

What is NGRL Manchester doing to help support unclassified variant interpretation?

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Introduction

The development of the Practice Guidelines for the Interpretation and Reporting of Unclassified Variants (UVs) in Clinical Molecular Genetics provided a good opportunity to see how relevant NGRL Manchester's work in informatics, quality assurance and technology assessment has been to this area, and to steer future work in the right direction. This poster shows what work we are doing, and where we are going.

Guideline development

Supporting guideline development and maintenance is one component of NGRL's Quality Assurance theme. For the UV guidelines NGRL collaborated with the CMGS and VKGL in The Netherlands to help facilitate the workshop and discussions involved in the guideline development.

Technology assessment

NGRL has undertaken an assessment of the software tool Alamut from Interactive Biosoftware. Alamut is a decision-support software application designed to help molecular geneticists with variant diagnostics. It combines data from many sources with in-silico prediction methods to help interpret variants, and these correspond with the lines of evidence specified in the UV guidelines. By working with Interactive Biosoftware NGRL has been able to highlight the exact requirements of the guidelines and thus help Alamut evolve into a tool that meets the needs of diagnostic molecular genetics. A report on the assessment will be issued in the near future.

Variants Found												
	Gene	Reference Sequence	URL	Name	Exon	Sample ID	Variant Type	AA Change Type	Genotype	Interpretation	Int. Reasons	Browser
Edit	BRCA1	U14880	NCD	c.823G>A	11	1	substitution	Missense	Heterozygous	Unclassified		Browser
Edit	BRCA1	U14880	NCD	c.115T>C	3	1	substitution	Missense	Heterozygous	Unclassified		Browser
Edit	BRCA1	U14880	NCD	c.787_798delTT	11	1	deletion	Frameshift	Heterozygous	Pathogenic		Browser

DMuDB variant data, showing co-occurrence of pathogenic and unclassified variants

Developing informatic tools

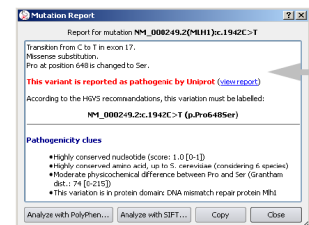
DMuDB, the Diagnostic Mutation Database, (www.dmu-db.net) is a central part of NGRL Manchester's Informatics theme. It is designed to be a central, confidential repository of variant data generated by UK diagnostic laboratories which allows details of interpretations to be shared and data on the occurrence of unclassified variants to be aggregated. One relevant aspect of DMuDB is its ability to show co-occurrences of UVs with known pathogenic variants and for this knowledge to be shared with other labs.

DMuDB now contains over 10,000 individual variant records. These include 396 and 455 unique variants respectively for BRCA1 and 2, around 50% of which are not present in BIC. Diseases/genes that currently have information in DMuDB include Breast Cancer (BRCA1, BRCA2), Lowe Syndrome (OCRL), Sotos Syndrome (NSD1), HNPCC (MLH1, MSH2), Cystic Fibrosis (CFTR), X-Linked Retinitis Pigmentosa (XLRP), Neurofibromatosis Type I&II (NF1, NF2), Alstrom Syndrome (ALMS1), CADASIL (NSD1), Familial adenomatous polyposis (APC) and Muscular Dystrophy (DMD). Any other gene can be easily set up to accept data.



Practice guidelines for the interpretation and reporting of Unclassified Variants (UVs) in Clinical Molecular Genetics

- External Quality assessment
- Mutation nomenclature
- Mutation submission
- Mutation databases
- Co-occurrence
- Species conservation
- In-silico prediction
- In-silico splice-site prediction
- Presence in SNP databases



A variant report from Alamut

Building links

NGRL maintains and builds links with organisations and projects nationally and internationally to support its work programme. These help us to develop new projects and to represent the needs of diagnostic laboratories.

Recently, we took advantage of EB's 'geek for a week' programme, which allows a member of staff to spend a period of attachment alongside the bioinformatic team behind Ensembl. One of the ideas that we developed is a repository of species alignments in order to meet the requirements of the UV guidelines and to ensure that all labs are using the same sets of data. We also discussed options to allow Ensembl to display data in HGVS coordinates.

NGRL is also a partner in the EU Framework 7 project Gen2Phen, which seeks to unify genetic variation and phenotype databases through tool and technology development, in particular by developing the Ensembl browser. Other partners include those behind mutation database projects LOVD and UMD, and nomenclature tools such as Mutalyser. NGRL will ensure that the needs of diagnostic and clinical users are represented, and the UV guidelines help us to demonstrate these needs.

HGVS Nomenclature	Alternative Name	Exon	Protein/Feature	Type	SEC	STRAND	dbSNP
c.823G>A	823G	11	substitution	5	+	+	
c.115T>C	115T	3	substitution	4	+	+	
c.787_798delTT	787-798	11	deletion	5	+	+	

The Universal Browser, showing tabulated and graphical views of variant data from different sources

The **NGRL Universal Browser** has been developed to display variant information graphically on a DNA sequence using HGVS nomenclature. Originally designed to be used with DMuDB, the browser can accept data from multiple sources and present them on the same display (ngri.man.ac.uk/Browser/).

Currently all genes on the UK Genetic Testing Network (UKGTN) website are covered by the browser, and variant data from dbSNP, the Breast Cancer Information Core Database, DMuDB and now the MMR Genes Variant Database are accessible. The Universal Browser therefore allows laboratories to look for variants in dbSNP using HGVS nomenclature, and for an increasing number of genes to combine this with variant data from other laboratories and variant databases.

Training

In response to requests from the molecular and cytogenetics communities, NGRL recently delivered a course entitled 'Bioinformatics for cytogeneticists and molecular geneticists'. The course introduced the participants to computing and bioinformatics before providing more specialised guidance on the Decipher database and on the application of bioinformatic resources in support of the UV guidelines. The course was well supported: there were 21 participants and many bookings have already been received for the next course on 9-10 September 2008 – see the www.nowgen.org.uk events pages for details.

Future work

NGRL Manchester's work programme will continue to address UV interpretation. We will:

- Continue to collect variant data and develop DMuDB and the Universal Browser – let us know which genes to target next
- Provide training in bioinformatic tool use – let us know if different courses/formats are needed
- Collaborate with others to ensure that tools and services meet diagnostic lab needs – let us know what you think of them
- Devise new projects to address laboratories' concerns – let us know what you need.