

A Positron Emission Tomography Ligand for Mutant Huntingtin Sheds Light on Disease

Bertoglio D, Bard J, Hessmann M, et al. Development of a ligand for in vivo imaging of mutant huntingtin in Huntington's disease. *Sci Transl Med* 2022;14(630):eabm3682.

Huntington's disease, a rare dominant degenerative disorder, manifests with neuropsychiatric changes and progressive cognitive and motor impairments. These diverse clinical manifestations reflect neurodegeneration initially in striatal medium spiny neurons and progressing to involve the entire brain. Disease-causing expansions of a CAG/polyglutamine tract in the gene encoding huntingtin (HTT) protein trigger protein misfolding underlying the occurrence of histopathologically visible intranuclear and cytoplasmic inclusion bodies. As is likely for the eight other polyglutamine expansion disorders, proteotoxicity, as well as possibly RNA toxicity, underlies significant aspects of the pathogenic cascade, providing the rationale for HTT-lowering therapeutics.

Although HTT levels measured in cerebrospinal fluid correlate well with brain expression, visualization of mutant HTT in patients, particularly those entering trials of HTT-lowering therapeutics, would provide insight into the regional distribution of pathology, assess target engagement, and permit in vivo evaluation of regional durability of therapeutic effects. A significant step forward is the development of a positron emission tomography (PET) imaging radioligand with high affinity and selectivity for mutant HTT.^{1,2} The radioligand described by Bertoglio and colleagues,¹ dubbed CHDI-180, binds mutant, but not wild-type, HTT with low nanomolar affinity and recognizes a nonmonomeric species distinct from intranuclear inclusion bodies. CHDI-180 identified age- and region-specific pathology in three mouse models and detected pharmacological effects of two intervention paradigms: direct striatal delivery of adeno-associated virus (AAV)-expressing zinc-finger protein repressors of mutant HTT and genetic suppression of mutant HTT in a regulatable mouse model. Lowering of HTT in these models was associated with positive effects on imaging markers of striatal neuron dysfunction.

These findings reveal a promising step toward development of a mutant HTT-specific PET ligand. As with other neurodegenerative proteinopathies, the identity of the relevant toxic protein species is unclear.³ Further studies are needed to define the precise HTT species recognized by

CHDI-180, to determine whether this is the optimal target for PET imaging and to establish whether reported binding of CHDI-180 to β -amyloid² confounds results in patients. β -Amyloid binding may not be an issue in this largely younger to middle-aged population. Additional PET ligands for mutant HTT are in development^{2,4} and may offer complementary tools. The efficacy of any PET ligand depends on the abundance of the target protein. Murine models tend to have less overt neurodegeneration than humans with relative persistence of inclusion-expressing neurons. Whether murine-human differences present a significant challenge for imaging patients with Huntington's disease is yet to be established. This PET tracer holds significant promise for translational studies, particularly evaluating HTT-lowering therapeutics.

Data Availability Statement

The data that support the findings of this study are openly available in PubMed.

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