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NEUROGENETICS NEWS

Call for participation in the neurogenetics consortium within the Human Variome Project

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Abstract The rate of DNA variation discovery has accelerated the need to collate, store and interpret the data in a standardised coherent way and is becoming a critical step in maximising the impact of discovery on the understanding and treatment of human disease. This particularly applies to the field of neurology as neurological function is impaired in many human disorders. Furthermore, the field of neurogenetics has been proven to show remarkably complex genotype-to-phenotype relationships. To facilitate the collection of DNA sequence variation pertaining to neurogenetic disorders, we have initiated the "Neurogenetics Consortium" under the umbrella of the Human Variome Project. The Consortium's founding group consisted of basic researchers, clinicians, informaticians and database creators. This report outlines the strategic aims

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established at the preliminary meetings of the Neurogenetics Consortium and calls for the involvement of the wider neurogenetic community in enabling the development of this important resource.

Keywords Human Variome project · Neurogenetics consortium · Database · Genetic variation · Standardisation · Phenotype

Meeting report

The vision of the Human Variome Project (HVP) is to develop a global collaboration with the aim of building systems and strategies for the collection, storage, interpretation and sharing of human genetic variation and its implications for disease [1, 2]. To reach these objectives, the HVP is organised in working groups to produce consensus recommendations for areas such as variant nomenclature, clinical data collection, laboratory data collection, informatics data integration, ethics and other relevant issues. In addition to these problem-driven working groups, the HVP has two complementary approaches to ensure data collection: country-specific collections and disease-specific collections (see Roadmap at www.humanvariomeproject.org, adapted in Fig. 1) [3].

Neurological diseases are a particularly complex range of disorders. Neurological dysfunction is often insidious and progressive, with age-associated penetrance and with variable expressivity. Genetic and allelic heterogeneities are the norm, with many different disorders sharing phenotypic features in addition to biological mechanisms. This leads to a continuum of both phenotype and genotype in this group of diseases, hampering the construction of neurogenetic locus-specific databases (LSDBs) [4]. A neurologic diagnosis is best informed through longitudinal clinical observation, brain imaging and postmortem pathology, to which molecular genetics analysis of leucocyte DNA can make a major contribution. The latter may inform the development of novel targeted therapeutics and appropriate selection of patients for phase II clinical trials (for efficacy and to avoid adverse drug responses, based on an individual's molecular aetiology). A number of databases related to neurological diseases have already been developed, most of them thanks to individual efforts [5–7]. The routine use of these databases by both the research and clinic communities in their daily work reflects the fundamental need for these repositories [8]. However, databases maintained by resources of individual groups or centres are always at risk of no longer receiving the support they need. Furthermore, as the number of genetic variants associated with neurologic traits rapidly increases, the necessity for efficient organisation of the genotype-to-phenotype information becomes even more crucial. This is especially true if the opportunities of whole exome/genome sequencing are to be fully realised. Thus, with the objective of making a global and coordinated effort to develop this key resource for clinicians and researchers focused on neurogenetic disorders, a Neurogenetics Consortium (NGC)

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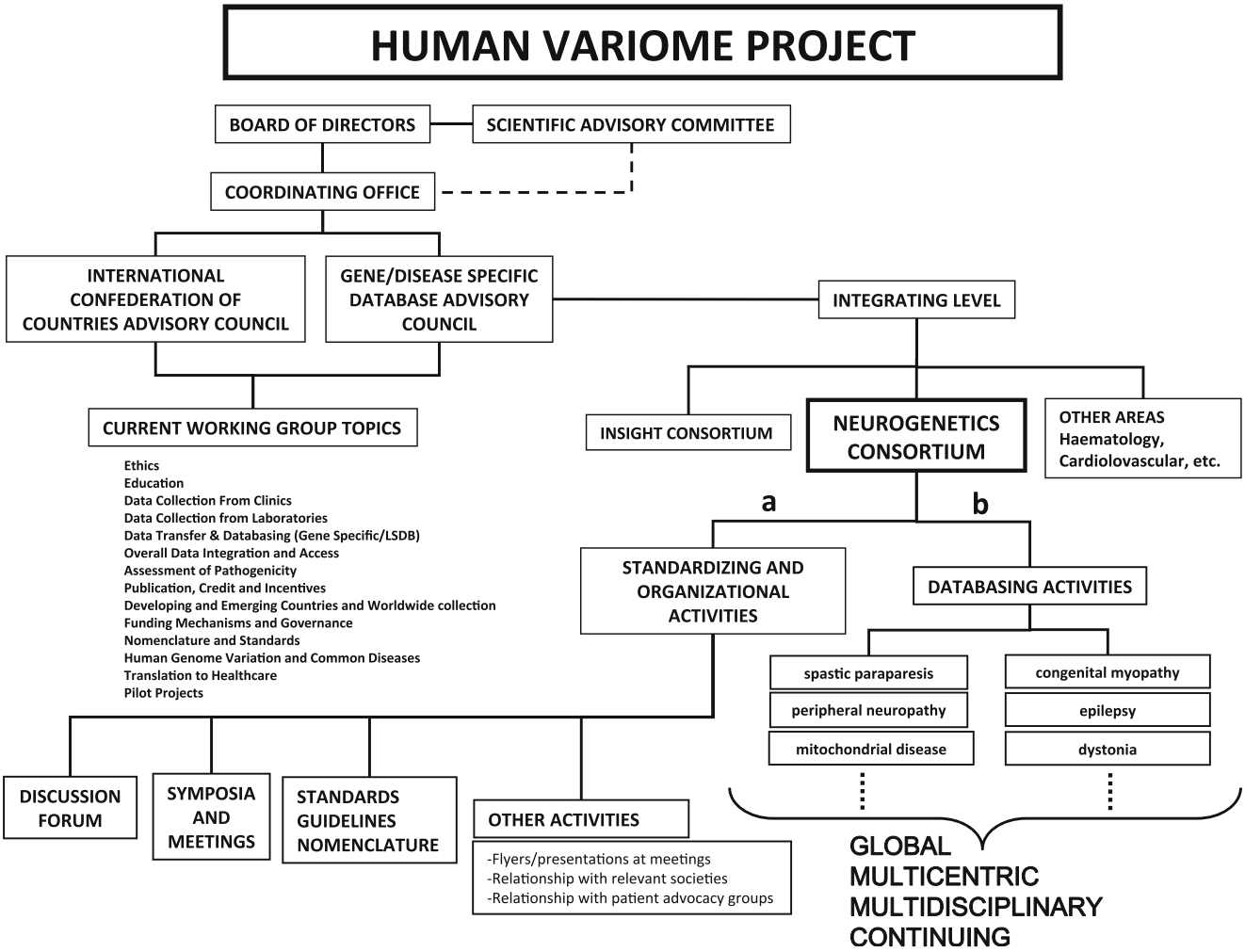

Fig. 1 Schematic representation of the potential organisation structure of the Neurogenetics Consortium and its relationship to other activities within the Human Variome Project. Two sets of actions will be needed: (*a*) those directed to meet standardisation and organisation goals and (*b*) activities dedicated to database development and curation by multidisciplinary, disease-centred, expert working groups

was initiated within the HVP. The aim of this consortium is to discuss the most important challenges and actions towards the construction of coordinated neurological LSDB resources.

The first meeting of the NGC was held in Honolulu, 19th October 2009, as a satellite of the American Society of Human Genetics meeting. It was a full-day meeting with over 70 attendees including expert speakers on neurogenetic disorders, researchers, informaticians and database curators. Among the main problems identified and discussed regarding neurogenetic LSDBs were:

1. The need for a coordinated and standardised system to collect and curate human variants and their associated clinical manifestations in LSDBs, this vision of the HVP being especially important for the field of neurogenetics.
2. Among the main reasons making the current neurological LSDBs inefficient are: (a) diverse structure and nomenclature of the existing databases; (b) lack of coverage for many genes/disorders; (c) duplication of efforts for some genes/disorders across independent databases, sometimes with overlapping or contradictory information; and (d) insufficient multidisciplinary knowledge in the curating teams. Much effort is lost when databases are constructed but there is no legacy plan developed to maintain the database after key individual(s) move on. Furthermore, "fossil" databases that are left behind uncurated could be subject to misuse by non-experts who may be unaware that the data are no longer current.
3. The need for standards and strategies for: (a) phenotype coding; (b) phenotype registration in the databases; (c) assessment of pathogenicity; (d) collection of specific types of variants relevant in neurogenetics (mitochondrial variations, repeat expansions, copy number variations); and (e) ethical and legal aspects, both general and specific to neurodegenerative disorders.

4. The need to capture and interpret the impact of genetic variants on complex disorders (e.g. as assessed by association studies), modifying genetic factors and epigenetics.

Other important issues regarding neurogenetic mutation databases brought up at the meeting were the lack of sufficient quality control of submissions, the frequently inadequate interpretation of mitochondrial variants, and the need for increased engagement from the clinical community and basic neuroscientists to achieve success in this endeavour.

The second meeting of the Neurogenetics consortium (UNESCO headquarters, Paris, 10th May 2010) was a follow-up of the inaugural meeting. The main points raised and discussed at the meeting, as well as proposed strategies and directions, were:

1. It was emphasized that it would be advantageous to have neurogenetic databases tailored towards specific diseases or syndromes (Fig. 1), allowing database queries for clinical terms as well as by gene. This would enable usage in both clinical and research settings, ultimately improving the health of patients with inherited neurological conditions. During the course of the meeting, several existing databases, both in-house and publicly available, were demonstrated, ranging from approaches based largely on collecting data from the literature to those that were used in clinical settings to collect longitudinal data. Commitments were undertaken to explore database construction/amalgamation for motor neuron diseases, Charcot–Marie–Tooth disease (CMT)/hereditary sensory neuropathies, mitochondrial diseases and disorders related to mutations in genes for neuromuscular ion channels. A working meeting for the hereditary spastic paraparesis/motor neuron disease mutation database occurred in September 2010.
2. Country-driven initiatives may be a very useful complement to international, disease-centred working groups. Country nodes should facilitate local collection of genetic variants under specific cultural, ethical and legal frameworks. In this respect, two pilot country-centred initiatives were described from Italy (for hereditary spastic paraplegias) and Spain (for CMT) with the ultimate aims of establishing an international network of experts to aid database curation and establish a global registry. One possible option for the envisioned NGC is to build networks of such country-wide disease-specific databases all linked at an operational level. This approach would help ensure maximum integration and minimum overlap.
3. To allow interoperability between such networks, efforts are being made to address uncontrolled vocabulary use in phenotype description, e.g. as in the Human Phenotype Ontology described at the meeting by Peter Robinson [9]. Standardisation of platforms was discussed in depth, as well as database structure and the integration of networks of databases. Demonstration of the Leiden Open Variation Database by Johan den Dunnen showed how this particular platform could be used to create either a disease or gene "front-end". Another suggestion was to implement a "Wiki-like" format and environment.
4. The quality and interpretation of data was the focus of several talks. Accurate assignment of pathogenicity is of utmost importance, and even though there is no "gold standard", it is reassuringly apparent that independent groups have developed similar systems/pipelines to analyse variants in both nuclear and mitochondrial genomes. Where the development of these databases will excel is the coherent, accurate inclusion of all relevant data related to genotype, phenotype, family history, healthy controls and functional studies to facilitate a more accurate interpretation for clinicians and their patients.
5. Patient access and input were discussed, e.g. the possibility that patients could enter their own longitudinal phenotypic data. The advantages and disadvantages of this approach were discussed at length. Concerns included the lack of standardised phenotype descriptors and the ethics involved in such a venture. Most participants agreed, however, that patient involvement would be positive and useful. It was also agreed that the consortia should participate in and be overseen by the HVP ethics working group.
6. The importance of involving a wide range of experts, such as population geneticists in database curation, was highlighted by two presentations on mitochondrial genetics, a field in which the lack of phylogenetic knowledge has caused a number of errors in the literature [10]. This is of particular importance as it is estimated that up to 1 in 200 people carry a pathological mtDNA mutation.

In summary, the field of neurogenetics is extensive and the confluence of many experts will be needed in systematic attempts to collect and annotate as much of the relevant data as possible in order to build high-quality databases of genetic variation and its significance. The issues related to information and data collection for different neurogenetic disorders should be worked out in a coordinated manner if the best possible level of integration is sought. Funding support will be a key issue to provide the necessary continuity and to guarantee the delivery of open-access, high-quality and up-to-date information. Involvement of the wider neurogenetics community as a whole, including patient advocates, will be crucial and is highly encouraged. To this end, we invite all members of the neurogenetics community worldwide to join this effort, which we believe will be for a widespread benefit

of patients suffering from neurological disorders. If you are interested in joining this effort, you can write to the corresponding author of this paper, María-Jesús Sobrido, and/or join as a Human Variome Project Consortium member free of charge on the Human Variome Project web site www.humanvariomeproject.org

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