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THE ROLE OF TWIST1 IN MUTANT HUNTINGTIN-INDUCED TRANSCRIPTIONAL ALTERATIONS AND NEUROTOXICITY

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Huntington's disease (HD) is a fatal neurodegenerative disorder caused by an abnormal expansion of polyglutamine repeats in the huntingtin protein (Htt). Transcriptional dysregulation is an early event during HD progression and is thought to contribute to disease pathogenesis. But how mutant Htt causes transcriptional alterations and subsequent cell death in neurons is not well understood. By RNA-sequencing analysis in primary cortical neurons, we found that expression of a mutant Htt fragment leads to robust gene expression changes before neuronal death. Basic-helix-loop-helix transcription factor Twist1, which is essential for embryogenesis and is normally expressed at low levels in mature neurons, was substantially upregulated in mutant Htt-expressing neurons in culture and in the brains of HD mouse models. Knockdown of Twist1 by RNA interference in mutant Htt-expressing primary cortical neurons reversed the altered expression of a subset of genes and, importantly, abrogated neurotoxicity. We investigated the possible interaction between Twist1 and DNA methyltransferase (DNMT3A and DNMT1) both in HD mouse models at endogenous level, and in 293le cells overexpressed by PEI co-transfection. Together, these results suggest that Twist1 is an important upstream mediator of mutant Htt-induced neuronal death and may in part operate through epigenetic mechanisms.