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Close genetic relationships between a spousal pair with autism-affected children and high minor allele content in cases in autism-associated SNPs

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ABSTRACT

Parents of children affected with autism spectrum disorders (ASD) often have mild forms of autistic-like characteristics. Past studies have focused on searching for individual genetic risk loci of ASD. Here we studied the overall properties of the genomes of ASD trios by using previously published genome-wide data for common SNPs. The pairwise genetic distance (PGD) between a spousal pair with ASD-affected children was found smaller than that of a random pair selected among the spouses in the ASD trios, and spousal relatedness correlated with severe forms of ASD. Furthermore, for a set of 970 ASD associated SNPs, cases showed higher homozygous minor allele content than parents. These results indicate new genetic elements in the broad phenotypes of parents with ASD-affected offspring and in ASD pathogenesis.

Professor Sir Simon Baron-Cohen's rubbish only gets this mention because these researchers have to kowtow to him due to his power in the autism research bureaucracy.

BUT ONLY TWO

1. Introduction

Autism spectrum disorders (ASD) is a common disease today. The prevalence of ASD is increasing and reached 14.6 per 1000 (one in 68) children aged 8 years in the United States at 2012 [1]. About four times as many males as females are autism [2,3]. Twin and family studies show that siblings of children with ASD are at a significant higher risk for autism than the general population [4,5,6]. Strict (STR) and spectrum (SPC) definition of ASD differ mainly in social deficits [7]. Parents of ASD children are in general of high social economic status (SES) with similar background in science and engineering fields but often have mild forms of autistic-like characteristics or the 'broad phenotype' of autism, such as social and communicative difficulties [8,9,10,11]. High SES and educational attainment are strongly correlated, both of which are also correlated with general intelligence [12,13]. There is also a genetic component to educational attainment [14]. ASD children also show wide distribution in general intelligence with high functioning individuals performing better than the general population or even their high SES parents in certain tasks [15,16,17].

ASD remains poorly understood but may have a strong genetic component with a heritability of 40–80% [18,19,20,21]. ASD are genetically highly heterogeneous, with no single gene accounting for >1% of cases [22]. Recent work has shown a substantial contribution of de novo variations [23,24,25,26]. However, genome-wide association studies have revealed few replicable common polymorphisms associated with ASD [27,28,29,30].

Theories of ASD are numerous. According to the hyper-systemizing theory [31,32], people with ASD have an unusually strong drive to systemize. A comprehensive hypothesis of ASD, taking intelligence and nearly all aspects of ASD into account, has emphasized the role of an optimum level of a suppressive force of innate traits [12].

It has been reported that similar phenotypes and genetic parameters influence preferential mating [33,34,35]. Consanguineous marriages appear to increase the prevalence of ASDs [36,37,38]. The prevalence of autism might increase by 1.5-fold after 1 generation of assortative mating (≥2.4-fold in the long term) depending on several assumptions [39]. Common genetic variants are individually of little effect but may be a major source of risk for autism [40]. Preferential mating may bring about additive genetic influences in concentrating inherited ASD susceptibility [41]. These observations suggest a potential role for combination of common variants in ASD.

Consistent with the notion of a collective and additive effects of common variants, recent studies indicate a role for genome wide minor allele content (MAC) of an individual in a variety of complex traits and diseases [42,43,44,45]. The more the number of minor alleles of common SNPs in an individual (i.e., the higher the MAC values), the higher the risk in general for many complex diseases such as lung cancer and Parkinson's disease [42,43,44,45]. Such findings indicate an optimum level of genetic variations that an individual can tolerate. Too much lower or higher than the optimum may result in lower fitness and complex diseases [46,47]. In this study, we investigated whether spousal pairs with ASD-affected children are more genetically alike and whether changes in MAC values may be linked with ASD.

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Those very positive comments on my theory, 23 years after its publication, show it to be the World Champion theory of autism. Anyone comparing mine to that of Professor Sir Simon Baron-Cohen can easily see how vastly superior it is. And that's only one of my great discoveries. And I'm not even particularly interested in autism . And with no qualifications or training.

analysis. After outlier exclusion, there were 320 spouses in AGP stage 1 trios, 283 spouses in AGP stage 2 trios, 133 spouses in Miami ASD trios, 125 spouses in OZALC data and 22 spouses in CEU data (Supplementary Fig. S1).

4.3. Comparison of parental pair distance with a random pair distance

To generate random pair distance for comparison with a parental pair, we calculated the distance between a father in a parental pair and each of the female individuals in the parents cohort. We then compared the parental pair distance with the middle ranked distance among the randomly paired distances. We did this for all parental pairs and performed pairwise *t*-test to determine whether the parental pair distance is significantly smaller than the middle ranked random pair. The middle ranked distance among the random pairs, relative to average distance of random pairs, should be less sensitive to influence by very large or very small distances from certain random pairs that may be due to paring of demographically very distant or very close individuals that may represent a small fraction of our selected cohort despite our best effort to select homogeneous populations. For example, 20 outliers in an otherwise homogeneous cohort of 300 may significantly raise the average random pair distance but would only marginally affect the middle ranked random pair distance.

4.4. Selection of SNPs within ASD-associated genes

The ASD associated genes were obtained from the published papers [49]. We first selected the ASD-associated SNPs as those that are located within the ASD associated genes, or within 1000 base pairs upstream or downstream and the UTR regions of these genes. Using the pairwise linkage disequilibrium (LD) option of PLINK, we calculated the LD of each neighboring SNPs (the LD window was 1 million base pairs on the same chromosome). If there were two or more SNPs in LD with $R^2 > 0.5$, we randomly selected one among these SNPs.

4.5. Statistical analysis

The population used for calculating the pairwise genetic distance (PGD) were homogeneous groups with outliers excluded by "GCTA" (genome-wide complex trait analysis). PGD were scored using a software as described in previous studies [43,44]. Every non-repetitive pair within a population was scored to produce the average PGD. The PGD software measures genetic distance between two individuals by the number of mismatched SNPs. For homozygous (Hom) vs Hom mismatch such as CC vs TT, a difference of 1 was scored. For Hom vs Het such as CC vs CT, a difference of 0.5 was scored. For Het vs Het such as CT vs CT, a difference of 0.5 was scored, which is based on the following reasoning. When there is AB v AB match, there are two situations depending on the haplotypes. First, if haplotypes are matched, the two hets would be identical (AB matched with AB) and it would take 0 mutation to convert AB to AB. Second, if haplotypes are not matched, AB would be matched with BA. It would take 2 mutations to convert AB into BA. Since only 50% of het vs het matches would be AB vs BA, so the overall number of mutations required to make AB and BA equal to AB in terms of haplotype matches is $0.5 \times 2 = 1$, which is 50% lower than that required for changing AA to BB. Since we score AA v BB as a difference of 1, the score for AB v AB is naturally 0.5. We verified this approach by comparing the PGD in X chromosome for CEU females vs CEU males using HapMap SNP data and found them to be similar as expected. In contrast, a software based on IBS (identical by status) such as PEAS that score A/B vs A/B as 0 showed the males to have much greater PGD in X than females [53]. For the missing genotypes N/N, N/N vs Hom was scored as 0 and N/N vs Het as 0.5. All the PGD (or the ratio of homozygous genotype) were expressed as total number of the distance (or homozygous SNPs) divided by the total number of SNPs that actually used except the N/N.

The MAF of each SNP was calculated by PLINK and SNP Tools for Microsoft Excel [52,59]. From MAF data of controls we obtained the MA set, which excluded non-informative SNPs with MAF = 0 in both cases and controls or with MAF = 0.5 in controls.

Minor allele content (MAC) means the ratio of the number of minor alleles divided by the total number of SNPs scanned.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygeno.2016.12.001.

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A THEORY OF GENERAL IMPAIRMENT OF GENE-EXPRESSION MANIFESTING AS AUTISM

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Summary—This is the first part of a combined theory of autism and general intelligence (IQ). It is argued that general impairment of gene-expression, produced by a diversity of environmental and genetic causes, is in moderation advantageous in suppressing genetic idiosyncracies. But in excess it will produce a condition involving abnormalities of appearance and behaviour, with a particular relationship to high parental social class and IQ and with particular sex distributions. Characteristics and findings relating to schizophrenia, manic-depressive illness, or neuroses indicate that they cannot reasonably be considered manifestations of excessive general impairment of gene-expression. By contrast, characteristics and findings relating to autism accord very well with this conception. The suggestion is that autism involves primary abnormalities in diverse parts of the brain and in diverse psychological functions. By this means are explained not only the diverse behavioural abnormalities but also such peculiarities as the physical characteristics and the differential distributions of autistic subcategories with respect to social class and sex. Random binding to DNA may be a substantial agent of general impairment of gene-expression.

It will be argued that the most prominent effect of general impairment of gene-expression is the production of individual differences in innate general intellectual ability, by variable degrees of suppression of certain characteristics that tend to produce slowing and errors in intellectual processing. But that in excess it causes the autistic syndrome. The full application of the theory to intelligence and its correlates will be presented in a separate paper.

There have been many theories of autism. But there appear to be no other theories of how general impairment of gene-expression would manifest itself.

The present theory differs from other theories of autism in having the following combination of characteristics.

It is founded on an argument from well-established biological principles, providing it with a basis in the context of evolution by natural selection. Indeed, several hypotheses that emerged in the course of development of the theory turned out to be already well-established findings, namely the association of reliability of expression with advantageousness, the re-emergence of long-suppressed characteristics and the conservatism and resistance to change of characteristics other than of appearance and behaviour.

It provides an explanation of why such a severely biologically disadvantageous condition is not eliminated by natural selection, and of why it is a relatively common mode of failure of the brain.

It addresses an exceptionally broad range of findings about autism (and IQ). These include the wide diversity of behavioural abnormalities (listed in Table 2), including some particularly odd ones, such as the distinctive hand-flapping and posturing, and also the physical stigmata, attractiveness of appearance, special skills, above-average parental IQ and differentially elevated parental social class, the fourfold preponderance of males among the severely autistic, and the tenfold preponderance among the mildly autistic.

Numerous specialist readers have found not one finding to cast doubt on the theory, nor any flaw in the arguments presented here. This was not for want of hostility.

And yet the theory cannot validly be dismissed as untestable, or as equally compatible with any conceivable findings. Were such a criticism justified, it would be possible to provide some substantiation by substituting, in place of findings about autism, the findings about other conditions such as schizophrenia, manic-depressive illness, or the like, and then rewriting the pages that follow so as to explain all those findings instead. It will become clear that any such explanations would be not merely speculative but absurd and incredible. For example, why should general impairment of gene-expression manifest as alternating mania and depression? Why should

Alzheimer's disease as a syndrome of overloaded amyloidic synaptic tagging in memory networks

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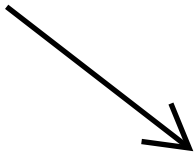

The notion that AD could be caused by overload of memory circuits is not entirely new. In an article published nearly 20 years ago, Clarke presented a similar hypothesis reasoning that differential phosphorylation of tau embodies stored information (Clarke, 2000). Clarke reasoned that the large number of phosphorylation sites possessed by tau provides a digital encoding mechanism with up to 17 billion variations. Once all variations are exhausted, pTau forms NFTs driving neurodegeneration. Clarke did not elaborate specifically on how cells could recognize and distinguish 17 billion variations in tau phosphorylation, or for example how the many molecules of tau found in the same cell could be distinguished. Nor was an explanation of how this would manifest in neuroplasticity and circuit connectivity provided. Nonetheless, Clarke essentially proposed that pTau acts as a mnemonic tag. Additionally, Clarke proposed that Aβ acts as an anti-overload mechanism noting that Aβ initially promotes plasticity before switching to an inhibitory and ultimately a toxic role. Indeed, the notion that Aβ transitions from positive and beneficial mnemonic effects to neurotoxic effects is by no means novel - several others have made the same suggestion (Morley et al., 2019; Puzzo, 2019).

Around the same time as Clarke's article, Mesulam published his "plasticity-based theory of the pathogenesis of AD" (Mesulam, 2000). Noting the correlation between areas of high plasticity and deposition of Aβ and NFTs, his article made a number of remarkably relevant statements. Asking "Could the increased vulnerability of limbic areas to NFT formation be based on the increased neuroplasticity load they have to bear throughout the life span?" Mesulam went on to surmise "Ultimately, AD arises when the brain can no longer keep up with the work needed to repair itself or encode new experiences" and that "AD of old age may not be a disease at all, but the inevitable manifestation of a failure to keep up with the increasingly more burdensome work of plasticity". Additionally, Mesulam suggested that in areas of high plasticity tau phosphorylation and Aβ turnover initially act adaptively and independently to meet neuroplasticity needs – a concept similar to that presented here. Eventually, Mesulam proposed, such processes would "lead to chronically high and eventually unsustainable levels of plasticity-related cellular activity" following which such pro-AD factors transition to neurotoxic effects. Moreover, Mesulam made what proved a particularly prescient prediction, suggesting that attempts at reactive remodeling to counter increasing plasticity burden, NFTs would form and undergo a "horizontal" spread in inter-connected brain regions – interest in prion-like spread of tau forms was not to take off until a decade later (Goedert et al., 2010).

Is there any tangible *direct* evidence supporting the prediction that long-term memory overload causes AD? The short answer is no, or at least very little. Perhaps because studies attempting to deliberately overload memory in humans or experimental animals are practically non-existent. That said, very recent studies by De Risi *et al* suggest that week-long memory capacity in aged cognitively impaired mice is limited by an autophagic process that eliminates fibrils of Aβ and α-syn (De Risi et al., 2020). However, studies such as this are unusual, obliging one to look to correlative evidence. Aside from the risk of developing AD increasing with age and the notion held (by some) that all individuals will develop AD if they live long enough, epidemiological evidence may be supportive. As outlandish as it may sound, several studies show television viewing correlates with AD risk (Lindstrom et al., 2005) and mortality (Grace et al., 2017; McDonnell et al., 2016; Veerman et al., 2012). Though naturally these studies are difficult to interpret as time spent watching television is time not spent doing activities such as exercise – activities that themselves may be negative risk factors in their own right. If one supposes industrialization has brought concomitant increases in exposure to information rich experiences, one might look to comparing AD rates in industrialized versus non-industrialized countries. Comparing African Americans with Nigerians finds higher rates of AD in the former (Josefson, 2001). AD incidence is generally higher in North America and Europe than in developing countries (see Qiu et al., 2009).