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TOWARDS UNDERSTANDING THE PATHOGENETIC MECHANISM OF *PQBP1* MUTATIONS IN X-LINKED MENTAL RETARDATION

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Mutations in the polyglutamine binding protein 1 (*PQBP1*) gene cause X-linked mental retardation. Identical and similar mutations result in high clinical variability, ranging from moderate mental retardation to much more severe forms, including microcephaly, short stature and spasticity. Recently we have begun to unravel the pathomechanism of this disease and have found that *PQBP1* mutant transcripts with a premature stop codon are partially degraded by nonsense mediated mRNA decay (NMD) and that *PQBP1* mutations cause altered splicing. Interestingly, some of the mutations resulted in an upregulation of naturally existing *PQBP1* protein isoforms. Additional studies demonstrated that the *PQBP1* protein is part of a large multiprotein complex containing RNA-binding proteins that are established components of RNA granules and play distinct roles in post-transcriptional RNA regulation and metabolism. Interestingly, we have found that *PQBP1* is present in dendritic shafts of primary cortical neurons in discrete granular structures and co-localises with newly found interacting proteins in these granules. Taken together, our findings strongly suggest that *PQBP1* plays a hitherto unknown role in post-transcriptional RNA regulation and metabolism. Disturbance of one or several of these processes may contribute to the clinical phenotype in patients with a *PQBP1* mutation.