

# LSDBs for Neurological Disorders: Is there a rationale for a Neurogenetics Database Consortium?

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Since the discovery of the first mutations causing disorders of the nervous system (NS) two decades ago, genes responsible for all the major and numerous rare neurological diseases have been identified. The finding of genetic variants associated to common neurological disorders such as migraine and Alzheimer's disease must be added to the list, leading to an increasing accumulation of an enormous amount of data on mutations and genetic variations linked to neurological phenotypes. Thus, the field of Neurogenetics fully reflects the general need that the HVP initiative pursues to fulfill, namely to curate all genetic variation affecting human health and to facilitate a proper use of this information by researchers and clinicians for the public good. A number of LSDBs are already available for neurological conditions, most of them developed with the efforts of individual research groups, with variable amount and structure of information between them. A complex genotype to phenotype relationship poses additional challenges for neurogenetic databases, such as: 1) Ascertainment of neurological phenotypes (clinical overlap of different disorders, subjective measures and scales, time-dependent features, need for consensus phenotypic descriptors and classifications, etc); 2) Shared pathogenic mechanisms and biological routes by different diseases; 3) Frequent genetic heterogeneity in neurological disorders (same phenotype, different genetic basis); 4) Not less frequent phenotypic variability (same mutation, different phenotypic expression); 5) Mitochondrial disorders with their particular mode of inheritance, phenotype variability, genotyping and assessment of pathogenicity difficulties; 6) Peculiarities of mutation nomenclature and genotype-phenotype correlation for repeat-expansion mutations, the cause of a number of neurological diseases. A quick overview of the current landscape of available neurological LSDBs shows that uncoordinated initiatives are likely to lead to incompleteness, discontinuation, unnecessary redundancy and even contradictory information between different databases.

The main question that raised the need for today's meeting is: What can be done to help coordinate and accelerate this process for the neurological disorders? We suggest that syndrome-based consortia should undertake the construction of specific LSDBs. Previous initiatives, such as the InSiGHT Project for mismatch repair genes, may serve as a model of organization for such consortia, bringing together experts in the genotype, the biological mechanisms and the phenotype, establishing committees to accomplish the different tasks involved in curating. In turn, we suggest that a Neurogenetics database consortium within the Human Variome Project may be developed to work on common problems and solutions for neurogenetic LSDBs such as phenotype ontologies, nomenclature, algorithms for assessment of pathogenicity and informatics tools that should lead to integration and inter-navigation of the databases from the specific consortia. This global, coordinated approach, envisioned by the whole HVP initiative and applied to the disorders of the nervous system, is especially crucial to search for the most efficient use of funds in a time of economical constraint.