



Meeting
Report

A meeting to establish a
steering group for the
Diagnostic Mutation Database
(DMuDB)

May 2006

Title	A meeting to establish a steering group for the Diagnostic Mutation Database (DMuDB)
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Contributors	Organisation
Diana van Gent	NGRL(Manchester)
Andrew Devereau	
Ed Burke	
Marina Reeves	

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 An electronic version of this report can be downloaded free of charge from the NGRL website (www.ngrl.org.uk/Manchester/Publications) or by contacting:

National Genetics Reference Laboratory (Manchester)
 St Mary's Hospital
 Hathersage Road
 Manchester M13 0JH
 United Kingdom

Phone: +44 (0)161 276 8716
 Fax: +44 (0)161 276 6606

Email

andrew.devereau@cmmc.nhs.uk
edward.burke@cmmc.nhs.uk

Funded by the United Kingdom:



Meeting Attendees :

Andrew Devereau	NGRL(Manchester)
Ed Burke	NGRL(Manchester)
Marina Reeves	NGRL(Manchester) <i>Minutes</i>
Graham Taylor	Yorkshire Regional DNA Laboratory
Alastair Brown	MRC Human Genetics Unit, Edinburgh
Dick Cotton	Human Genomic Variation Society
Ann Curtis	Northern Molecular Genetics Diagnostic Service
Johan den Dunnen	Leiden University Medical Centre
Ian Frayling	All Wales Laboratory Genetics Service
Andrew Read	Emeritus Professor of Human Genetics, University of Manchester
Melissa Winter	Genetic Interest Group

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1. Introduction

Diagnostic molecular genetics laboratories in the UK analyse and report hundreds of mutations per year for a range of inherited diseases, some of them very rare. They are able to link the mutations to detailed phenotypic data, and work to accredited quality assurance standards, so the data are of high and measurable quality. However the mutation data that they generate are not generally added to the many online databases which exist for single or multiple genes, or reported in journal publications and thereby added to online literature and gene databases. This valuable source of mutation data is therefore not open to diagnostic laboratories and the wider genetics community for the support of diagnostic work. The barrier to sharing of the data is not the lack of suitable databases or journals to contain the data, or the means of accessing them, but the time and effort that are required to submit the data.

The diagnostic mutation database (DMuDB) project was established to provide a route for sharing mutation data within and between diagnostic laboratories in the UK and for publishing mutations from diagnostic labs, thereby unlocking this valuable resource to benefit patient diagnostic services. DMuDB is designed to allow easy submission of data which can then be shared with other laboratories while protecting patient confidentiality, and to be a route to allow publication of the data to existing databases.

DMuDB is being developed by NGRL (Manchester) and Certus Technology Associates Ltd. It has now reached the stage of a fully working prototype system. As it has been developed, issues such as standardisation of nomenclature and terminology, policies for protection of data and appropriate access to it, publication of the data and overall direction of the project have become increasingly important, and have emphasised the need for a steering group to oversee the project.

On 24 February 2006 a meeting was held at the Nowgen Centre in Manchester to establish a steering group to oversee the DMuDB project. This document firstly introduces the DMuDB project and presents its progress to date, and a summary of the meeting outcomes.

2. Project progress

2.1 Prototype development

The DMuDB database model was developed at NGRL(M) drawing on discussions with scientists involved in providing diagnostic services. It is shown in Figure 1.

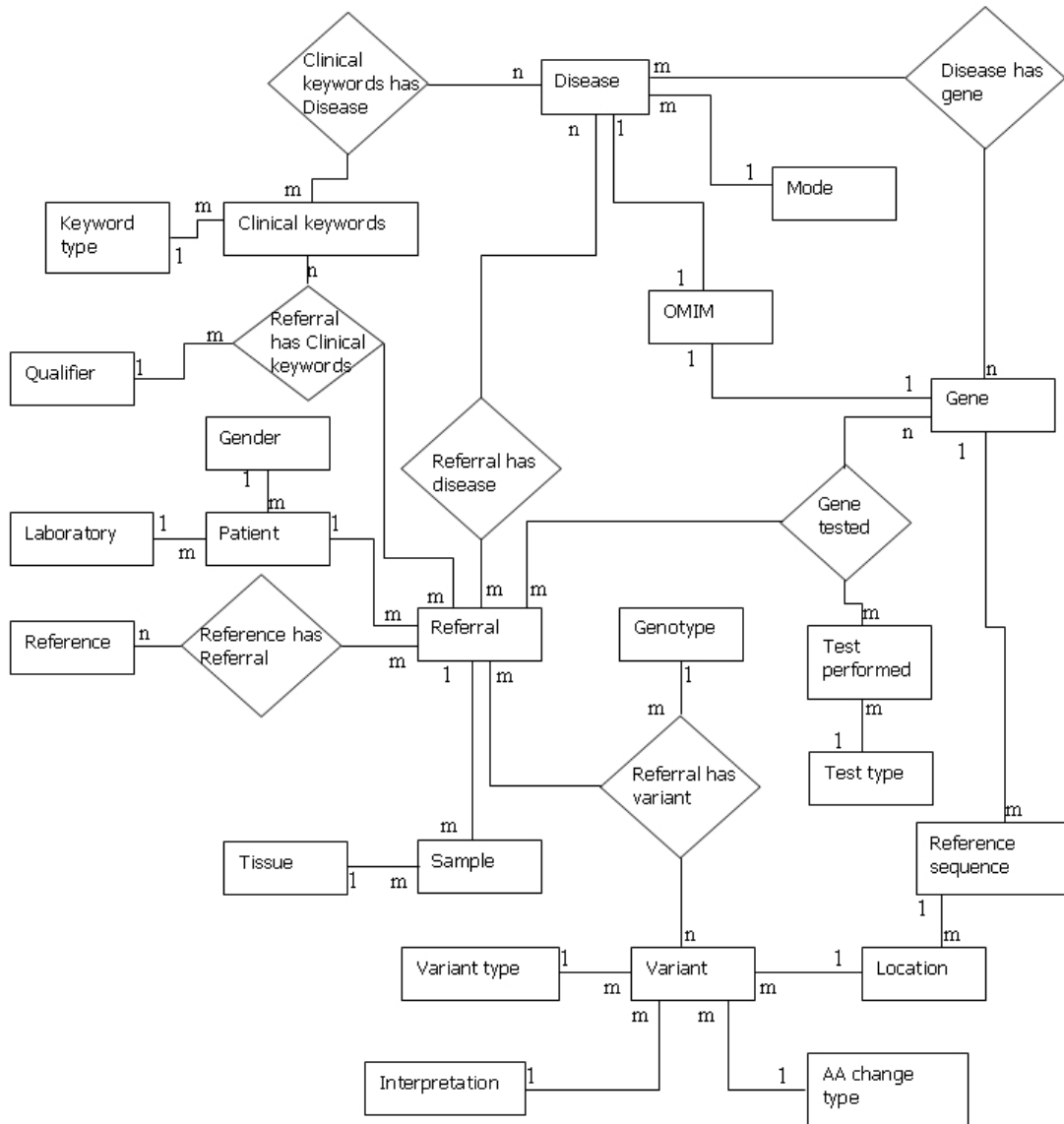


Figure 1. The database model used for the repository

Certus Technology Associates Ltd. have developed the current prototype repository from this model and the specification agreed with NGRL(M). The first prototype was made available to a

limited number of test sites in April 2005 and was presented that year at the Clinical Molecular Genetics Society (CMGS) conference in Salisbury.

The DMuDB repository is available on a secure web server at <https://secure.dmu-db.net>. NGRL(M) curate DMuDB and are responsible for issuing user names and passwords. There is currently no information available on the site for unregistered users.

During the pilot phase submission of data for Neurofibromatosis types I and II (NF1 and NF2), Cystic fibrosis (CFTR), Familial Breast Cancer (BRCA2) and Alstrom syndrome (ALMS1) have been assessed and highlighted important issues concerning the maintenance of data quality.

Key points in assuring the quality and security of data entered to the DMuDB are:

Submission to DMuDB – Aiming to mirror the flow of samples through a diagnostic laboratory, entries into DMuDB are centred around the referral. An extensive dataset is collected to allow an analysis of phenotype and genotype correlations.

Approval of Database Entries - All referral sample results submitted to DMuDB must first be approved by a named senior scientist from the submitting laboratory, who checks through the submitted data and can compare it to issued clinical reports, to ensure that the data is accurate and adheres to the controlled vocabulary used in the database.

Data Ownership - Data contained in DMuDB have an appointed “awaiting approval” or “approved” status. Once data have been approved they can either be visible to the submitting laboratory only or to all subscribers to DMuDB. Accessibility can be changed at any time, allowing the laboratory to maintain ownership of the data once submitted.

Database Permissions - Different levels of data access can be given to each submitting individual by the database administrator. Some users will only be allowed to submit data for approval, whereas others will be able to approve data as well as edit and withdraw existing data. Only the curators are able to assign and amend permissions.

Security - The database is hosted on a secure web server and a username and password is required to access the data.

Pseudonymisation - When submitting data a laboratory identifier can be used to allow data held in DMuDB to be re-associated with the laboratory database. To preserve confidentiality the laboratory identifier is pseudonymised using software developed in conjunction with the University of Manchester. It is only the original submitting laboratory that can then convert these pseudonyms back to their laboratory identifiers.

The repository is organised as a series of different areas. Different levels of permissions are available for each user: these are controlled by the curators, and give access to the different areas of the repository and control the ability of users to submit and approve records in the

repository. Users are also associated with a laboratory and therefore with an institutional management and accountability structure. Draft data are visible only to users from the same laboratory as the data submitter, and approved data (see below for details of the data submission and approval process) are only visible to users from other laboratories when each record is marked as 'public'. The ability to withdraw, re-edit or re-identify data records remains with the laboratory of the original data submitter.

The following sections demonstrate the operation of the repository.

2.2 Administration

The curators have access to the administration area of the repository. This allows curation of users and laboratories; gene, reference sequence and disease information; lists of controlled terms including clinical keywords (describing phenotypes), genetic test types, tissue types, interpretations, mutation types and predicted consequences of mutations; an audit trail showing records of each action carried out by repository users; the report manager which is used in the graphical interface (see section 2.4); and the Resource Admin which allows details of the repository display, such as column headings, to be changed. This is provided to allow some degree of customisation without recourse to the repository developers. Figure 2 shows a typical administration screen, in this case showing details of one of the diseases held in the repository.

The screenshot shows the DMuDB (Diagnostic Mutation Database) administration interface. The header includes the logo 'DMu DB' and the text 'Diagnostic Mutation Database'. A navigation menu on the left lists various administration functions: User Accounts, People and Labs, Audit, Laboratories, Configuration (highlighted), Clinical Keyword, Qualifier, Ethnicity, Tissue Type, Variant Type, Amino Acid Change Type, Reference Sequence, Gene, Disease, Test Type, Interpretation, Location, Report Manager, and Resource Admin. The main content area displays details for 'Alstrom Syndrome', including its description, OMM Number (203800), Mode (Autosomal Recessive), and Status (Active). Below this, there is a table of associated genes with columns for Name and OMM. The gene 'ALMS1' is listed with OMM number '606844'. The interface also includes buttons for 'Save', 'Cancel', 'Reset', and 'Delete', as well as 'Keywords' and 'Genes' tabs.

Figure 2. An administration screen showing details of a disease. Other administration functions are shown on the left

2.3 Data submission

The database model in Figure 1 shows how the repository is based around referrals, i.e. individual clinical cases, rather than mutations. Each referral represents an episode of testing for a patient in which one or more mutations were discovered. Data are therefore entered as referrals. This may be done 'manually' by initiating a new referral and typing in the data, or in bulk by preparing an XML encoded file of referrals. Once submitted, each type of referral is treated in the same way.

Bulk submission of referrals can only be made by the curators at present. They are made by firstly arranging the data into columns on a spreadsheet, with each row of the spreadsheet representing a single referral. This is converted into an XML file using a programme developed at NGRl. The XML file content or 'schema' was developed by Certus Technology to match the database model. The XML encoded referrals are loaded into the repository using the Repository Loader module which is shown in

Figure 3. A report is generated which identifies any errors or missing data in the submitted referrals. The bulk loading process is shown schematically in Figure 4.

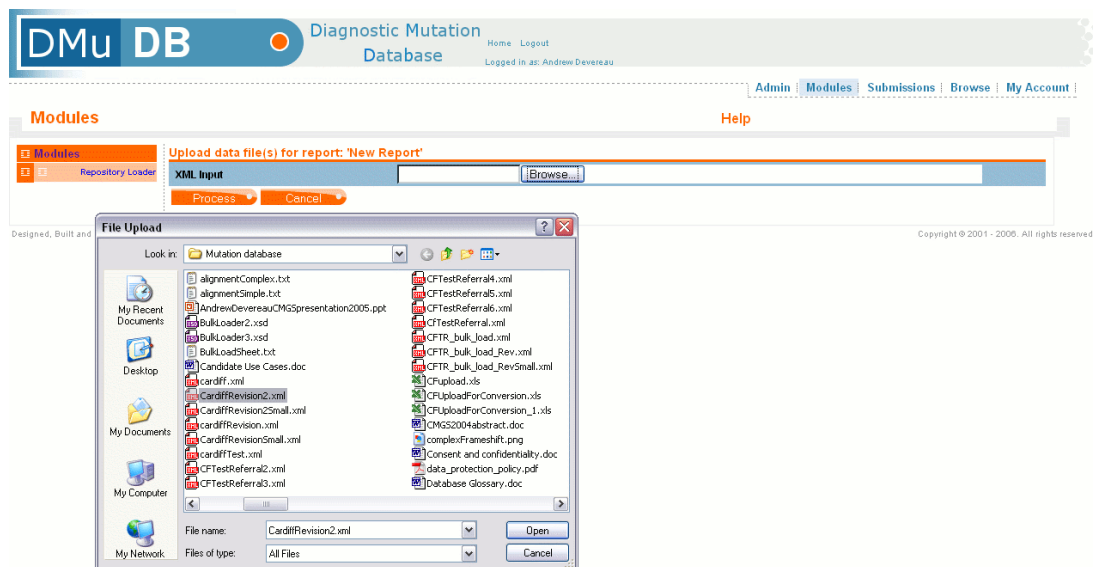


Figure 3. Uploading an XML file of referrals into the repository

	H	I	J	K	L	M	N	O	P	Q	R	S
	8	9	10		11	12	13	14	15	16	17	18
2				test		sample 1		sample 2		sample 3		variant 1
3	date	disease	gene	description	test	tissue type	id	tissue type	id	tissue type	id	name
4	07/03/2003	219700	602421		CF29	blood	1					I148T
5	13/11/2002	219700	602421		CF29	blood	1					deltaF508
6	16/03/2005	219700	602421	exon 18 sequence analysis	Sequencing	DNA	1					c.3600 G> A
7	08/03/2005	219700	602421	R117H ARMS PCR	ARMS	Buccal	1					R117H
8	17/03/2005	219700	602421	DeltaF/DeltaI gel exon 10 cystic fibrosis	PCR-PAGE	DNA	1					deltaF508
9	17/03/2005	219700	602421	DeltaF/DeltaI gel exon 10 cystic fibrosis	PCR-PAGE	DNA	1					deltaF508
10	14/10/2002	219700	602421		CF29	blood	1					deltaF508

Excel spreadsheet



```

<patient>
<id>BPmZRiPKc.IvYvAmD7X54lk4qELu2q12++RmjvTPchAJhs15DjorqD3d/JEflIA+8X3wB+K9v2ndWalWrtdDKexoFVEskZQZK3Ac7/U0Y=GAWMO</id>
<patient-details>
<gender>3</gender>
<ethnicity>Not Specified</ethnicity>
<region>Not Specified</region>
</patient-details>
<referral>
<submittingLab>Cardiff</submittingLab>
<case-notes>Age at Referral 5.5. Reference Griffiths et al., 2006. NIH Criteria for clinical diagnosis of NF1 n/a</case-notes>
<disease>
<omim>162200</omim>
</disease>
<gene>
<omim>162200</omim>
<description/>
<test>
<name>Not Specified</name>
</test>
</referral>
</patient>
</sample>
<tissue-type>Not Specified</tissue-type>
<id>1</id>
</sample>
    
```

XML document



Referrals in DMuDB

Referral ID	Referral Date	Created On	Created By	Data Source
00306	16 Mar 2005	28 Nov 2005 13:44	Andrew Devereau	CFTR_bulk_load_Rev
00307	08 Mar 2005	28 Nov 2005 13:44	Andrew Devereau	CFTR_bulk_load_Rev
00308	17 Mar 2005	28 Nov 2005 13:44	Andrew Devereau	CFTR_bulk_load_Rev
00309	17 Mar 2005	28 Nov 2005 13:44	Andrew Devereau	CFTR_bulk_load_Rev
00310	14 Oct 2002	28 Nov 2005 13:44	Andrew Devereau	CFTR_bulk_load_Rev

Figure 4. Bulk loading of referrals

The Submission area of the repository allows manual data entry and holds all draft submissions before they are passed on for approval. Bulk loaded referrals are placed into the 'New' folder of the submission area while manually entered referrals are placed in the 'Draft' folder – both folders provide the same ability to edit individual referrals, remove them or submit them to the Awaiting Approval area. Figure 5 shows a flow chart of the submission process. New manual referrals are created by entering data in a stepwise process which follows the content of the referral records. An example of a referral record is shown in Figure 6.

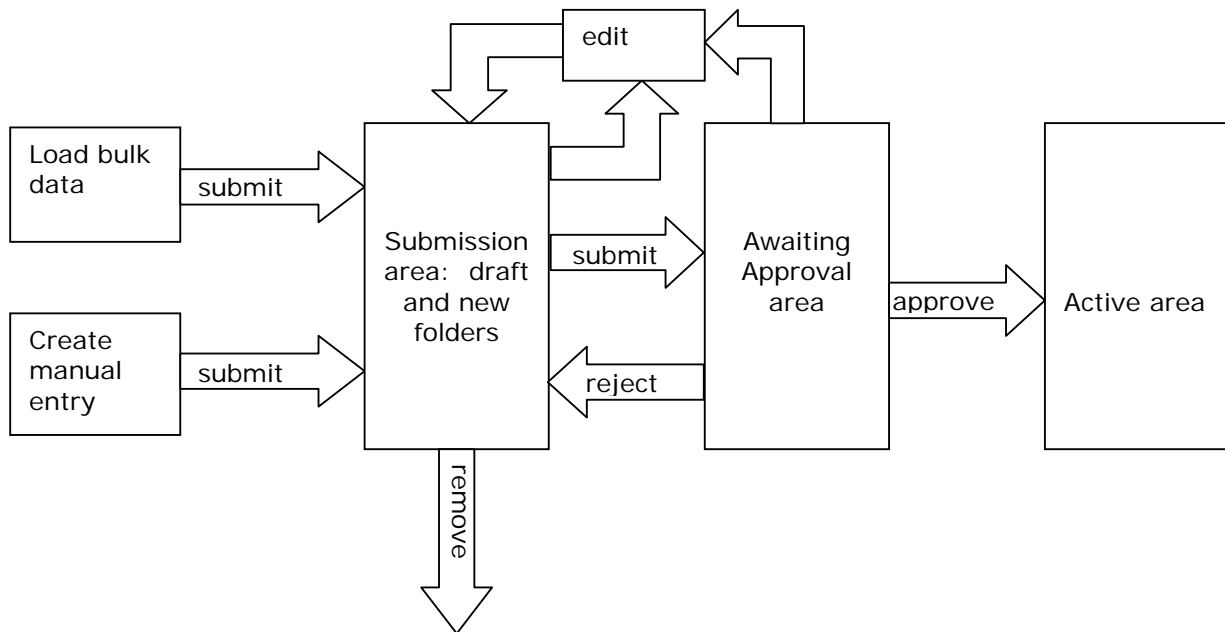


Figure 5. Flow chart showing passage of a referral through the submission and approval process

A patient identifier is used when entering the referral. A pseudonym is used to preserve patient confidentiality while maintaining the ability to re-identify patients from referrals. Currently a separate programme is used to generate pseudonyms: it was designed by the Department of Computer Science at the University of Manchester and implemented by NGRL using industry standard encryption algorithms. The identifier encrypted can be any piece of data: it is safe to use patients' names or similar personal identifiers, but to date laboratories have chosen to use their internal sample identifiers. The pseudonyms are not displayed in the repository but are replaced by a unique referral identifier.

Referral

Referral Identifier	00053
Submitting Lab	NGRL(M)
Submission Date	22 Mar 2005 10:15
Approval Date	11 Jan 2006 17:44

Diseases

Name	OMM	Mode
Neurofibromatosis, Type II	101000	Autosomal Dominant

Phenotype

Qualifier	Keyword	Quantity
Affected	Neurofibromatosis II	

Samples

Sample ID	Tissue Type
1	Peripheral lymphocyte DNA
2	Tumour DNA

Genes Tested

Description	Gene Name	OMM	Tests Performed
	NF2	607379	SSCP/Heteroduplex, Sequencing, Loss of heterozygosity analysis

Variants

Gene	Reference Sequence	Location	Variant	HGVs Name	Exon/Intron	Sample ID	Variant Type	AA Change Type	Genotype	Interpretation
NF2	L11353.1	676	T>G	c.676-7T>G	7	1	substitution	Splice site variant	Heterozygous	Pathogenic
NF2	L11353.1	676	T>G	c.676-7T>G	7	2	substitution	Splice site variant	Heterozygous	Pathogenic
NF2	L11353.1	D228260	No LOH	No LOH	-	2	---	---	---	Non-pathogenic
NF2	L11353.1	D228275	No LOH	No LOH	-	1	---	---	---	Non-pathogenic
NF2	L11353.1	NF2CA3	No LOH	No LOH	-	2	---	---	---	Non-pathogenic

Figure 6. A typical referral entry in the repository

When a referral is complete it is moved to the Awaiting Approval area, shown in Figure 7. Only those users with the correct privileges are able to access this area. If a referral is rejected it goes back to the draft area. If approved it is moved to the Browse area of the repository. The history of who created and submitted each referral and the dates that they did this are attached to each referral.

Submit new Referrals to the repository

Referral Search Filter
Enter values to search the list of Referrals by.

Referral ID

Data Source

[New Referral](#) [Filter](#)

[Draft](#) [New](#) [Awaiting Approval](#) [Active](#) [Rework](#)

Referrals awaiting Approval Found 110 Records. Page 1 of 3.

1 2 3 Next

			Referral ID	Referral Date	Created On	Created By	Submitted For Approval On	Submitted For Approval By	Data Source	Submitting Lab
Edit	Reject	Approve	00054	22 Jul 2004	22 Mar 2005 10:18	Ed Burke	10 Feb 2006 16:11	Andrew Devereau	Manual	NGRL(M)
Edit	Reject	Approve	00072	25 Aug 2004	23 Mar 2005 13:25	Ed Burke	10 Feb 2006 16:14	Andrew Devereau	Manual	NGRL(M)
Edit	Reject	Approve	00079	24 Sep 2004	31 Mar 2005 10:10	Ed Burke	02 Dec 2005 16:36	Andrew Devereau	Manual	NGRL(M)
Edit	Reject	Approve	00082	01 Nov 2004	31 Mar 2005 10:49	Ed Burke	02 Dec 2005 16:36	Andrew Devereau	Manual	NGRL(M)
Edit	Reject	Approve	00087	21 Jan 2005	01 Apr 2005 09:37	Ed Burke	02 Dec 2005 16:36	Andrew Devereau	Manual	NGRL(M)
Edit	Reject	Approve	00090	25 Apr 2001	07 Apr 2005 14:48	David Gokhale	11 Nov 2005 16:19	Andrew Devereau	Manual	Mersey
Edit	Reject	Approve	00093	13 Oct 2004	14 Apr 2005	Andrew	11 Nov 2005 16:16	Andrew Devereau	Manual	NGRL(M)

Figure 7. The Awaiting Approval area of the repository. Draft referrals are placed here to be verified as correct by an authorised person.

Once approved the referral is considered to be verified as a correct representation of the data issued from the diagnostic laboratory. Approved referrals are listed in the Active area of the data submission area. Submitters are able to withdraw and re-work any of their active referrals at any time, re-submitting them to the Approval area when they have been reworked so that they are re-checked.

Referrals may be marked as having Public or Private visibility. Private referrals are only visible to users from the submitting laboratory even after they are approved and placed in the Browse area. This allows laboratories to use the repository to collect and display mutation data which they do not wish others to see, e.g. if it is part of a study which is to be published. The visibility can be changed by re-working the referrals.

2.4 Browsing the referrals

Users are able to browse through the approved referrals either using the text-based Browse area of the repository or using the separate graphically-based browser developed by NGRL. The former allows searches to be performed for genes, diseases or mutations. The results are presented as a table of relevant referrals with a summary of the mutations described for each, as shown in Figure 8. The table contents can be sorted in ascending or descending order for any of the data fields displayed. Each referral can be opened to display the referral information in full as shown for a typical case in Figure 6.

The graphical browser is a separate application that connects to the repository via a secure internet connection using the same username and password. After logging on the user is able to

choose from the list of genes for which data are held in the repository, and then choose a reference sequence for the chosen gene. This can be a different reference sequence from the one used to name the mutations in the repository, allowing, for example, either a genomic or a cDNA sequence to be used for the display of the same mutation data. The stored mutations are displayed against the chosen reference sequence as shown in Figure 9. Each mutation can be selected and the predicted amino acid changes displayed, and the details of all referrals which contain the mutation can be shown.

Browse Repository

Advanced repository search for Gene and Disease

Gene: Disease: Mutation:

Matching Referrals

1 | 2 3 Next Found 111 Records. Page 1 of 3.

	Referral ID	Sequence	Gene	Exon/intron	HGVS Name	Alternative Name	Mutation	AA Change
<input type="button" value="View"/>	00007	L11353.1	NF2	15	c.1737+1G>C	c.1737+1G>C	G>C	Splice site variant
<input type="button" value="View"/>	00008	L11353.1	NF2	2	c.191_194dup	195insTGCA	dupTGCA	Frameshift
<input type="button" value="View"/>	00009	L11353.1	NF2	-	Negative for c.41_42del	None found	None	---
<input type="button" value="View"/>	00009	L11353.1	NF2	1	c.41_42del	c.36delCT	delCT	Frameshift
<input type="button" value="View"/>	00009	L11353.1	NF2	1	c.41_42del	c.36delCT	delCT	Frameshift
<input type="button" value="View"/>	00009	L11353.1	NF2	-	LOH	LOH	LOH	---
<input type="button" value="View"/>	00010	L11353.1	NF2	7	c.676-7T>G	c.676-7T>G	T>G	Splice site variant
<input type="button" value="View"/>	00011	L11353.1	NF2	7	c.676-7T>G	c.676-7T>G	T>G	Splice site variant
<input type="button" value="View"/>	00012	L11353.1	NF2	-	LOH	LOH	LOH	---
<input type="button" value="View"/>	00012	L11353.1	NF2	-	LOH	LOH	LOH	---
<input type="button" value="View"/>	00012	L11353.1	NF2	-	LOH	LOH	LOH	---

Figure 8. Results of a search for mutations in a specific gene

Diagnostic Mutation Database Browser v0.1

File Edit DMuDB Variants Sequence Feature Help

L11353

```

1  acggcagccgctcagggaccgtcccccaactcccctcttcgctcagcagggtctctgcggccatgctggccgctggggaccgcgacccagacgctt
101 cccggccgcccagccgaccatggtggcctgaggcctgtgcagcaactccagggggctaaagggctcagagtcagccgctggggcgcgaggggtcc
201 cgggctgagccccgcgcatggcggggccatcgtctcccgcatgagcttcctctcagaggaagcaaccaagcgttcaccgtgaggatcgtc
    MetAlaGlyAlaIleAlaSerArgMetSerPheSerSerLeuLysArgLysGlnProLysThrPheThrValArgIleVal
    c.154delT
    c.154delC
301 accatggagccgagatggagttcaattgcagctgaagtggaaaggaaggaacctcttgattggtgtgccgactctggggctccgagaaacctggt
    ThrMetAspAlaGluMetGluPheAsnCysGluMetLysTrpLysGlyLysAspLeuPheAspLeuValCysArgThrLeuGlyLeuArgGluThrTrpPhe
401 tctttgactgcagtcacaatcaaggacacagtgccctggctcaaatggacaagaagctactggatcatgatttcaaggaagaaccagtcacctt
    PhePheGlyLeuGlnTyrThrIleLysAspThrValAlaIleLysMetAspLysLysValLeuAspHisAspValSerLysGluGluProValThrPhe
    c.191_194dup
    c.211G>A
501 tcactcttggccaaatttatcctgagaatgctgaagaggctggttcaggagatcacacaacatttatctcttaccagttaagaagcagatttta
    PheHisPheLeuAlaLysPheTyrProGluAsnAlaGluGluGluLeuValGlnGluIleThrGlnHisLeuPheLeuGlnValLysGlnIleLeu
    
```

Sequence Overview

Exon, Poly-p & s, Site, CDS, Variants

DMuDB	Gene	Reference S...	Location	Mutation	HGVS Name	Alternative N...	Exon	Variant Type	AA Change Type	Status
	NF2	L11353.1	15	delT	c.154delT		1	Deletion	Nonsense	valid
	NF2	L11353.1	1737+1	G>C	c.1737+1G>C	1737+1G>C	15	Substitution	Splice site	valid
	NF2	L11353.1	715	del	c.715del		8	Deletion	missense	valid

232 to 234 | 13 to 15 | 5

Figure 9. The graphical mutation browser. The large I marks in the sequence show the intron positions and can be expanded to allow intronic variants to be displayed.

2.5 Mutation Nomenclature

HGVS nomenclature for mutations has been adopted as a standard for DMuDB. Mutation data are held in the repository in separate fields which represent the reference sequence used, the mutation location in the sequence, and the mutation itself. An additional field is provided to hold the complete mutation name in HGVS format, and a further field allows an additional name to be used, e.g. a legacy or protein level name.

NGRL(M) are developing software to assist with accurate assignment of mutation nomenclature. Mutation nomenclature guidelines (e.g. from HGVS, the Human Genome Variation Society) and reference sequences can change, as can the way that they are interpreted, making it difficult to know if two reported mutations are describing the same change. This will be a particular problem within the mutation database where mutation data are being collected from different sources. There is therefore a need for software to convert sequence trace data and a selected reference sequence into mutation nomenclature based on a defined standard. This software is still in its prototype phase and has yet to be released for testing by the molecular genetics community. At present it allows alignment of .ab1 trace files against GenBank reference sequence files (Figure 3) and generates HGVS nomenclature for nucleotide and predicted amino acid mutant sequences. Frameshift mutations are dealt with by ambiguous base calling. Further file formats will be included in the future and base calling using *Phred* will be incorporated. *Phred* reads DNA sequence chromatogram files and analyzes base peaks, assigning quality scores ("Phred scores") to each base call.

3. Summary of Key Outcomes from the Meeting

Steering Group Role and Organisation	
Steering Group Membership and data access	<p>Adopt appropriate Terms of Reference for the group</p> <p>Approach professional societies to approve representation on the group</p> <p>Access to the database to be primarily for laboratories but wider access to be investigated</p>
Committee Interaction	<p>Two to three group meetings to be held in 2006.</p> <p>Reduce physical meeting to once per year thereafter and establish a discussion forum.</p>
Administrative	<p>Information within the repository on individual genes and diseases to be maintained by chosen experts.</p> <p>More extensive automated data checking should be investigated</p>
Key Policies	
Standards	<p>HGVS nomenclature was confirmed as the standard for mutation identification.</p> <p>Laboratories will be allowed to submit data against a reference sequence of their choice</p>
Project Scope	<p>Single gene disorders to be included, and gene expansions to be investigated.</p> <p>RNA data collection to be investigated</p>
Terminology	<p>Terminology was agreed for representation of tissue types, mutation interpretation and test types, and the term 'predicted consequence' was preferred to 'amino acid change'.</p>

Appendix A : Agenda of DMuDB Meeting

1. Project description and update

- a. Aims and objectives of the project
- b. Update and demonstration of the database and software

2. Role and organisation of the steering group

- a. Agreement on the role of the steering group and how it should function
- b. Steering group membership
- c. Other administrative roles for the project, e.g. expert roles for curating gene and disease data.

3. Key policy decisions

- a. Standards for mutations, reference sequences etc.
- b. Project scope, e.g. genes/diseases or types of mutation data to include/not include in the project
- c. Data approval process
- d. Access to database, secondary use of data, publication of data and relationship to other database projects
- e. Phenotype representation – methods, curation, synonym issues
- f. Agreement of terminology: tissue types, mutation interpretation, test types, amino acid changes

4. Project planning

- a. Agreement on current and future goals
- b. Measures to encourage data submission