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Chorea Huntington: A thousand changes due to a single mutation

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Chorea Huntington is a fatal neurodegenerative disease with late onset. Common symptoms are loss of motor control, cognitive decline, dementia and pathopsychological behaviour. The disease causing mutation – a CAG repeat expansion in a single gene named *huntingtin* (*htt*) - is well known and can be accurately diagnosed. Despite of intensive research, however, no cure for this devastating disease has been found yet.

Although Chorea Huntington is a classical Mendelian disease, various processes are involved molecular level ranging from transcriptional dys-regulation, protein aggregation, excitotoxicity and disruption of vesicular transport and mitochondrial metabolism. Furthermore, strong inter-individual variability in the disease progression suggests the existence of further biological modifiers which could provide novel therapeutic targets.

To consolidate the seemingly unrelated molecular changes observed and to detect novel disease modifiers, we constructed an *HTT*-focused protein interaction network. Introducing a novel multi-level prioritization strategy based on complementary information, we were able to identify a set of potential modifiers. One of the identified modifiers was subsequently experimentally validated as an important factor for aggregation, neurotoxicity and disease progression in HD models. Complementary to the focused analysis of the *HTT* and its interaction partners, we also applied a global approach to reveal connections between distinct disease-related processes.

Our study demonstrates that not only the elucidation of complex diseases but also of apparently ‘simple’ Mendelian diseases can tremendously profit from a network approach. The strategy proposed here can provide a general framework for the study of a wide class of human diseases.