

Everyday Problems For A Diagnostic Neurogenetics Laboratory.

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Interpretation of results, particularly those analyses that involve DNA sequencing, is increasingly difficult. Up to 50% of variants found by our laboratory have not been described in the literature, have not previously been detected in either controls or other affected individuals and do not appear on any available public databases. While standard criteria are used to establish pathogenicity, these data are often inconclusive, particularly for missense variants. This has important implications for patient management and counselling. Accurate interpretation of variants detected is required to determine disease mechanisms, modes of inheritance and allow predictive and prenatal diagnosis to be offered to the family.

Currently, the established criteria to assess novel DNA variants include conservation across species, protein prediction, splice site prediction, functional assays, control data, segregation in the family, publication, and presence on LSDBs. Recent software, for example ALAMUT, have streamlined and standardised this process. However, as with all data mining tools the output is dependent upon the databases and resources searched and it is not uncommon for the results of such analyses to be ambiguous and on occasion incorrect.

A number of LSDBs are well funded, well curated and up to date. In addition the diagnostic genetic laboratory community in the UK has access to a curated database, DMuDB, where data can be deposited and viewed securely. However, at present there is no facility to include any additional data e.g. data on control individuals, functional work and phenotype. Ironically there is a wealth of data around, which is being gathered daily by many tens of individual laboratories working in relative isolation. This is particularly true of specialist areas, such as Neurogenetics, where there are one or two laboratories per country with significant scientific and clinical expertise in a particular group of diseases. Furthermore, as new technologies are introduced in routine diagnostic laboratories, the volume of data that cannot be accurately interpreted will only increase. It will be a case of technology overtaking our knowledge base.

A global, curated and extensive LSDB is a viable solution to the problems described above. However producing yet another 'list' of variants should be avoided, so while the variants may form the core of the database, additional information is essential and should include frequencies of pathogenic and non-pathogenic variants within affected and non-affected populations, ethnicity of patients and controls, as well as functional data and importantly clinical input in the form of reliable phenotypic data. Access to this data will not only allow accurate interpretation of variants detected but also avoid unnecessary duplication of expensive and time consuming work.

To illustrate the challenges facing the diagnostic community a number of cases will be presented from a spectrum of Neurological disorders with emphasis on the impact for the patient and their clinician. They will be discussed with reference to how the quality of a diagnostic service could be improved with access to such a database.