



# Genetic predominance of autism spectrum disorder and finding the risk genes

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## Abstract

### Introduction

The treatment of ASD is highly challenging as the causing factors and pathophysiology of the disorder is not clearly understood. It is widely believed that the major causing factor of ASD is rooted within the genes while a minor contribution of environmental factors is also taken into account. This strong belief was somehow biased by few recent studies. However, increased recurrence rate among half and full siblings of ASD families further validate the genetic predominance of this disorder. On the other hand, identification of those causing genes is a tremendous challenge for the scientists working in this field as the disorder is highly complex due to the presence of behavioural features which overlap with other psychiatric disorders. However, the progress made in the last two decades has provided deeper knowledge on genetic architecture of ASD. The main objective of this review is to discuss the issue of genetic predominance of ASD and to highlight some of the important findings and hypothesis that are promising toward identifying ASD causing genes.

### Conclusion

The highly complex nature of ASD is the difficult challenge towards finding the cause, treatment and preventive measures of this disorder. Various studies have consistently supported the genetic involvement to be the major contributing factor on the development of this disorder.

However, the causing genes and their connecting pathway leading to ASD phenotype are yet to be identified. To fetch this issue it is necessary to investigate with various intelligent approaches.

### Introduction

Autism spectrum disorder is a group of childhood onset lifelong developmental disorders which include autistic disorder, asperger's syndrome and pervasive developmental disorder-not otherwise specified (PDD-NOS). The three disorders share common features in three domain behaviours such as lack of social interaction, lack of communication and having stereotype behaviours and interests while varying in severity<sup>1</sup>. There has been an enormous rise in the prevalence rate of ASD over the last ten years and it reaches up to 1.47% according to the latest report<sup>2</sup>. In the past few decades, among many areas of biological researches on ASD; genetics, immunology, imaging and electrophysiology are in great progress with the development of advance methods and technologies. However, the underlying pathophysiology is largely unclear. On the other hand, without knowing the root cause of the disorder, to develop a suitable drug for treatment or cure might not be possible. Since, several lines of studies have indicated that genes play a major role on the development of ASD, finding those affected genes would be a best way to trace the root cause. Meanwhile, few recent studies reported bias to the genetic predominance of ASD<sup>3,4,5</sup>, this intends to weaken the strong belief of genetic nature of this disorder. On the view point this bias and the complexity of the disorder, this review is dedicated to discuss on firmness of the faith of genetic origin

of ASD as well as suggestions towards overcoming the difficulties of finding those affected genes.

### Discussion

#### ASD prevalence is increasing: Is there a solution?

Autism spectrum disorder is a complex neurodevelopmental disorder which has become a major health issue due to the sharp rise in prevalence rate over the past decade. According to the latest report provided by the Center for Disease Control and Preventions' Morbidity and Mortality Weekly Report 28<sup>th</sup> March 2014, the prevalence rate is 1 in 68 children<sup>2</sup> which is much higher than the earlier report of 1 in 88 children<sup>6</sup>. While the reason for the rise in prevalence is still unclear, it is widely believed that the broadening of diagnostic criteria, greater public awareness and improved case identification methods may cause this elevation<sup>7</sup>. However, this large prevalence is a signal for the urgent need to find a solution. On the other hand, it is a tremendous challenge for every researcher working on ASD as the pathophysiology is highly complex and the aetiology is not clearly known. Without knowing the causing factors and the mechanism underlying the pathophysiology of the disorder, to develop a proper treatment and find a cure will not be possible.

#### Understanding ASD: the concept of genetic predominance

##### Twin studies

The high heritability of ASD has been well documented in several twin-based as well as sibling-based studies. The predominance of genetic involvement towards the cause of autism has become more prominent after the study report of Baily et al.<sup>8</sup> His group showed that concordance rates of autism among monozygotic (MZ) and dizygotic

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(DZ) twins were 60% and 0% respectively. However, when broader spectrum (such as cognitive and social abnormalities) was considered concordance rates were increased to 92% (MZ) and 10% (DZ) respectively.

Similar findings were replicated in several later studies. The average concordance rates of these studies were estimated at 69-95% (MZ) and 3-8% (DZ) as reviewed by Dawson<sup>9</sup>.

The rates were further raised when broader phenotype was considered (88-91% for MZ, 9-30% for DZ)<sup>9</sup>. This pattern has been consistent with the recent study of Rosenberg et al. which showed 31% concordance of DZ and 88% concordance of MZ with larger sample size that derived from existing clinical twin data<sup>10</sup>. These studies collectively demonstrate genetic contribution on ASD reaching up to 95% approximately. Thus far, minor contribution of environmental factors remains significant.

Meanwhile, another three recent studies demonstrated heritability of ASD to be moderate suggesting increased role of environmental factors<sup>3,4,5</sup>. These reports tend to dilute the well accepted concept of high heritability of this disorder. However, these reports which use existing clinical twin data are potentially confounded by various factors such as low sample size, inconsistency in case definition, de novo mutation that roughly accounts for 20% of ASD cases, and possible genetic causes of ASD twins could result in environmentally endangered affection of non-identical co-twin in utero when mediated via humoral or immune mechanisms<sup>11</sup>. To minimize these confounds, Constantino and his group compared the autism recurrence between half siblings and full siblings. I will discuss more elaborately on the result of this study in the next paragraph.

#### *Half and full sibling studies*

Constantino et al.'s approach on full and half siblings constitute more than five thousand families (n=5237). They

observed the recurrence rate of autism among full siblings (0.095) which was approximately twice the number of half siblings (0.052) which validates the high heritability of ASD and its major contribution through inheritance from parents to the offspring.

While the full sibling data is consistent with several earlier reports<sup>12</sup>, the half sibling recurrence rate was entirely represented by maternal half siblings as 0 recurrence rate and was observed from the paternal side. However, this 0 recurrence does not firmly stand as the number of paternal half sibling families which was only 55 compared to that of 619 families of maternal half siblings. Interestingly, when they examined gender bias, the recurrence rate of maternal male half siblings was 4 times higher than that of the females. This ratio is higher than the full sibling data of 3:1 suggesting risk allele carried through the mother up to some extent. This observation not only supports the genetic inheritance of ASD in the pedigree that contribute to genetic predominance of ASD and higher occurrence of autism in males than females but also reveals the genetic mechanism of a long standing 4:1 (male to female) ratio that could be traced via preferable risk allele transmission from mother to offspring.

Here, participation of X chromosome is also highly suspicious even though it has been assumed that this bias between males and females are not necessarily due to the X-linked risk factors<sup>13,14</sup>. It may be noted that one of the most extensively studied ASD candidate gene NGLN3, is located in Xq13.1. Moreover, Rett syndrome gene, MECP2 and fragile X syndrome gene, FMR1 are also present within the X chromosome. The two disorders have co-morbid features of ASD and recently such monogenetic disorders have given importance for the identification of ASD genes<sup>15</sup>.

Therefore, the possible role of X-linked genes remains valid. In connection to the idea of risk allele

carried by the mother, few studies have found that the affected children and their normal parent have the same duplication of proximal 15q duplications that include the critical region for Prader-Willi syndrome and Angelman syndrome<sup>16,17</sup> and the duplications all originating from the mother<sup>18,19,20,21</sup>.

Subsequently, a more recent study with full and half siblings using remarkably large sample size comprising more than 13 thousand ASD cases born in Denmark further supports the genetic root of ASD<sup>22</sup>. However, the authors suggested that the contribution of risk gene inheritance to the recurrence of ASD in the siblings to be lower than that of the previous findings on the basis of their observation on relative recurrence risk measurement (that accounts to both the genetic origin of ASD from the genes and the environmental factors shared within the family). They found a significant difference of recurrence rate between the maternal full and half siblings but not between paternal full and half siblings.

To my view, this data further supports the belief of risk genes carry through the mother. There could be more clarity if authors would have examined biased recurrence rate between male and female full/half siblings. Earlier, several studies on siblings have also reported that recurrence of ASD within the family is 20 times higher than the general population<sup>23,24</sup>. Gronborg et al. recently showed a bit less<sup>22</sup>. It is reasonable to assume that this biased might be due to the use of two diagnostic criteria (ICD-8 and ICD-10) for a single study group in Gronborg et al.'s study.

Further, in support of the participation of genetic transmission in the pedigree, substantial evidences are also available from various peripheral serotonin studies. Abnormally high peripheral serotonin level observed among the 30% of ASD population is one of the most consistent findings in ASD research and thereby it has been considered as an ASD endophenotype.

In these studies the presence of high serotonin level was found in the first degree relatives and within the family lines of ASD individuals<sup>25,26,27</sup>. The serotonin level of the offspring was approximated with that of their parents<sup>26</sup>. Thus, these evidences continue to support risk allele transmission from parent to offspring contributing to genetic predominance to the cause of ASD.

### Is it possible to find the genes that cause ASD?

In the past three decades, several studies have focused on identifying causing genes of ASD and thereby the aetiology of the disorder. As the disorder is highly complex and includes several overlapping behavioural features of other psychiatric disorders, it is a highly challenging task for the researchers working on ASD. Although several candidate genes have been named, there is no clear evidence available to show an apparent link of a gene to the disorder. However, development of advanced techniques and methodology in the past few years is highly promising towards uncovering the hidden genes<sup>14</sup>. The several researches in the past few decades have resulted in a deeper understanding of the genetics of ASD and now able to provide information on some genetic factors that include defined mutations, genetic syndromes and de novo CNV which together have shown to account for about 10-20% of ASD cases as reviewed elsewhere<sup>28</sup>. However, the variants of these known factors individually accounts for not more than 1-2% of ASD individuals<sup>14</sup>.

This reveals the extreme heterogeneity in the ASD aetiology involving gene-gene and gene-environment interaction in a complex manner<sup>29</sup> and there is a possibility that the role of each gene may be unique to discrete intermediate phenotypes that together put forth the final ASD.

In search of the risk locus both the common and rare variants are necessary to be examined. The fact

that common variants have a low effect and rare variants have a larger effect to the disorder, but none could individually count for more than 1 to 2% of cases<sup>29</sup> suggesting interactive events of both the common and rare variants in the ASD aetiology. This implicates participation of multiple alleles (both rare and common) from different genes in a common pathway leading to the final ASD phenotype. Besides, common variants are important for estimating disease proportion in the population level, rare variants account at the individual level.

On the other hand due to the presence of many overlapping features of other psychiatric disorders, it is highly complicated for researchers to dissect a behaviour and search for the gene that regulates the particular behaviour. At this juncture, Abrahams and Geschwind<sup>29</sup> emphasized on the possibility of common and rare variants individually linking to intermediate phenotypes which would collectively define ultimate presentation, rather than their strong association to ASD diagnosis, which is noteworthy. This possibility was supported by the observation that first-degree relatives often possessed the features of broader autism phenotypes<sup>30,31</sup>, such as subclinical language dysfunction, autistic-like social abnormalities, or increased behavioural rigidity compared to controls<sup>32,33</sup>. And some studies had already demonstrated the importance of targeting intermediate phenotypes in finding the ASD risk genes<sup>34,35</sup>.

Subsequently, Abrahams and Geschwind<sup>14,29</sup>, described the importance and usefulness to study single gene disorders such as fragile X syndrome, tuberous sclerosis and Joubert syndrome etc. Because these disorders have a defined aetiology and individuals with these disorders have also showed some types of autism features, a careful contrast can be made between the individuals with defined genotypes that would help in the identification of some quantitative traits for certain mutations. Successful

testing of such hypothesis looks promising towards overcoming the complexity of genetic dissection of ASD.

There have been several reports hypothesizing gene-gene and gene-environment interaction in multiple underlying aetiologies of ASD. Levitt and Campbell postulated the possible involvement of extracellular signal-regulated kinase (ERK) and intracellular phosphatidylinositol 3-kinase (PI3K) signalling pathways via activation of the mammalian target of rapamycin (mTOR) pathway<sup>36</sup>. Because, in several syndromic disorders with high penetrance of ASD a primary disruption in signalling these pathways were implicated. Recently, Poot, has reviewed several studies that demonstrate genetic architecture of ASD through the interaction of several genes that include neuroligins/eurorexins, the contactins, mTOR pathway genes (such as TSC1, TSC2 and AKT3), CYFP1, SCN1A, EN2, SLC6A4 and BCKDK<sup>37</sup>. While SLC6A4 and BCKDK genes were implicated in epilepsy, mTOR pathway was found to be involved in tuberous sclerosis and in a hemimegalencephaly syndrome<sup>38</sup>.

Thus, the classical candidate genes of ASD that include the neuroligins/eurorexins family, the contactins have so far been given the most attention<sup>38,39</sup>. On the other hand, searching for ASD risk genes through genetic linkage and association studies using common variants have identified few such genes but their contribution is little to explain the phenotypic variability among ASD individuals<sup>37</sup> and replication of the results have been difficult<sup>40</sup>. Further, sequencing of candidate loci that based on linkage or cytogenetic findings together with genome-wide characterization of structural variation has also identified rare variants of some of those genes<sup>29</sup>, but they are not expected to contribute to the broader phenotype of the individual due to occur de novo<sup>28</sup>. Thus, it is believed that rare variants may act as either susceptible or strong risk alleles in conjunction with common variants contributing towards the ASD phenotype<sup>41</sup>. It is a huge battle for the

researchers to identify the ASD causing genes and to uncover the underlying mechanism that link the genes and brain circuitry system, then to the characteristic behaviours of ASD.

However, the tremendous effort in the last two decades is incredible and has opened the door and is promising towards achieving this goal.

### Future research directions to combat the complex genetic architecture of ASD

An overview of several studies using twin and sibling constantly reveals genetic predominance in the aetiology of ASD. Therefore, identification of affected genes is necessary to understand the underlying mechanism in the pathophysiology of this disorder, which will subsequently provide a more precise diagnosis and treatment. However, genetic architecture of ASD is highly complex and the interaction between multiple genes, between gene and environment, and the transmission of risk loci from normal parents to affected offspring were supposedly involved within the curtain of this complexity. Some hypotheses have tried to plot connecting pathways of several genes that would lead to specific intermediate-phenotypes or phenotypes of ASD, and different approaches for dissecting the behaviours that would be regulated by certain genes through the studies on monogenic disorders.

Now, the question is how to get insight of these interactions and what could be the reliable experimental models that could provide some meaningful answers. Mostly, rodents have been used as genetic models in various studies, and very few studies are available using simpler organisms such as drosophila. While the results provided by the studies using higher organisms could reveal a closer connection to humans and less complex simple organisms will be useful to understand the small change effect. On the other hand it is well known that participation of single

genes or single variants effect is unlikely to reveal a noticeable phenotype. There are several statistical tools already available to test gene-gene and gene-environment interactions, such as multifactor dimensionality reduction (MDR), MDR-phemonics etc. In my view, development of experimental approaches to demonstrate statistically significant interactions from the available data would be useful to provide a clear picture of the interaction of the risk loci that would lead to disease phenotype or endophenotype. Moreover, it is also a highly challenging task to develop a good experimental model for the study. At this juncture, it would be a thoughtful idea to select simple social organisms as a model system to get some basic knowledge of gene regulatory mechanisms underlying social behaviours. Organisms like, ants, termites, bees etc. may provide a useful model system as they have well organized social structures. Finding the genes that regulate these social behaviours may provide some clues towards the behavioural features in the higher animals and humans and ASD individuals that are socially isolated.

### Conclusion

The high complexity of the disorder is the major challenge towards finding the cause, treatment and preventive measures. Therefore, it is important to investigate with various study approaches to find the causes and understand the mechanisms underlying the pathophysiology of the disorder. Concerning genetic causes, some thoughtful studies have opened the door already promisingly towards finding the affected genes. Many experts in this field have also provided some thoughtful directions for future researches. With the increased development of advance techniques and methods, there is great hope of finding a solution.

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