RESEARCH COMMENTARY

Autism genes: the continuum that connects us all

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A recent study appeared in *Nature Genetics* in the May issue (Robinson *et al.* 2016), revealed the casual relationship between genetic variations and behavioural traits in human, including those with the autism spectrum disorders (ASD). The study demonstrated that the genetic variations associated with ASD—*de novo* as well as inherited mutations, could possibly influence a wide spectrum of behavioural trait, including those that are seen in the normal population, and that ASD phenotype possibly represent one end of the spectrum—the more severe form. This commentary is essentially to discuss the significance of this study and its potential outcome.

Recent advances in the genomic analyses have led to the discovery of hundreds of causative genes for the monogenic disorders (Antonarakis and Beckmann 2006). These studies have also led the development of sensitive and reliable diagnostic tools, better understanding the pathophysiological process and disease management (Antonarakis and Beckmann 2006). As against this, the common complex disorders are thought to be resulting from the involvement of multiple genes with additive effects and in combination with environmental factors (Badano and Katsanis 2002). Therefore, the progress in finding genes for complex disorders has been rather slower and challenging, since the traditional family-based mapping approaches could not be applied here. The HapMap project and genomewide association study (GWAS) have made major impact on discovering genetic risk factors for a number of complex disorders, although the specific role for these risk factors in the disease process is far from clear (Manolio and Collins 2009). Nonetheless, the risk alleles in common disorders are often thought to increase the susceptibility of developing the disease rather than being the cause. Therefore, the distribution of such risk alleles differ only marginally in the normal population as compared with the affected (Manolio and Collins 2009). The frequency of 'disease causing' alleles of monogenic disorders on the other hand are rarer in normal population and hence are known as 'disease-causing alleles'.

The neuropsychiatric disorders represent a heterogeneous group with varied expressions and symptoms, and some of them are thought to be developmental anomalies (Homberg *et al.* 2016). Among these, the ASD represent a condition where the affected child exhibits deficit in social interaction and communication (Boyd *et al*. 2013; de la Torre-Ubieta *et al*. 2016). Such children also tend to show repetitive behaviours (Boyd *et al.* 2013). The severity varies from being very mild (hard to detect) to very severe, disabling conditions such as lack of communication and often parents are the first to notice the unusual behaviour of their children. The diagnosis of ASD can be difficult and time-consuming (Boyd *et al.* 2013; Samadi *et al.* 2016). Intriguingly, some children with ASD could show cognitive abilities higher than average age-matched normal population (Charman *et al.* 2011). For example, individual with ASD could have a higher IQ, and might excel in one or the other stream of studies or skill sets. With the overall incidence of around 1%, the ASD appears to be about four times more common among boys than in girls (Matelski and Van de Water 2016). Thus, sex of the individual appears to be one of the risk factors. Siblings with ASD, children born to older parents, and environmental factors are a few of the other risk factors (Matelski and Van de Water 2016). Twin studies have shown a major role of genetics in ASD aetiology; a monozygotic twins show a concordance rate between 60 and 90% for ASD, while it is about 5% for a dizygotic twins (Bailey *et al.* 1995). Considering the skewed male ratio, i.e. males are more affected with ASD, a potential role of X chromosome in ASD has been debated and explored (Marco and Skuse 2006). Indeed, several studies have suggested possible roles of two X-linked genes, *FMRP* and *MECP2*, in the aetiology of ASD. Defects in the *FMRP* gene are known to cause one of the common forms of mental retardation—the fragile X syndrome (FXS), mostly affecting the males as in the case of ASD (Lozano *et al.* 2014). Although, the FXS patients share many of autistic features, the *FMRP* locus appears to be involved only in a minor

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fraction (~2%) of ASD cases (Reddy 2005). *De novo* mutations in the *MECP2* gene are known to cause Rett syndrome—a neurodevelopmental disorder predominantly affecting girls. Rett syndrome patients show autistic-like behaviour in early stages and eventually develop symptoms that are unique to Rett syndrome (Feldman *et al.* 2016). The *MECP2* gene mutations, however, are rarer in ASD cases (Lobo-Menendez *et al.* 2003), thus excluding its role in ASD. Mutations in two other X-linked genes, *NLGN3* and *NLGN4*, have been shown to associate with ASD but only in a few cases (Jamain *et al.* 2003). Similarly, anomalies in X chromosome, both structural and numerical, have also been implicated in ASD and again only in a smaller number of ASD cases (Evers *et al.* 2015), suggesting a major role for autosomal genes in the ASD aetiology. Indeed, a large number of studies have tested this possibility and have used either the GWAS or whole-exome sequencing approach to identify ASD associated genetic signatures. The outcome of such studies can be grouped into two distinct classes: (i) rare inherited or *de novo* mutations in a large number of genes occurring more predominantly in ASD cases (Iossifov *et al.* 2014; Krumm *et al.* 2015), and (ii) the common gene variants which are also present but at a lower frequency in the normal population contributing to the risk of ASD (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; Gaugler *et al.* 2014). Given the fact that the 'risk alleles' are also found in the normal population, one could argue that the ASD being a quantitative phenotype, a few of the ASD 'symptoms' could also be seen in so-called normal population. The ASD diagnosis being subjective and often based on the observations and the feedback response, individuals who show marginal 'phenotype' yet fall below the threshold of being called as ASD, can be considered as 'normal'. Indeed, studies have shown the increased incidence of a few of the autistic traits in the biological relatives of ASD cases who are otherwise not diagnosed as ASD. This raises an intriguing question on the genetic similarities between the individuals that show ASD and those that show ASD-like traits but considered as normal in the population. The paper by Robinson and colleagues (2016) tested this possibility and demonstrated that the genetic influence for ASDs could result in a continuum of 'behavioural and developmental traits'. The authors of this article have used different datasets to build their model and to validate. These include the genomic data (common nucleotide variants and *de novo* mutations—derived from GWAS and whole-exome sequencing data) and their correlation with the ASD phenotype as well as with the social and communication difficulties (SCD), as defined by the Social and Communication Disorders Checklist (Boyd *et al.* 2013), in individuals representing the general population. These data were derived from large consortium studies, some of them have already been in the public domains, thereby involving a substantially large sample size (exceeding 10,000 for each group). A significant aspect of the study was to compare the genomic profile between the ASD cases and the individuals from the normal population who showed SCD and replicating the studies with other cohort. The authors have also compared the genetic signatures of individuals with other neuropsychiatric disorders, such as schizophrenia, with those that show ASD to see the overlap in the genetic risk factors. The authors demonstrated that nearly one fourth of the genetic risk factors associated with the ASD phenotype are also associated with SCD and that this correlation is independent of the race or the geographical location of the population studied. The authors also demonstrated a similar level of overlap for the genetic signatures in individuals from the same cohort having neuropsychiatric disorders such as schizophrenia and other manic disorders. To further strengthen their observations, the authors have also looked at the occurrence of the *de novo* mutations in the cohorts they have studied. Their data correlated a continuum of genetic burden with the continuum in behavioral traits in the study subjects. Thus, the ASD could represent the one end of the behavioural spectrum. The siblings of ASD cases, who often share many of the genetics signatures of ASD are at higher risk of developing SCD. This study thus provides a genetic basis to suggest that social behaviour is indeed a continuous trait and its distribution/expression in the population varies along a continuum, just like the other textbook examples of the quantitative traits—the height, learning ability and skin colour. This study and its approach are first of its kind, and therefore, is a seminal contribution in understanding the complexity of a polygenic trait in humans. Similar approach can now be extended to investigate other traits, such as neuropsychiatric or neurodevelopmental disorders, and to understand their genetic basis.

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