Genetics Week 8 Recitation Article Calvin Tran

# Identification of genetic variants associated with Huntington's disease progression: a genome-wide association study

https://www.sciencedirect.com/science/article/pii/S1474442217301618

*Identification of genetic variants associated with Huntington's disease progression: a genome-wide association study, Davina J Hensman MOss MBBS, ANtonio F Parinas PhD, Prof Douglas Langbehn PhD, The Lancet Neurology Volume 16, Issue 9, September 2017, Pages 701-711*

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"Huntington's disease is caused by a CAG repeat expansion in the huntingtin gene, HTT"

Late-onset & Autosomal Dominant
Goal: **Generate a novel measure of disease progression**, **identify genetic markers** with this progression measure.

- Transition from early symptoms to Huntington's manifest proper is **gradual**, making clinical definition challenging.
- Biomarker Study
    - "*the inverse correlation of HTT CAG repeat length and age at motor onset accounts for 50–70% of the observed variance in onset*"
    - However what about the remaining 30-50%?: *"Part of the remaining difference in age of onset was also recently shown to be genetically encoded, and genes of the DNA damage response were identified as being likely to modify onset of Huntington's disease."*

Since Huntington's is a disorder that affects movement, psychiatric, and cognitive function, they sought to replace the old measure = age at onset → **testing motor, cognitive and imaging scores which could be tested earlier in life** and used as a quantitative measure of disease progression.

- Researchers state this study argues for the power of **improving phenotypic measures** in genetic studies.
- Scores had to be processed based on the predictive effects known about # of CAG repeats, gender, and age
- Connect progression scores to genome and run statistics

216 individuals in Huntington's carrier cohort, and 1776 individuals in European Huntington's disease network REGISTRY (also HTT mutation carriers). Recall Huntington's is autosomal dominant. Data collected for 3 years: 2008-2011

- Individuals tested on the 3 scores above
- Scores as quantitative measures of phenotype → compare to genome based on scores

Results

- In the cohort, the 3 scores were found to be perfectly correlated and  were replaced with a single cross-domain measure.
- Cohort and Registry scores were correlated with each other
- Together, meta-analysis of progression **narrowed down to 3 genes on chromosome 5**
    - MSH3, DHFR, MTRNR2L2
        - Potential markers and controllers of that last 30-50% variability of when you will actually get Huntington's
    - P values: MSH3 p=2·94 × 10−8 DHFR p=8·37 × 10−7 MTRNR2L2 p=2·15 × 10−9
- The lead single nucleotide polymorphism
    - was genome-wide significant in the meta-analysis (p=1·58 × 10−8), gene-wide p-value
    - encodes an aminoacid change (Pro67Ala) in **MSH3.**
        - "**each copy of the minor allele** at this SNP was associated with a 0·4 units per year (95% CI 0·16–0·66) **reduction in the rate of change of the Unified Huntington's Disease Rating Scale (UHDRS) Total Motor Score**, and a reduction of 0·12 units per year (95% CI 0·06–0·18) in the rate of change of UHDRS Total Functional Capacity score. These associations remained significant after adjusting for age of onset."
        - **Knockout of Msh3 reduces somatic expansion in Huntington's disease mouse models**, suggesting this mechanism as an area for future therapeutic investigation.
        - **MSH3 is usually involved in the DNA mismatch repair pathway**
            - DNA mismatch repair known to be related to when you will get Huntington's
            - Topic of future research
- Second most significant association region was on chromosome 15, which was previously known to be associated with age of onset for Huntington's
    - Verified the efficacy of their technique of matching phenotype → genotype