Advance in Different Approaches to the Measurement of Heritability of Autism Spectrum Disorder in Quantitative Genetics

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Abstract: Autism spectrum disorder (ASD) is one of the most prevalent groups of neurodevelopmental disorders. It is defined by defects in social and linguistic abilities, and limited interests as well as repetitive behavior, with a few exceptions. Based on the autism spectrum disorder concordances, monozygous twins have a higher prevalence of bipolar disorder and Asperger's syndrome, and Asperger's syndrome is more vital to the diagnosis of autism. The coherence of high overall function, psychiatric comorbidity, and Asperger's syndrome between monozygous and dizygotic twins indicates genetic differences in various autism spectrum disorders. For a family in which monozygous twins are diagnosed with autism spectrum disorder, the second twin is unlikely to be diagnosed after 12 months. The correlation of monozygous and dizygotic twins underlines the influence of adjusting the assumed thresholds in statistical models and raises the question of how autism spectrum disorder can be defined, which is important due to its social impact. In the full model of the effects of additive genetic, shared environmental, and nonshared environmental, non-additive genetic effects may have an important contribution to total genetic variation of complex traits? The risk of recurrence of autism spectrum disorder can be influenced by pregnancy, maternal intrauterine environment, birth sequence, gender, ethnic origin and birth interval.

1. Introduction

Autism spectrum disorder (ASD) is a developmental disorder that presents early in life, the symptoms of which occur within the first 3 years of life. ASD is defined as the defects in social abilities and language capability, and limited interests as well as repetitive behaviors. However, some children with ASD present severe intellectual obstruction and poor capability for doing basic daily life skills, while others have a high level of intellect and competence for independence, which means the symptoms are heterogeneous [1]. Social interaction and relationships (93.3%) as well as language (92.4%) were the most common types of early symbols. There are 41.9% of ASD cases presenting symptoms between 7 and 12 months, while cases diagnosed between 13 and 24-months account for 27.6%. The sign urging initial medical consultation for the possibility of being diagnosed with ASD was the delay in spoken language. Patients without intellectual disability had shown more instances of stagnation than delay or regression in the early stages, while patients with serious intellectual incapability experience more developmental delay or regression [2].

ASD is one of the most common group of neurodevelopmental disorders, the diagnosis of which account for around 1–2% of the population and is approximately four times more frequent in males

than in females. There are about 31% of individuals with ASD suffer from intellectual defects at the same time, and 20-37% have epilepsy. Besides, medical and psychiatric disorders generally occur in children with ASD. There are about 75% of ASD patients are diagnosed with essential autism spectrum disorder, while syndromic ASD presents in nearly a quarter of patients. The popularity of essential ASD is close to 35% in siblings and around 20% in cases where the family history of ASD is positive. Furthermore, recurrence risk in siblings is lower than in essential ASD, and it is also less common in family history. The concordance rate in full siblings is twice that in half-siblings, which indicates that genetic factors have a great contribution to the development of ASD [3].

In addition to genetic factors, environmental factors impacting the developing brain can influence ASD. Prenatal, perinatal, and postnatal environmental factors can regulate genetic risk among some patients. It is reported that advanced maternal and paternal age can give rise to a climbed risk of having an ASD child. Besides, both shorter and longer intervals between pregnancies can contribute to the growth of ASD risk. Except for other neurodevelopmental disorders, infants born prematurely present a greater risk of ASD. An earlier epidemiologic review demonstrated that obstetric factors were the few factors more consistent with autism [4]. Slight growth in the mean and variance of autistic traits was observed, especially among people born during the period of 2004-2008. This growth can be explained by the rising awareness and reporting of ASD, which could have led to the broader dissemination of autistic trait scores. Besides, over time, genetic and environmental variance behind autistic traits had climbed slightly, which means the environmental aspects related to autistic traits might present modest changes [5].

2. Concordance rate of autism spectrum disorder

In 2012, the autism and Developmental Disorders Monitoring Network reported a combined prevalence of autism of 11.3 cases per 1,000 eight-year-olds or 1 case per 88 children [6]. In any disease, the consistency rate of identical twins raised together is an essential parameter for estimating heritability. In Autism Spectrum Disorder (ASD), the concordance reports of identical twins published range from 65% to 90% [7]. The reconciliation rate of identical twins (MZ) is relatively low for ASD, and the reconciliation rate of fraternal twins is relatively low, establishing the most important genetic neurological disorder of ASD. However, studies have found that autism symptoms are completely continuous in the general population.

Based on the background information of this article, current estimates show that 40 out of every 10,000 children have autism, and the prevalence of ASD is about 1%. The study of siblings found that the consistency rate (if one child has this disorder, the probability that other children will also have this disorder) is as high as 14% [8].

The pairwise ASD agreement of DZ and MZ was 31% and 88%, respectively. The agreement between female and male MZ twins was 100% and 86%, respectively. After the first twin is diagnosed with MZ and DZ twins, the risk ratio of ASD diagnosis in the second twin is 7.48. Affected DZ twins received parental attention earlier than MZ twins and were diagnosed with intellectual disability more frequently; MZ twins have a higher prevalence of bipolar disorder and Asperger’s syndrome, and the latter is consistently higher. In more than 90% of cases, the results of autism screening are related to the ASD status reported by the parents. The ASD consistency between the MZ group and the DZ group was more vital. The consistency of overall high function, psychiatric comorbidity, and Asperger's syndrome between MZ and DZ twins may also indicate genetic differences in different ASDs. For a family where MZ twins are diagnosed with ASD, the second twin is unlikely to be diagnosed with ASD after 12 months [9].

There is growing evidence that genetic factors in school attendance support the etiology of autism through genetic mutations such as heritability and twins. So many genes have been studied for their essential role in the etiology of autism. In some cases, the opposite is true. The importance of environmental risk factors and their role in the etiology of autism has been revealed through studies of identical twins and the lack of complete agreement between them, and numerous genetic studies with inconclusive results. Therefore, the interaction between sensitive genes and environmental factors is

considered the primary mechanism of autism. No single environmental factor is sufficient to cause autism, but their aggregation may be associated with the incidence of autism.

3. Correlation among twins with autism spectrum disorder

The correlation between monozygous twins (MZ) and dizygotic twins (DZ) can be calculated to estimate how similar the twins are. There will be a higher correlation within MZ twin pairs than DZ twin pairs if a trait is affected by genes. For autism spectrum disorder, numerous studies have suggested a higher correlation of MZ twins versus DZ twins, indicating a strong genetic influence.

In a study on twins of the UK population, the DZ relationship is more than half the MZ relationship for Autism Diagnostic Interview-Revised assessment (ADI-R), showing hereditary and shared natural impacts. The MZ: DZ proportion of the cross-twin cross-trait relationships of the Childhood Autism Spectrum Test (CAST) score also shows hereditary effects. Nonshared, instead of shared, environmental impacts, however, are underlined by the ratio of MZ and DZ twins' CAST scores [10].

However, applied prevalence rate, or fixed threshold, in multiple-threshold models are found to influence the estimation of the exact correlation. In a Swedish cohort study, tetrachoric cross-twin cross-cutoff correlations (95%CI) are calculated using 4 dichotomous cutoffs: high cutoff (HiC), low cutoff (LoC), 10th percentiles, and 15th percentiles, to get the correlation of MZ twins that ranges from 0.78 to 0.83 and the correlation of DZ twins that ranges from 0.35 to 0.54 [11]. The correlation of both MZ and DZ twins decreases as the cutoff level decreases and the assumed prevalence decreases. A meta-analysis also suggested a similar effect of using varying thresholds: For all included studies with their original prevalence rate, the correlation is 0.98 for MZ twins and 0.62 for DZ twins; when the adjusted prevalence rate decreases from 5% to 3% to 1%, the DZ correlation increases, while the MZ correlation stays the same [12]. The differences are speculated to be due to an increase in the proportion of shared environmental contributions. These results direct further studies to adjust the threshold in order to facilitate the yielding of precise heritability of ASD.

Since scientists studying autism in the context of the general population have found that autistic traits measured are continuously distributed, and that autism spectrum disorder is the extreme accumulation of autistic traits, the question of how we define autism spectrum disorder needs to be addressed in order to determine the influence of adjusting thresholds. This is particularly important because of its social impact. The criteria of ASD diagnosis might change due to the extreme property of this disorder. We should be aware that earlier interventions can be given to children who have or may have ASD, the better the chances of patients receiving successful treatment. General perception and cognition of ASD might also alter based on the large spectrum of autistic disorder.

4. Bivariate genetic model of autism spectrum disorder

4.1 Standardized Estimates of the Reduced Bivariate Twin Model

For behavioral genetic analysis, we hope to measure a proportion, that is, how much of the trait similarity between people can be explained by genetic similarity. For a trait (variable), the covariance matrix can represent the covariance of the trait between twin pairs, which can be understood as non-standardized correlation coefficient, reflecting the degree of unit covariance. The most important assumption in the model is that the shape similarity between twins can be determined by gene, common environment including prenatal fetal environment, family environment, socioeconomic status, residential area. And their unique environment includes some special experiences, diseases, injuries, random biological effects, self-perception differences, and measurement errors. This model is called ACE models, which models different measurements as the effects of additive genetic (A), shared environmental (C), and nonshared environmental (E), which is called ACE models [10]. According to previous meta-analysis using twin and family studies, the additive genetic influences were significant for all clinical measures about 74%-83% [12], the non-shared environmental effect is significant and the variance of shared environmental influence to ASD is small about 0.1-3% or even non-significant in ACE models from different studies [13].

Recently, there is a model was used to more accurately calculate the heritability that divided the variance in liability to ASD into factors for additive genetic effect, nonadditive genetic factors, shared environmental factors as well as non-shared environmental factors. In this complete model, the shared environment variance was estimated to be 4% (95% CI, 0.00-0.38); the variance of the non-shared environment is estimated to be 16%; the non-additive genetic variance was estimated to be 10%; the additive genetic variance was estimated to be 69%. Using twins only, the heritability was estimated to be 87% [14]. When we evaluated the results, we found that this method led to a low estimate of heritability, which could be interpreted as autistic spectrum disorder is rare, heritability estimates depend on several families with more than one affected child and are combined with the temporal trend of ASD prevalence. Therefore, heritability estimation is very sensitive to the choice of methods. In previous studies, the selected method led to a low estimate of heritability. However, the heritability of ASD was high, and the risk of ASD increased with the increase of genetic relatedness in both analyses.

4.2 Comparison of Additive and Non-additive Genetic Influence

The first thing that should be clarified is the difference between additive genetic influence and non-additive genetic model. The key difference between them is its effect on phenotype. In the additive genetic model, both alleles contribute to the phenotype in measurable quantities, while in the non-additive genetic model, only one allele contributes to the phenotype through dominance or epistasis. When genome-wide markers are used to study the genetic structure and genome prediction of complex human traits, non-additive genetic variation is usually ignored [14]. However, non-additive genetic effects may make an important contribution to the total genetic variation of complex traits. Sandin state that nonadditive genetic has an estimated variance of 0.10 (0.00-038) in the ACDE model [14]. Therefore, nonadditive genetic should be considered when testing a genetic variation of complex traits.

5. Familial recurrence of autism spectrum disorder

5.1 Risk of Recurrence of Autism Spectrum Disorder

Risch defines recurrence risk as to the probability of a child who is born after the first ASD child being affected, which means unaffected individuals born before the first affected child are excluded [15]. Grønborg suggests that the general relative recurrence risk for ASDs was 6.9 (95% CI, 6.1-7.8), and no time bias is found in the ASDs recurrence risk. In maternal and paternal full-siblings, similar risks were observed. However, for maternal half-siblings, the relative recurrence risks were 2.4 (95% CI, 1.4-4.1), and for paternal half-siblings, this figure dropped to 1.5 (95% CI, 0.7-3.4). The distinctness in the recurrence risk between full and half-siblings emphasizes the genetic contribution in ASDs, since full-siblings are genetically more similar than half-siblings. The notable figure in maternal half-siblings may show that the recurrence risk can be influenced by pregnancy and the maternal intrauterine environment in ASDs [16]. Besides, Beenstock states that the recurrence risk of ASD children in Israel, who are born during the period of 1992-2007, is about 4.6%, after excluding families with both ASD twins and families involving half- siblings [17]. However, by analyzing all individuals born in California between 1990 and 2003 who had ASD, the total sibling recurrence risk was 10.1%, in which second-born children was higher (11.5%) than their younger siblings (7.3%). An identical pattern was noticed for maternal half-siblings whose recurrence risk was twice those of paternal half-siblings [15]. The higher recurrence risk for full-siblings compared with half-siblings displays the significance of genetic contribution in ASDs. The differences between maternal half-siblings and paternal half-siblings, and higher recurrence risk in second-born children indicate the environmental factors on ASDs.

5.2 Potential Risk Factors for the Recurrence of Autism Spectrum Disorder

Except for the aforementioned factors related to genes, environmental factors can also contribute to ASD recurrence risk. There are several familial environmental factors impacting the recurrence risk of ASD, such as maternal perinatal aspects and intrauterine environment and the family's habits.

Maternal half-siblings inherit genes from their mother, and similar exposures stem from their mother's intrauterine environment and perinatal history. However, paternal half-siblings only inherit genes from their father and have an absence of shared environmental factors related to pregnancy. As there is a significant raise of recurrence risk for ASDs in maternal half-siblings, as well as the lower risk in paternal half-siblings, environmental factors that are exclusive to the mother's reproductive history may have an impact on ASDs [16]. Beenstock finds that compared with girls, ASD recurrence risk is higher for boys. However, among the younger siblings of sisters with ASD, ASD recurrence is greater [17]. Besides, Werling also states that there was a sex-differential recurrence among children born after the first two children with ASD born in the family. In children born after two probands, evidently higher recurrence in males than in females and in siblings of female probands compared to siblings of male probands [1]. Similarly, a same sex-differential recurrence pattern was found in dizygotic twin pairs. Moreover, according to Beenstock, recurrence rates are highest for Jews and lowest for Arabs, but they are not related to the ages of parents. Besides, recurrence rates in the birth-orders of ASD children, as well as that of their younger siblings are in the reverse ratio [17]. Additionally, Risch suggests that an exponential effect of the short interbirth interval was observed. With an interbirth interval within 18 months, recurrence risk was nearly doubled for an interval of over 4 years. Likewise, a similar phenomenon was observed in maternal half siblings [15]. In general, familial environment, gender, race, birth-orders, and interbirth interval are the potential risk factors for the recurrence of ASD.

6. Conclusion

This paper introduces the coincidence rate of autism spectrum disorder, the correlation between twins with autism spectrum disorder, the bivariate genetic model of autism and family recurrence, and the risk factors of autism spectrum disorder. Among these components, genetic and environmental effects have been proved to be of great significance for the etiology of ASD. Gender difference, birth interval and race are the risk factors of ASD. By understanding these data and information of ASD, people can further understand ASD. However, the contribution of gene environment interaction or gene environment correlation to ASD risk is an important question that has not been answered. Nevertheless, we believe that some interventions and treatments will be found in the future.

References

[1] D.M. Werling, D.H. Geschwind, "Recurrence rates provide evidence for sex-differential, familial genetic liability for autism spectrum disorders in multiplex families and twins," Molecular Autism, 2015.

[2] A. Parmeggiani, A. Corinaldesi, and A. Posar, "Early features of autism spectrum disorder: a cross-sectional study," Ital J Pediatr, 2019, vol. 45, pp. 144.

[3] B. Wiśniowiecka-Kowalnik, B.A. Nowakowska, "Genetics and epigenetics of autism spectrum disorder-current evidence in the field," J Appl Genet, 2019, vol. 60, pp. 37-47.

[4] H. Hodges, C. Fealko, and N. Soares, "Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation," Transl Pediatr, 2020, vol. 9, pp. S55-S65.

[5] M.J. Taylor, M.A. Rosenqvist, H. Larsson, C. Gillberg, B.M. D'Onofrio, P. Lichtenstein, and S. Lundström, "Etiology of Autism Spectrum Disorders and Autistic Traits Over Time," JAMA Psychiatry, 2020, vol. 77, pp. 936-943.

[6] P. Karimi, E. Kamali, S.M. Mousavi, M. Karahmadi, "Environmental factors influencing the risk of autism," J Res Med Sci, 2017.

[7] L. Castelbaum, C.M. Sylvester, Y. Zhang, et al, “On the Nature of Monozygotic Twin Concordance and Discordance for Autistic Trait Severity: A Quantitative Analysis,” Behav Genet, 2020, vol. 50, pp. 263-272.

[8] “Genetic component of autism spectrum disorders may be moderate compared to environment, twin study suggests,” JAMA and Archives Journals, 2011.

[9] R.E. Rosenberg, J.K. Law, G. Yenokyan, J. McGready, W.E. Kaufmann, and P.A. Law, “Characteristics and Concordance of Autism Spectrum Disorders Among 277 Twin Pairs,” Archives of Pediatrics & Adolescent Medicine, 2009, vol. 163, 907.

[10] E. Colvert, B. Tick, F. McEwen, C. Stewart, S.R. Curran, E. Woodhouse, et al, “Heritability of Autism Spectrum Disorder in a UK Population-Based Twin Sample,” JAMA psychiatry, 2015, vol. 72, pp. 415-423.

[11] S. Lundström, “Autism Spectrum Disorders and Autisticlike Traits,” Archives of General Psychiatry, 2012, vol. 69, pp. 46.

[12] B. Tick, P. Bolton, F. Happé, M. Rutter, and F. Rijsdijk, “Heritability of autism spectrum disorders: a meta-analysis of twin studies,” Journal of Child Psychology and Psychiatry, and Allied Disciplines, 2016, vol. 57, pp. 585-595.

[13] D. Bai, B. Yip, G.C. Windham, A. Sourander, R. Francis, R. Yoffe, et al, “Association of Genetic and Environmental Factors With Autism in a 5-Country Cohort,” JAMA psychiatry, 2019, vol. 76, pp. 1035-1043.

[14] S. Sandin, P. Lichtenstein, R. Kuja-Halkola, C. Hultman, H. Larsson, and A. Reichenberg, “The Heritability of Autism Spectrum Disorder,” JAMA, 2017, vol. 318, pp. 1182-1184.

[15] N. Risch, T.J. Hoffmann, M. Anderson, L.A. Croen, J.K. Grether, and G.C. Windham, “Familial recurrence of autism spectrum disorder: evaluating genetic and environmental contributions,” Am J Psychiatry, 2014, vol. 171.

[16] T.K. Grønborg, D.E. Schendel, E.T. Parner, “Recurrence of autism spectrum disorders in full- and half-siblings and trends over time: a population-based cohort study,” JAMA Pediatr, 2013, vol. 167, pp. 947-53.

[17] M. Beenstock, R. Raz, and H. Levine, “Birth gap and the recurrence risk of autism spectrum disorders: A population-based cohort study,” Research in Autism Spectrum Disorders, 2015.