

Autism and Nonsense Mediated Decay (NMD)

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Autism is a complex childhood developmental disability that causes problems with social interaction and communication [1].

“Infantile Autism” was first diagnosed and classified by Kanner [2] and for nearly 50 years was viewed as relatively rare, low incidence condition. Autism has three unique features that include (a) reduced motivation for social interaction, (b) restricted interests and repetitive behaviours, and (c) severe communication disorders. In the beginning a patient has to present with all three of the criteria to be diagnosed with autism. The percentage of diagnosis thus stayed very low until the 1980s, when broadening of the diagnostic criteria and reclassifying autism as a spectrum was introduced. This diagnostic change led to a dramatic increase in the number of cases diagnosed with autism reaching 10 to 20 per 10000 children with a decrease in intellectual disability diagnosis (USCenters for Disease Control, 2012).

Autism Spectrum Disorder (ASD) includes an array of diseases in addition to autism such as Asperger’s syndrome, pervasive developmental disorder-not otherwise specified (PDDNOS), Rett’s syndrome, and childhood disintegrative disorder. In ASD, symptoms usually start at a very young age and can cause delays or problems in many different skills that develop from infancy to adulthood [3,4].

ASD is multifactorial, with many risk factors acting together to produce the phenotype. The dissimilarity between monozygotic and dizygotic twin rates suggests that some risk factors interact and influence it at different levels, such as gene–gene or gene–environmental interactions [5]. 10-15% of ASD cases are associated with known genetic causes. The most common causes include fragile X syndrome, where about 3 % of patients are also diagnosed with autism, tuberous sclerosis (2%) and various cytogenetic abnormal findings such as maternal duplication of 15q1-q13 (2%), and deletions and duplications of 16p11 (1%). None of these causes is specific to ASD, but rather are specific to a range of other autism spectrum phenotypes [3,5-7].

Only a few common variants have been identified as possible ASD candidate genes in linkage and association studies, pointing to the difficulty of finding common causes. The difficulty in finding robust common variants is not unique to autism spectrum disorder alone. Evidence for synaptic dysfunction as a unifying cause has come from findings of rare mutations in neural cell adhesion and synaptic molecules such as X-linked neuroligin 4

(*NLGN4X*), neuroligin 3 (*NLGN3*) and SHANK3 genes [8-10]. The study of genetic factors associated with synaptic maturation is very important because the outcome from neuroimaging studies on autistic subjects demonstrates a defect in structural and functional brain connectivity [11].

At this point, autism could be caused by defects at a genetic level which includes all the susceptible genes, leading to dysfunction at protein synthesis level. This could lead to abnormal synaptic structure and function, which affects ASD core regions of the brain, causing atypical neural system in the whole brain.

In 2010 large scale screening study of a number of families with neurodevelopmental disorders including autism, a family from Belgium with two brothers and one brother was presented with ID and autism; it was found that he has a single nucleotide substitution in *UPF3b* 1103G>A forming Arg368Gln (R368Q). The mother of the boy was found to be a carrier too. Interestingly, the missense mutation in this family (368) is at highly conserved locations throughout a large number of species indicating its importance [12].

In another recent study, a family with two brothers diagnosed with childhood onset schizophrenia - a severe and very rare form of schizophrenia with undefined genetic cause - autism and attention deficit hyperactivity syndrome were found to have mutations in *UPF3b*. A scan of several hundred probable genes revealed a novel four nucleotide deletion in *UPF3b* 683-del686AAGA leading to a frame shift translational and production of UPF3bQ228fs*18open reading frame [13].

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Massive advances in sequencing techniques revealed large number of rare mutations associated with numerous conditions either neurodevelopmental or psychiatric. Many of these diseases could result from mutations that influence various aspects of mRNA metabolism, including processing, export, stability, and translational control. Example of these rare mutations causing diseases include mutations in JPH3 which is associated with Huntington's disease, FMR1 associated with fragile X syndrome [14], UPF3b which was associated with neurodevelopmental disorders, eIF4e in autism [15], DISC1 and HDAC9 with schizophrenia (Matsuzaki and Tohyama, 2007).

Additionally, a number of studies on neurons of patients suffering from schizophrenia, autism or XLID showed that there is a change in the neuronal morphology. Hippocampal neurons of autistic and schizophrenic and ID patients were shown to have a decreased dendrite branching with high spine density [16,17]. Additionally, Nguyen in 2011 analyzed lymphoblasts of patients lacking UPF3b and found that there was an increase in the expression of ARHGAP24 isoform1. ARHGAP24 isoform1 mRNA is a known as an NMD target due to an uORF and a long 3'UTR [18]. Furthermore this gene is important for actin skeleton remodelling. Interestingly ectopic over expression of ARHGAP24 isoform in primary mouse hippocampal neurons caused a reduction in axonal outgrowth and decreased neuronal arborization. Additionally, over expression of ARHGAP24 isoform1 in differentiating PC12 cells inhibited the outgrowth of neurites [18].

Recently, Alrahbeni and their group demonstrated that the presence of the UPF3b reported mutations in stem cells differentiated in to neurone, leads to a significant decrease in neuronal branching and arborisation [19].

Thus it could be concluded that the UPF3b mutations found in subjects with autism, may affect neuronal growth and differentiation in a manner consistent previous reports on neuronal morphology studies of neurons from autistic patients. Additionally, these mutations appear to act in a dominant negative way, by overriding the normal functioning UPF3b which is still present in these neurons and inducing its morphological changes. The presence of these mutations may alter the levels of neurotoxic NMD substrates that otherwise in a fully functional NMD are degraded. A number of these NMD substrates have been reported to have an altered expression in patients with abolished UPF3b. Nguyen and colleagues demonstrated that just the elevation of the expression of one of these NMD substrates, ARHGAP24 isoform1, in the presence of a normal NMD leads to a decreased neuronal branching and differentiation (Nguyen et al., 2013).

In conclusion, there is a clear link between autism and defective NMD, which could be studied and investigated further more.

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