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Full UPF3B function is critical for neuronal differentiation of neural stem cells

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Mutation in the UPF3B gene on chromosome X is implicated in neuro-developmental disorders including X-linked intellectual disability, autism and schizophrenia. The protein UPF3B is involved in the Nonsense-Mediated mRNA Decay pathway (NMD) that controls mRNA stability and functions in the prevention of the synthesis of truncated proteins. Here, we show that NMD pathway components UPF3B and UPF1 are down regulated during differentiation of neural stem cells into neurons. Using tethered function assays we found that UPF3B missense mutations described in families with neuro-developmental disorders reduced the activity of UPF3B protein in NMD. In neural stem cells, UPF3B was detected in the cytoplasm and in the nucleus where it was enriched in the nucleolus. A similar distribution was observed in neurons. Using GFP tagged UPF3B proteins; we found that the missense mutations did not affect cellular localisation. Expression of missense mutant UPF3B disturbed neuronal differentiation and reduced the complexity of the branching of neurites. Neuronal differentiation was similarly affected in the presence of the NMD inhibitor Amlexanox. The expression of mutant UPF3B proteins lead to a subtle increase in mRNA levels of selected NMD targets. Together this indicates that despite the down-regulation of NMD factors, functional NMD is critical for neuronal differentiation. We propose that the neuro-developmental phenotype of UPF3B missense mutation is caused by impairment of NMD function altering neuronal differentiation.

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Genetic variability of the human *SRD5A2* gene: Implications for public health

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Knowledge of *Steroid 5 Alpha-Reductase type 2* (*SRD5A2*) gene mutations is expanding and its role has been implicated in various disease susceptibilities concerning reproductive health. Most mutations of the *SRD5A2* gene inhibit enzyme activity which causes masculinization defects of varying degrees leading to the birth of a child with ambiguous genitalia (male pseudo-hermaphroditism). *SRD5A2* gene mutations have also been implicated in various disease susceptibilities such as prostate cancer, isolated cases of hypospadias, micro-penis, benign prostatic hypertrophy, breast cancer, congenital adrenal hyperplasia and others. Due to the varying effect of *SRD5A2* gene mutations, the phenotypic expression of patients also varies considerably. Moreover, research has revealed the tendency for specific *SRD5A2* gene mutations to be passed along certain racial, ethnic and geographically isolated groups which suggests population specificity of these mutations. This information can be extremely useful for carrying out population-specific large scale screening and counseling programs for mutations and the disorders they may cause that are specific to an ethnic group.

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