is a developmental lifelong condition of the human brain, and a behavioral characterization as a spectrum (autism spectrum disorder: ASD) is the best way to illustrate this complex trait (Frith, 2001; Rapin, 1997; Wing, 1997). The predominant presence of autistic cases without comorbidity (idiopathic or primary ASD) (Freitag, 2007) clearly means that the biological effects associated with the known concomitant medical conditions (cytogenic abnormalities, fragile X syndrome, tuberous sclerosis, congenital infections, maternal thalidomide use, epilepsy, etc.) cannot be the common prerequisite for ASD at least in the majority of the cases. The presence of a strong genetic contribution is evident from the results of twin studies, which demonstrated that 70-90% of monozygotic twins are concordant for ASD, and the concordance in dizygotic twins and the recurrence rate in the proband's siblings are both less than 10% (Rapin & Katzman, 1998). A broadening of the criteria of diagnosis leads the monozygotic concordance ratio to more than 90%, but 100% concordance is never obtained (Rapin & Katzman, 1998). Therefore, it is claimed that genetic factors contribute about 90% to ASD with environmental factors contributing no more than 10% (Garber, 2007). Although a flood of genetic information in the field of ASD is continuously growing, even the newest genome-wide molecular studies cannot detect the universal genetic prerequisite for idiopathic cases with ASD, compelling some researchers to speculate that ASD has a huge inter-case heterogeneity of the related gene variants.

Many gene variants, which seem to affect brain development and synaptic functions, have been reported in association with the autistic development (Betancur, 2011; Garber, 2007; Persico & Bourgeron, 2006; Pinto et al., 2010). In families with the candidates for autism gene variants, however, the strict co-segregation, in which the gene variant is found only in individuals with ASD among family members including parents, is still exceptional (Table 1). To explain this fact, the broader distribution of the more primary phenotype or pre-behavioral phenotype (endophenotype) beyond the categorical border is introduced as the speculative solution through this research maze (Viding & Blakemore, 2007). It may be quite difficult to detect and evaluate such endophenotypes because of the configurational or hierarchical structures of human cognitions and behaviors. Even if such speculations were

all true, it is too early to conclude that "a single gene variant causes a small percentage of cases with this complex trait" (Garber, 2007; Beaudet, 2007). As clearly demonstrated in the case of human disease-associated mutations found as wild-type alleles in normal chimpanzee (L. Azevedo et al., 2006), a deleted or mutated allele does not necessarily contribute to the disease development. Because evidence consistent with a theory is not proof of that theory (Cannell, 2010), until one could delineate the molecular or biological trajectory underlying autistic development which is quantitatively different from the parents, there is still a huge black box between the *de novo* variant allele and complex human behaviors in the sporadic cases with idiopathic ASD. The reported gene variants are, at present, nothing but one of the concomitants in a small percentage of cases (5-7%, in Table 1). The possibility that the variantsare mere relative risk factors remains to be elucidated (Jones & Szatmari, 2002). As a general rule, a genetic link does not necessarily imply neurological damage (Simpson,

Variants	Prevalence		References
SHANK3 variants	In ASD families	15 / 227 (6.6%)[a]	(Durand et al., 2007)
	Co-segregated cases	3 / 227 (1.3%)[b]	
	In controls	5 / 270 (1.9%)[a]	
SHANK3 variants	In ASD families	3 / 400 (0.8%)[c]	(Moessner et al., 2007)
SHANK3 variants	In ASD individuals	34 / 427 (8.0%)	(Gauthier et al., 2009)
	In controls	16 / 190 (8.4%)	
SHANK3 deletion	In ASD individuals	1 / 427 (0.2%)[c]	(Gauthier et al., 2009)
	In controls	0 / 190	
SHANK3 deletion	In ASD individuals	2 / 2,195 (0.1%)	(Glessner et al., 2009)
	In controls	2 / 2,519 (0.1%)	
SHANK2 *de novo* deletion	In ASD individuals	2 / 996 (0.2%)	(Pinto et al., 2010)
	In controls	0 / 1,287, 0 / 3,677	
NLGN3 variants	In ASD individuals	0 / 96	(Yan et al., 2005)
NLGN3 duplication	In ASD individuals	1 / 2,195 (0.05%)	(Glessner et al., 2009)
	In controls	0 / 2,519	
NLGN4 variants	In ASD individuals	4 / 148 (2.7%)[d]	(Yan et al., 2005)
	In controls	0 / 336	
NRXN1 deletion	In ASD families	1 / 1,181 (0.1%)	(AGPC, 2007)
NRXN1α variants	In ASD individuals	5 / 116 (4.3%)	(Yan et al., 2008)
	In controls	1 / 192 (0.5%)	
NRXN1 deletion	In ASD individuals	10 / 2,195 (0.5%)	(Glessner et al., 2009)
	In controls	0 / 2,519	
NRXN1 *de novo* variants	In ASD families	4 / 996 (0.4%)	(Pinto et al., 2010)
	In controls	5 / 1,287 (0.4%)	
NRXN1β variants	In ASD individuals	4 / 203 (2.0%)[d,e]	(Feng et al., 2006)
	In controls	0 / 535	
NRXN2β variants	In ASD individuals	0 / 72	(Feng et al., 2006)
NRXN3β variants	In ASD individuals	0 / 72	(Feng et al., 2006)
CNTN4 deletion	In ASD individuals	10 / 2,195 (0.5%)	(Glessner et al., 2009)
	In controls	0 / 2,519	
CNTN4 duplication	In ASD individuals	9 / 2,195 (0.4%)[c]	(Glessner et al., 2009)
	In controls	1 / 2,519 (0.04%)	

Variants	Prevalence		References
AUTS2	In ASD individuals	1 / 2,195 (0.05%)	(Glessner et al., 2009)
	In controls	0 / 2,519	
DDX53/PTCHD1 deletion (maternally inherited)	In ASD cases	7 / 996 (0.7%)	(Pinto et al., 2010)
	In controls	0 / 1,287, 0 / 3,677	
CNVs at 15q11-13 (UBE3A)	In ASD individuals	15 / 2,195 (0.7%)[f]	(Glessner et al., 2009)
	In controls	0 / 2,519	
CNVs at 15q11-13	In ASD individuals	4 / 522 (0.8%)[g]	(Depienne et al., 2009)
CNVs at 16p11.2	In ASD families	12 / 751 (1.6%)	(Weiss et al., 2008)
	In controls	5 / 4,234 (0.1%)	
	In ASD individuals	3 / 299 (1.0%)	
	In controls	7 / 18,834 (0.04%)	
16p11.2 duplication	In ASD individuals	9 / 2,195 (0.4%)[c]	(Glessner et al., 2009)
	In controls	4 / 2,519 (0.2%)	
16p11.2 deletion	In ASD individuals	8 / 2,195 (0.4%)[h]	(Glessner et al., 2009)
	In controls	4 / 2,519 (0.2%)	
CNV gain at 1q21	In ASD families	3 / 1,181 (0.3%)[d]	(AGPC, 2007)
CNV at 17p12	In ASD families	3 / 1,181 (0.3%)[i]	(AGPC, 2007)
CNV gain at 22q11.2	In ASD families	2 / 1,181 (0.2%)[d]	(AGPC, 2007)
22q11.2 duplication	In ASD individuals	9 / 2,195 (0.4%)	(Glessner et al., 2009)
	In controls	0 / 2,519	
De novo CNVs	In ASD families	10 / 1,181 (0.8%)	(AGPC, 2007)
	Co-segregated cases	3 / 1,181 (0.3%)[j]	
De novo CNVs	In ASD individuals	14 / 195 (7.2%)[k]	(Sebat et al., 2007)
	In sporadic cases	12 / 118 (10.2%)	
	In multiplex families	2 / 77 (2.6%)[k]	
	In controls	2 / 196 (1.0%)	
De novo CNVs	In ASD families	27 / 427 (6.3%)	(Marchall et al., 2008)
	In sporadic cases	4 / 56 (7.1%)	
	In multiplex families	1 / 49 (2.0%)	
De novo CNVs	In ASD families	50 / 876 (5.7%)[l]	(Pinto et al., 2010)
	In simplex families	22 / 393 (5.6%)	
	In multiplex families	19 / 348 (5.5%)	

ASDs: autism spectrum disorders; NLGN: neuroligin gene; NRXN: neurexin gene; CNTN: contactin gene; AUTS: autism susceptibility candidate gene; CNV: copy number variation; AGPC: the Autism Genome Project Consortium. [a]Two nonsynonymous SHANK3 mutations were revealed in 4 ASD families and 2 control individuals. [b]In the SHANK3 study, *de novo* truncating mutations in two families and a chromosomal rearrangement in one family were demonstrated as the strict co-segregated cases whose gene variants were found only in individuals with ASD among family members including parents. [c]One *de novo* case is included. [d]Strict co-segregation was not shown. [e]Two cases with mild facial dysmorphism are included. [f]Two *de novo* cases are included. [g]Three *de novo* cases are included. [h]Five *de novo* cases are included. [i]One case is included as a co-segregated family. [j]In ASD families with two or more affected individuals (multiplex families), three *de novo* CNVs were found in both ASD sibs. [k]Two multiplex families whose variant-phenotype co-segregation is not mentioned are included. [l]>0.6% cases are carrying two or more *de novo* events.

Table 1. The prevalence of variants in gene regions recently implicated in idiopathic ASD

2003), and high heritability does not vindicate the condition as a diagnostic category (Keller & Miller, 2006). There is as yet no qualitative biological marker including microscopic lesions that can reliably help to categorize a genetically homogeneous autism subtype (Amaral et al., 2008; Moldin et al., 2006; Santangelo & Tsatsanis, 2005; Schmitz & Rezaie, 2008). In this article, the significance of gene variants which have currently been detected in autistic individuals is carefully reconsidered and the outstanding questions are addressed from multidisciplinary points of view. Such an attempt may highlight the importance of the notion that the evolutionally survived trait is the phenotypic diversity itself, in which ASD is included as an extreme tail. In addition, important concepts and mechanisms for the genetic basis of phenotypic diversity are also reviewed.

2. Facts and questions

Although some authorities appreciated the smooth behavioral continuum between individuals with ASD and the non-autistic majority (Frith, 2001; Happé, 1999; Rapin, 1997; Wing, 1997), idiopathic ASD has sometimes been misinterpreted as a qualitative disorder which can be clearly distinguished from normal development. The boundary between individuals with low-functioning ASD and a communicative subtype (Asperger syndrome) has also been misrepresented as to be qualitatively distinct (Simpson, 2003). Even the differentiation between Asperger syndrome and high-functioning ASD could be made with authority (Kamp-Becker et al., 2010). These biased constructions may be attributable to referral bias in general practice or increased probability of clinical ascertainment in individuals with low achievement (Skuse, 2007). Although ASD can still be documented as a categorical entity in clinically ascertained samples (Frazier et al., 2010), the fact that the autistic phenotype extends beyond its formal diagnostic boundaries has underscored the significance of quantitative evaluations (Lamb et al., 2000; Maestrini et al., 2000), and many population studies revealed that ASD including high-functioning subtypes are best characterized as an extreme of some bell-shaped behavioral dimensions that distribute quantitatively (Constantino & Todd, 2000; Constantino & Todd, 2003; Happé et al., 2006; Hoekstra et al., 2007; Posserud et al., 2006; Ronald et al., 2005; Ronald et al., 2006a, 2006b; Skuse et al., 2005). The description 'qualitative' in the autism criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM) is removed and Asperger's disorder (Asperger syndrome) is subsumed into ASD in the draft of DSM-5 (http://www.dsm5.org /Pages/Default.aspx). The three quantitative domains including sociability, communication, and rigid/repetitive behavior correlate modestly to each other in the population (Dworzynski et al., 2007; Ronald et al., 2005, 2006a, 2006b), and the coincidence of these phenotypic extremes is also observed in hyperactive individuals with attention-deficit/hyperactivity disorder (AD/HD) (Hattori et al., 2006; Ijichi & Ijichi, 2007; Reiersen et al., 2007; Ronald et al., 2008). The diagnosis of autism is highly affected by the circumstantial consequence of social adaptability and autistic recognition and behavior sometimes does not become fully manifest until social demands exceed the individual's limited capacities (the draft of DSM-5). The clinical picture can change with increasing age and in different circumstances (Wing, 1997), and the behavioral plasticity or clinical improvement is evident in supportive circumstances by structured behavioral interventions, mentoring, and/or social involvement with appropriate accommodation (Garcia-Villamisar & Hughes, 2007; Ijichi & Ijichi, 2007; McGovern & Sigman, 2005; Tonge et al., 1994).

The most unique and potentially meaningful property of autistic cognition is savant skill. The estimated prevalence of the cognitive superiority in ASD varies from 10% to surprising

numbers (Dawson et al., 2007; Happé, 1999; Rapin & Katzman, 1998). The supposed common 'high intelligence' in autistic individuals with low IQ may involve high processing speed, prodigious memory capacities, and heightened primary sensory processing (Boddaert et al., 2005; McCleery et al., 2007; Scheuffgen et al., 2000). These cognitive superiorities are believed to have the same origin as the social difficulties in ASD (Brosius & Kreitman), and the term, 'autistic savant skills', is used to describe one of the core cognitive features of ASD (Badcock & Crespi, 2006; Scheuffgen et al., 2000). As a unifying explanation which covers the manifold autistic characteristics, excessive neuronal processing (a hyper-functionality model) is also implicated as opposed to usual hypo-functionality explanations (Markram et al., 2007).

The ratio of sibling recurrence risk to population prevalence is approximately 50 with an overwhelming predominance of sporadic cases, suggesting the multifactorial nature of ASD (AGPC, 2007). The high monozygotic concordance rate in twins and the modest recurrence risk in dizygotic twins and among siblings may also suggest that the genetic architecture for ASD has the same complexity as those for human physical appearances including facial characteristics and brain gray matter volume (Ijichi & Ijichi, 2004). In traditional views, the modest correlation between autistic behavioral domains in population studies implies that there is no single (genetic or endophenotypical) cause for the three autistic extreme characteristics and a mere coincidence of the phenotypic extremes might be the true nature of autistic social difficulties (Happé et al., 2006). Although positive assortative mating might cause phenotypic anticipation and a negative assortative mating between the couple might gather the non-overlapping genetic components in a baby (Ijichi et al., 2008), there is no evidence for such assortative mating (Hoekstra et al., 2007).

As exemplified in Table 1, there is, so far, no universal genetic marker which is co-segregated with ASD in the affected families. In contrast to the early prediction (30-40%) (Beaudet, 2007), no more than 5-7% of ASD cases may be traceable to single or multiple genetic concomitant(s) (Table 1). Although many whole-genome scans for autism susceptibility loci have identified a lot of linkage peaks, the reproduction of the results is exceptional and association studies have failed to identify the gene variants (Sykes & Lamb, 2007). The regions of structural variants including copy number variations (CNVs) seldom conform to the linkage peaks (Sebat, 2007). The lack of an unambiguous pathophysiological marker is also one of the important characteristics of idiopathic autism (Amaral et al., 2008; Moldin et al., 2006; Santangelo & Tsatsanis, 2005; Schmitz & Rezaie, 2008). The only anatomical candidate which can be consistently co-segregated with ASD including masked autistic savants may be a quantitative increase in the number of processing units of cortex (minicolumns) (Casanova, et al., 2002, 2007). The increase in the number of minicolumns is thought to be associated with mammalian brain evolution, and the finding can explain other apparent tendencies revealed in some autistic individuals, including increases in the volume of brain structures and the prevalence of epilepsy (Casanova et al., 2006). Recent preliminary findings suggest that the tendency of brain overgrowth originates prenatally (Hobbs et al., 2007; Leonard et al., 2008). Furthermore, there is no biological deficit including chemical and molecular findings which is universal in individuals with ASD or can reliably help to identify putative subgroups that are genetically homogeneous (Lauritsen & Ewald, 2001). Over-expression of neuron-associated genes is still one of the candidates for molecular markers (Lepagnol-Bestel et al., 2008; Maussion et al., 2008; Rinaldi et al., 2007).

The scientific puzzle, which is metaphorically described as "myopic investigators are still patting the elephant" (Rapin, 1999) remains to be solved (Baron, 2008). Why is the male to

female ratio biased (3-4 to 1)? Why cannot the behavioral uniformity with strong genetic contribution be interpreted by common gene variant alleles? Why is the disparity between monozygotic and dizygotic concordances so large? Why do the autistic behavioral domains correlate modestly? Although these questions may provide very important clues and are encouraging researchers to speculate on reasons, the jigsaw is still incomplete. Missing puzzle pieces include the solution of the evolutionary mystery of autism prevalence. Human conditions can be selected and survive when it is somehow associated with increased reproductive success (Nesse & Williams, 1994). However, in spite of the hypo-reproductive tendency of behaviors in extreme cases with ASD (Lord et al., 2000), the estimated high prevalence has never declined (Baird et al., 2006; CDC, 2009; Fombonne, 2009).

3. Genetic and environmental explanations

It is recently recognized that ASD has the highest prevalence (more than 0.5%) in childhood neurodevelopmental conditions (CDC, 2009; Fombonne, 2009). In traditional frameworks, in which researchers are searching the human genome for the condition-specific genetic variants, three genetic models should be considered as the genetic mechanism for such a common phenotypic condition (Gibson, 2009). The quite low effect size of each ASD-related variant is suggested to be the cause of difficulty in replication of the positive findings in the common disease-common variant (CD-CV) model (Anney, 2010). Although a rare alleles of major effect (RAME) model is one of the core principles for recent genome-wide association studies in ASD (Gibson, 2009), the replication may also be complicated by chance findings, as well as differences in ascertainment, because of the modest relative risk of the rare alleles (Anney, 2010). The third model, the infinitesimal model, can make an excuse for the situation of genetic studies, because it is very hard to identify rare variants of small effect by genetic means (Manolio et al., 2009). It is, anyhow, clear that it's time to reconsider and question simple intuitive models that link a human complex condition to mutation (Gibson, 2009).

3.1 Genetic factors

The non-universality of the candidate gene variants which have previously been implicated in ASD may be consistent with the speculation that heterogeneous sets of gene variants can contribute to ASD (Betancur, 2011; Beaudet, 2007; Garber, 2007). Furthermore, in order to explain the modest correlations between the three autistic behavioral domains, the presence of domain-specific heterogeneous sets of gene variants are also suggested (Happé et al., 2006). However, even novel genetic means including whole genome screening using microarray-based hybridization cannot fully confirm these speculations (Table 1). The frequent absence of diagnostic history of ASD in the parents of an idiopathic ASD proband may suggest that the supposed variants should be carried by a non-ASD parent (incomplete penetrance) or the proband should have *de novo* mutations (Beaudet, 2007; Constantino & Todd, 2005; Zhao et al., 2007) (Table 2). However again, such genetic transmission is still one of the hypotheses and the concomitant *de novo* variants can be detected only in a minor part of the cases (Table 1). The number of candidate gene regions is still increasing without a convincing and comprehensive demonstration of the link between such variants and autistic developmental trajectory (Glessner et al., 2009).

The genetic contribution to a quantitative trait may be attributable to the cumulative effect of a set of quantitative trait loci (QTLs) (Plomin et al., 1994, 2009; Plomin & Kosslyn, 2001). Each QTL is neither necessary nor sufficient for the overall phenotypic outcomes, the effect size of each QTL may fluctuate according to other genetic backgrounds (epistasis, non-

additive gene-gene interactions) and the environment (gene-environment interactions), and a QTL may affect more than one phenotypic trait (pleiotropy). The concept of epistasis had initially been introduced for ASD as an alternative explanation of the incomplete penetrance or as a risk factor model (Bradford et al., 2001; Folstein & Rosen-Sheidley, 2001; Jones & Szatmari, 2002). Because natural chromosomal and segmental shuffling during normal meiosis is a strong random modifier of epstatic effects among QTLs in a sib-pair and dizygotic twins, the big disparity between monozygotic and dizygotic concordances in autism may be explained by the presence of epistatic QTLs. Pleiotropy can account for the presence of autistic savants. The modest correlation among autistic behavioral domains can also illustrated by unsynchronized epistatic pleiotropy (Ijichi et al., 2008). To explain the sporadic manner of the prevalence and the survival of hypo-reproductive autistic extremes, the implication of epistasis-associated intergenerational oscillation of phenotypic outcomes was introduced (Ijichi et al., 2008). Some candidates for autism QTLs have been reported (Ashley-Koch et al., 2006; Coutinho et al., 2007; Jiang et al., 2004; Weiss et al., 2007), linkage analysis with quantitative measures of some autistic characteristics revealed QTL signals (Alarcón et al., 2002, 2005; Chen et al., 2006; Duvall et al., 2007), and a quantitative covariance analysis can confirm the high genetic correlation between 'social motivation' and 'range of interest/flexibility' (Sung et al., 2005). Although the supposed contribution of QTLs ought to be traced in family studies or genome scans according to a traditional logic, "the causal gene variant can be cosegregated with the phenotypic variant", the delay and difficulty in detecting the causal variant alleles at QTLs is strangely common to all idiopathic quantitative traits including autism, physical and physiological characteristics, and personalities (de Geus et al., 2001; Fullerton, 2006; Palmert & Hirschhorn, 2003; Willis-Owen & Flint, 2006).

Facts and questions	Explanations			
	Penetrance	*De novo*	QTLs	Environment
The quantitative feature	(○)	—	○	(○)
Partial behavioral plasticity	—	—	—	○
The presence of autistic savants	—	—	(○)	—
Strong genetic contribution	○	○	○	—
Usually sporadic without family history	(○)	○	(○)	○
Domain-specific genetic factors	—	—	(○)	—
Lack of the common genetic marker	○	○	○	—
Lack of the common pathological lesion	—	—	—	—
Lack of the common chemical marker	—	—	—	—
Lack of the common molecular marker	—	—	—	—
Why is the male to female ratio biased?	(○)	(○)	(○)	(○)
Why is it so difficult to detect autism genes?	—	—	—	—
Why do hypo-reproductive extremes survive?	—	○	—	(○)

Penetrance: Poor penetrance of heterogeneous gene variants; *De novo*: *De novo* involvement of heterogeneous gene variants; QTLs: Quantitative trait loci; Environment: Environmental contribution; ○: explainable; (○): unexplainable by itself but explainable with some further speculation; —: hard to explain

Table 2. Genetic and environmental explanations for the facts and outstanding questions in idiopathic autism researches

3.2 Epigenetic factors and ASD

Phenotypic outcomes with robustness or plasticity cannot be exclusively determined by the DNA sequence itself which looks like the core genetic factor of the phenotype (Goldberg et al., 2007). Epigenetics is the study of changes in gene expression that occur without a change in DNA sequence and the epigenotype is meiotically and mitotically transmissible (Morris, 2005; van Vliet et al., 2007). Although the significance of the contribution made by epigenetic factors to human complex traits remains unclear, it is speculated that epigenetic factors can influence gene-environment interactions and the liability/outcomes of the traits (van Vliet et al., 2007). Epigenetic changes in gene expression are achieved through RNA-associated silencing, DNA methylation, and histone modifications (Morris, 2005), and cis-acting expansion of the epigenetic influences on the flanking genes is referred to as genomic imprinting which results in parent of origin-specific gene expression (Pauler et al., 2007). The epigenetic factors and genomic imprinting may be implicated in syndromic autistic individuals with some single gene/chromosomal disorders including Rett syndrome, fragile X syndrome, Prader-Willi syndrome, and Angelman syndrome, and a variety of factors associated with epigenetic modifications have been considered as candidates for autism genes (Badcock & Crespi, 2006; Jiang et al., 2004; Persico & Bourgeron, 2006; Schanen, 2006; Skuse, 2000; van Vliet et al., 2007). These factors, however, cannot be the common prerequisite for idiopathic ASD at least in the majority of the cases (Jiang et al., 2004; Persico & Bourgeron, 2006), and the power of epigenetic factors are recognized as an accidental cue to shift the quantitative distribution of the autistic traits in a threshold model (Skuse, 2000). If the epigenetic factors act only in gene-environment interactions in idiopathic cases, the epigenetic contribution should be modest in the overall underpinnings. Given an unforeseen transmissible powerful architecture connecting genotype and phenotype for phenotypic diversity independent of genetic diversity, the epigenetic mechanism should be referred to as merely one of the molecular-level environments derived from gene networks.

3.3 Environmental factors

Environmental factors contribute no more than 10% to ASD (Garber, 2007). However, the environmental factors including rubella, thalidomide, and valproic acid embryopathies may still be important as additive triggers of the clinical manifestation (Jones & Szatmari, 2002; Persico & Bourgeron, 2006). Environmental contributions including behavioral experiences are originally misunderstood to explain the patterns of familial recurrence risks observed in autism studies (Jorde et al., 1991). Because the genetic components affecting autistic traits seem to be the same across the sexes (Constantino & Todd; Hoekstra et al., 2007), it can be speculated that the lower prevalence of autistic traits in girls is the result of increased sensitivity to early environmental influences that operate to promote social competency (Constantino & Todd, 2003). The minimal contribution of shared environmental influences (Ronald et al., 2006a) may be associated with the autistic behavioral manifestations including resistance to change or insistence on sameness.

Combinations of the traditional theories (poor penetrance, *de novo* mutations, and QTLs and the environmental contribution) may answer not a few of the outstanding questions in idiopathic autism research (Table 2). However, in spite of the presence of a big genetic contribution to the autistic development, the question, "Why is it difficult to detect autism gene variants?", still remains to be resolved. In addition, the significance of both *de novo* mutations and the environmental modification is just a speculation in a part of the ASD cases.

4. Evolutionary explanations

Does idiopathic ASD really represent many distinct conditions with numerous etiologies (Geschwind, 2007)? Is it really time to give up on a single explanation for autism (Baron, 2008; Happé et al., 2006)? A variety of qualitative concomitants, including gene variants and environmental factors, have already been demonstrated in part of autistic cases as exemplified above. However, it may be still too early to reach the conclusion even in such frameworks, because no single qualitative process associated with the concomitants can indicate the molecular or chemical differences between the autistic developmental extremes and the non-autistic majority. In order to understand human complex traits, genetic, molecular, and biochemical explanations should be combined with evolutionary explanations (Nesse & Williams, 1994). In autistic individuals, ASD *per se* does not shorten the span of life (Gillberg et al., 2010). Although high or preserved androgenic competence is suspected in ASD (Tordjman et al., 1997), the extreme cases almost never marry (Lord et al., 2000). The hypo-fertility results from reduced opportunity or behavioral ability in the mating arena. Therefore, we must probe into who is enjoying the reproductive benefits of the genetic architecture for ASD in the evolutionary framework (Table 3).

Who gets the reproductive benefits?	Hypotheses or mechanisms	References
None (an inevitable outcome)	Mutation-selection balance theory	(Keller & Miller, 2006)
Unaffected carriers of genetic factors	Hyper-systemizing theory (extreme male brain theory) Extreme imprinted brain theory	(Baron-Cohen, 2002) (Badcock & Crespi, 2006)
All of the non-autistic majority	Population benefit theory Monomorphic loci theory	(Fitzgerald, 2002) (Ijichi et al., 2011)

Table 3. Evolutionary explanations for the survival of autistic extremeness

4.1 Mutation-selection balance theory

In the mutation-selection balance theory, individuals with a high load of mutations are postulated to be at higher chance of passing risk on to their offspring, and it is not necessary that there are individuals with the reproductive benefits (Keller & Miller, 2006). Importantly, according to the proposed model, everyone alive has minor brain deviations that cause them to be a little bit abnormal in behavioral and cognitive dimensions (Keller & Miller, 2006). The non-autistic majority in the population is regarded as the genetic carrier-state for ASD and the mutation load and the risk of having autistic offspring may vary quantitatively. In the mutation-selection balance theory, balancing selection for genetic diversity is recognized to be unsuitable to explain persistent heritability in human conditions (Keller & Miller, 2006; Zhang & Hill, 2005). One of the grounds of this exclusion of balancing selection is the absence of an ongoing homeostatic mechanism that counteracts the homogenizing effect of genetic drift and stabilizing selection, and the reproductive benefits of the genetic burden for autism are not addressed (Keller & Miller, 2006). The mutation-selection perspective can be an evolutionary interpretation of a cumulative effect

of *de novo* mutations and is at least consistent with the quantitative distribution of autistic domains.

4.2 Extreme male brain theory

The second is a group of theories in which only a part of the population is regarded as the genetic carrier-state for ASD. The prevalence or maintenance of positive assortative mating between the non-autistic carriers is critical to accumulate genetic factors in these theories, and the remaining non-autistic majority does not have the genetic components for ASD. In the hyper-systemizing theory, the unaffected carriers of the genetic factors are high systemizers and ASD is the result of both parents being the high systemizers (Baron-Cohen, 2002, 2004, 2006). Systemizing is the drive to understand and predict the next step of inanimate events and acts contrary to empathizing. In males, the systemizing mechanism is set at a slightly higher level than non-autistic males (Baron-Cohen, 2004). This extreme male brain theory of autism had originally been proposed by Asperger in 1944. Individuals including both parents of individuals with autism, who are placed in the adjacent part to the autistic extremeness, systemize at a higher level than average (above average systemizers) and account for approximately a half of the vast majority. Over successive generations, the above average systemizers carry the genetic components for ASD and might enjoy the reproductive benefits. As one of the genetic bases of the hyper-systemizing theory, the extreme imprinted brain theory had been proposed (Badcock & Crespi, 2006).

4.3 Population benefit theory and individual benefit theory

In the third framework, it is suggested that the evolutionarilly selected and conserved phenotype is not the hypo-reproductive extremeness but the whole quantitative distribution itself. A group selection theory has been introduced to bring sense into the link between autism and exceptional creativity (Fitzgerald, 2003). In this population benefit theory, the creativity, which can be concomitant with autism, benefits all members of the human community and the community can survive. On the other hand, the third framework can also include individual benefit concepts (the monomorphic loci theory) (Ijichi et al., 2011). In the individual benefit concepts, everybody has both the genetic architecture for ASD and the possibility to enjoy the reproductive benefits of autism genes. Each phenotypic outcome, however, varies individually mainly according to the differences in genetic background noise and environmental factors, whose functions are not necessarily related to ASD phenotypes directly. In the process of reaching the monomorphic loci theory, the epistasis-mediated intergenerational oscillation of phenotypic outcomes has been advanced in a QTL model (Ijichi et al., 2008). The monomorphic loci theory does not dismiss the comprehensive view of the known genetic contributions, including major gene effects and additive genetic networks (Ijichi et al., 2011). The postulated involvement of monomorphic loci can be valid as merely one of the genetic constituents in complex (additive and/or non-additive) interactions with polymorphic loci.

4.4 The monomorphic loci theory and gene networks

Because both positive and negative epistasis may be byproducts of evolution (L. Azevedo et al., 2006; R.B.R. Azevedo et al., 2006; Harrison et al., 2007), the invisibility of the contribution of monomorphic epistatic loci from the traditional genetic view is an attractive candidate for the explanation of the black box between polymorphic genotype and phenotypic diversity (Ijichi et al., 2011). Complex phenotypes have hierarchical structures, including RNA

(transcript traits), protein, metabolite, and functional levels. It has been suggested that less heritability of metabolite traits than transcript traits is associated with the difference in the quantity of biological noise between the genetic determinants and the trait (Rowe et al., 2008). The more steps that are involved between genotype and the trait level, the more biological noise may reside in the process. Such biological noise originates from inter-locus interactions and gene-environment interactions, and the inter-locus interactions may have an important role in the biological noise. Additive and/or non-additive inter-locus interactions with other loci are available in a variety of processes including cis-, trans-, and inter-cellular interactions (Figure 1). The presence of gene-environment-gene circuits may make it difficult to distinguish inter-locus interactions from gene-environment interactions in the biological noise (Ijichi et al., 2011). In these interactions, an intergenerational change in the number or property of factors (environment and/or other related loci) in the regulatory circuit may easily individualize the balance of each hierarchical trajectory (coding RNA, non-coding RNA, translation, autocrine, paracrine, and endocrine levels) and individually determine the developmental outcomes. The net non-additive effects of the biological noise are metaphorically interpreted as hub-and-spoke structures of regulatory networks among polymorphic loci (Benfey & Mitchell-Olds, 2008).
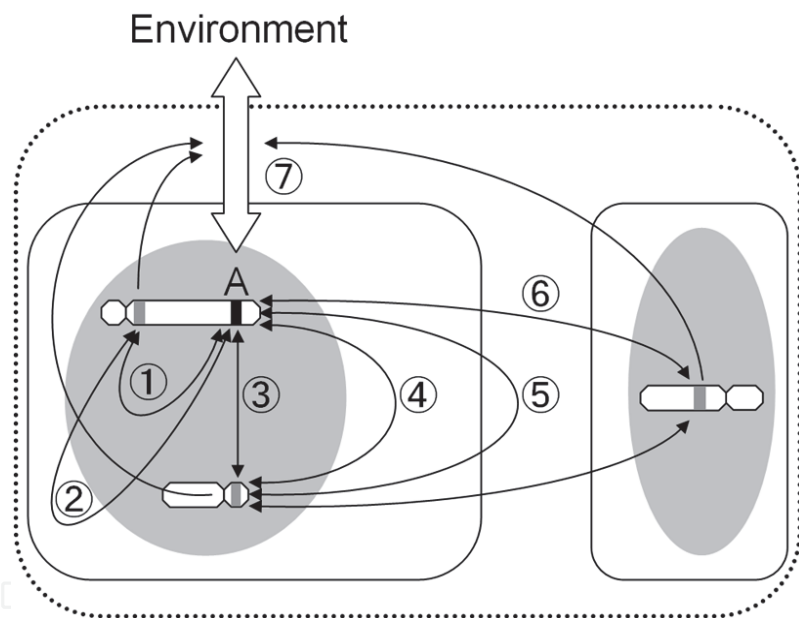

Fig. 1. Cellular and molecular interactions of biological noise in regulatory networks around a gene locus (A). Additive and/or non-additive phenomena can be involved in each interaction (Ijichi et al., 2011). In this explanation, an arrow represents the net contribution between loci and the gene-environment relationship. The locus A can interact with other loci in association with coding RNA and/or non-coding RNA level in cis-acting manner (①, ②) and trans-acting manner (③, ④). The cis-acting interactions are involved in genetic imprinting. After translation, interactions can be mediated through autocrine, paracrine, and endocrine mechanisms (⑤, ⑥). Gene-environment interactions can modify penetrance of the outcomes affected by the locus A. The network constituents can change the sensitivity to environmental influences (⑦), that can provide gene-environment-gene circuits. In the monomorphic loci theory, the gene A can be monomorphic and the link between monomorphic A and the A-associated polymorphic noise is usually invisible in the context of traditional genetics.

5. Quantitative domains and genetic factors

The distributional shift of a bell-shaped curve and the change in the curve shape illustrates the mean value change and the variance alteration of the quantitative dimension, respectively (Gibson, 2009). These changes can affect the proportion of individuals with autism to those without as determined by a liability threshold. The biased male to female ratio (3-4 to 1) in ASD is plausibly interpreted as a distributional shift of the quantitative bell-shaped curve as a gender gap. In the hyper-systemizing theory, the male systemizing mechanism is set at a slightly higher level than in females (Baron-Cohen, 2004). In an imprinted-X liability threshold model, actions of some X-linked genes, which are expressed only from paternal X-chromosome, are suggested to be associated with the male predisposition to ASD (Skuse, 2000). The gender is a bimorphic genetic variation and there is a gender gap in sensitivity or vulnerability to environmental factors (Constantino & Todd, 2003). The relationship between a bell-shaped quantitative distribution and the genetic factors underlying the complex phenotype still remains to be elucidated.

5.1 Polygenic liability model

The traditional concept of polygenic liability supposes a normal distribution of frequencies of susceptibility variant alleles (Gibson, 2009). The manner of the allele contribution is additive, and each allele contribution usually results in a positive or negative effect on the phenotype in the carrier individual and the quantitative population dimension results from such additive allele contributions. To explain the smooth normal distribution, an environmental variance of each allele contribution is addressed in this model.

In a genetic model, oligogenicity with epistasis, the contributing genes are likely to be common ones in the population (Folstein & Rosen-Sheidley, 2001). There is no evidence that the genetic causative processes affecting the autistic extreme are different from those contributing the autistic dimension including individuals without autism (Ronald et al., 2006a). If the presence of epistasis, pleiotropy, and gene-environment interactions are all supposed, the polymorphic genetic underpinning is referred to as QTLs (Plomin et al., 1994, 2009; Plomin & Kosslyn, 2001). However, it is also the fact that the delay and difficulty in detecting the causal variant alleles at QTLs is common to all idiopathic quantitative traits including ASD, physical and physiological characteristics, and personalities (de Geus et al., 2001; Fullerton, 2006; Palmert & Hirschhorn, 2003; Willis-Owen & Flint, 2006).

If the genetic factors for a tail of the bell-shaped curve are different from those for the majority and have extremity-specific properties including serious involvement of coding gene segments (Mitchison, 2000), the variant alleles should be more detectable. Because the genetic contribution in ASD is the biggest in human complex traits and the environmental influence on ASD is quite minimal as described above, the difficulty in finding the universal genetic marker for ASD warrants the necessity of a paradigm shift.

5.2 Additive and non-additive interactions between mono- and poly-morphic loci

It has been emphasized that the three behavioral domains of ASD modestly correlate to each other and the set of genes for each domain may be partly different (Dworzynski et al., 2007; Happé et al., 2006; Ronald et al., 2005, 2006a, 2006b). The speculated modest genetic overlap among autistic domains may be indistinguishable from that among human complex phenotypes including ASD, bipolar disorder, and schizophrenia (Rzhetsky et al., 2007), suggesting that the autistic domains and these psychiatric conditions might share the same

genetic architecture at least in part (Craddock & Owen, 2010). In an argument about domain-specific genes for cognitive functions, it is expected that the domain-general genes are responsible for the brain infrastructure including receptors, neurotransmitters, dendritic spines, synapse vesicles, and axonal filaments (Marcus & Rabagliati, 2006). Although the universality of the domain-general genes for cognitive functions among other human complex phenotypes is controversial, genes for the brain infrastructure are also current topics in the field of ASD (Garber, 2007; Persico & Bourgeron, 2006). Both the heterogeneity of genetic markers for ASD and the modest correlation among autistic core domains can be explained by epistasis-mediated oscillation of the domain-general effect values and unsynchronized epistatic pleiotropy in the monomorphic loci theory, which never dismiss the comprehensive view of the known genetic contributions, including major gene effects and additive genetic networks (Ijichi et al., 2011). The assumption of the random outcomes mediated by the non-additive interactions between functional monomorphic loci and polymorphic backgrounds may transform the traditional complementary roles of some monomorphic loci (Gjuvsland et al., 2007) to active and leading roles for the phenotypic diversity (Ijichi et al., 2011). However, the controversy concerning the importance of non-additive effects in phenotypic diversity still exists (Gale et al., 2009; Hill et al., 2008; Malmberg & Mauricio, 2005).

5.3 Social environmental changes and decanalization

The decanalization concept may have sizable significance in searching the cause of the maintained or increasing prevalence of ASD. Canalization is an evolutionary phenomenon characterized by robustness to genetic or environmental perturbation, and most individuals tend to cluster around the optimal phenotype in canalized populations (Gibson, 2009). If the phenotypic dimension consists of multiple endophenotypic vectors which have nonlinear relationships to each other and are partially determined by genetic factors, overt environmental perturbations for one of the endophenotypes can be the cue of decanalization, which changes the shape of the phenotypic demensional distribution (Gibson, 2009). Social environmental perturbations may also shift the entire distribution of ASD liability, or move the liability threshold.

6. Conclusions

The difficulty in detecting the universal biological marker for the predisposition to ASD presents significant challenges and conflicts to researchers in related fields. The reported gene variants in some sporadic cases with idiopathic ASD are nothing but one of the concomitants, until the molecular or biological trajectory underlying autistic development is clearly delineated or association studies reproduce the causal relationship. Before the speculation that idiopathic ASD represents many distinct conditions with numerous etiologies, the quantitative manner of the distribution of the behavioral domains and the fact that ASD is a mere tail of the behavioral dimensions should strictly be considered and emphasized. Even combinations of traditional theories including poor penetrance, *de novo* mutations, quantitative trait loci, and environmental contribution cannot fully account for the entire genetic underpinning. Importantly, the almost monolithic insight into the prevalence of ASD can only be obtained in an evolutionary framework on the assumption that the complex genetic networks are responsible not for the individual cases but for the human behavioral diversity itself. Gender differences, environmental factors, epigenetic

mechanisms including genetic imprinting, and major gene effects may all be mere accidental modifiers of the relationship between the diversity and the liability threshold.

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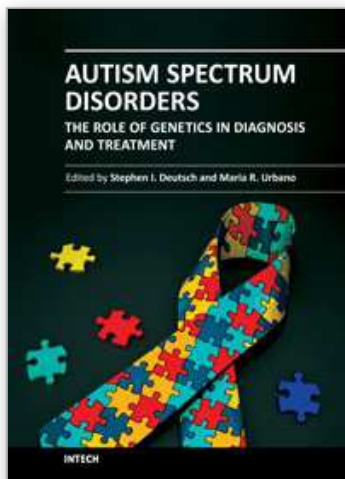
Autism Spectrum Disorders: The Role of Genetics in Diagnosis and Treatment

Edited by Prof. Stephen Deutsch

Estimated prevalence rates of autism spectrum disorders (ASDs) have increased at an alarming rate over the past decade; current estimates stand as high as 1 in 110 persons in the population with a higher ratio of affected males to females. In addition to their emotional impact on the affected persons and their family members (in fact, the latter are often unrecognized unaffected â€œpatientsâ€ themselves), the economic and social impacts of ASDs on society are staggering. Persons with ASDs will need interdisciplinary approaches to complex treatment and life planning, including, but not limited to, special education, speech and language therapy, vocational skills training and rehabilitation, social skills training and cognitive remediation, in addition to pharmacotherapy. The current book highlights some of the recent research on nosology, etiology, and pathophysiology. Additionally, the book touches on the implications of new research for treatment and genetic counseling. Importantly, because the field is advancing rapidly, no book can be considered the final word or finished product; thus, the availability of open access rapid publication is a mechanism that will help to assure that readers remain current and up-to-date.

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