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Interrogating Mechanisms of Huntington's Disease by Direct Neuronal Reprogramming of Patient Fibroblasts

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Interrogating Mechanisms of Huntington's Disease by Direct Neuronal Reprogramming of Patient Fibroblasts

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In Huntington's disease (HD), expansion of CAG codons in the huntingtin gene (HTT) leads to the aberrant formation of protein aggregates and the differential degeneration of striatal medium spiny neurons (MSNs). Modeling HD using patient-specific MSNs has been challenging, as neurons differentiated from induced pluripotent stem cells are free of aggregates and lack an overt cell death phenotype. Here we generated MSNs from HD patient fibroblasts through microRNA-based direct neuronal conversion, bypassing the induction of pluripotency and retaining age signatures of the original fibroblasts. We found that patient MSNs consistently exhibited mutant HTT (mHTT) aggregates, mHTT-dependent DNA damage, mitochondrial dysfunction, and spontaneous degeneration in culture over time. We further provide evidence that erasure of age stored in starting fibroblasts or neuronal conversion of presymptomatic HD patient fibroblasts results in differential manifestation of cellular phenotypes associated with HD, highlighting the importance of age in modeling late-onset neurological disorders.