Juvenile Huntington Disease: towards better understanding its unique disease characteristics

Bakels, H.S.

Stellingen behorend bij het proefschrift:

Juvenile Huntington Disease
towards better understanding its unique disease characteristics

1. Any type of clinical onset before the age of 21 years should be taken into account when defining JHD subpopulations (this thesis)
2. Every research design in the HD field, being clinical or pre-clinical, should attempt to include and compare mild, moderate and extreme HD phenotypes based on distinct AO-HD subtypes or CAG-repeat length (this thesis)
3. Due to differences in affected brain areas and pathomechanisms, JHD patients might benefit from therapeutics which have been shown to be ineffective in adult HD patients. Conversely, therapeutics that target mutant huntingtin might be disproportionally damaging in JHD patients due to its effect on concurrent brain maturation (this thesis)
4. The development of prediction models for disease severity and progression should be applicable to the entire range of disease phenotypes that may result from the predictive markers (this thesis)
5. Triplet repeat-expansion diseases are only the pathological extreme of a more general mutational process that also contributes to normal brain function and development. (*Van der Plas E et al. Journal of Huntington's Disease 2020; 9: 217-229*)
6. The presence and caudal to rostral distribution of pathologic HTT inclusions are a phenotypic expression of HTT gene CAG expansion that does not necessarily signify clinical disease or pathologic grade. (*Hickman RA et al. Acta Neuropathologica Communications 2022*; 10:55)
7. A potential interpretation is that the apparent threshold for an inherited *HTT* allele to be disease causing (36–40 CAGs) reflects not that such alleles encode toxic RNAs or proteins but that such alleles are sufficiently unstable as to be likely to expand beyond 150 repeats within a human lifetime. (*Handsaker RE et al. Cell 2025*; 188(3): 623-639.e19)
8. It maybe that treatment should be given very early in life; it remains to be seen whether reducing mHTT levels in adulthood, even in the prodromal stage, would be sufficient to forestall symptom progression, because the brain circuitry is already altered. (*Barnat et al. Science 2020*; 369(6505): 787-793)
9. Een goede onderzoeker kijkt niet alleen naar wat er is, maar denkt verder – naar wat er (nog) niet bekend is. Zoals Floris Bakels het verwoordde in *Verbeelding als wapen* (1979): "verbeelding is het vermogen om niet alleen te denken over wat is, maar ook over wat er niet is."