

# **LOVD 2.0 MANUAL**

## **Build 2.0-30**

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## Table of Contents

<b>Table of Contents</b> .....	<b>2</b>
<b>Introduction</b> .....	<b>5</b>
<b>Installing LOVD</b> .....	<b>6</b>
Before you install.....	6
Download & Extract.....	6
Pre-install Setup.....	6
Install process.....	7
Administrator account details.....	7
Configuring LOVD system settings.....	8
Configuring LOVD modules.....	8
<b>LOVD Setup</b> .....	<b>9</b>
LOVD system settings.....	9
General system settings.....	9
Global LOVD statistics.....	10
Security settings.....	10
Legend settings.....	10
Gene databases.....	11
Creating new genes.....	11
General information.....	11
Links to information sources (optional).....	11
Customizations (optional).....	11
Security settings.....	11
Editing genes.....	12
Emptying genes.....	12
Deleting genes.....	12
Custom columns.....	13
Variant vs. patient columns.....	13
Managing patient columns.....	13
Creating new columns.....	14
Column name and descriptions.....	14
Data settings.....	14
Column settings.....	15
Editing custom column default settings.....	15
Deleting custom columns.....	16
Downloading custom column data to text files.....	16
Importing custom columns from text files.....	16
Authorized users.....	17
User levels.....	17
Database administrator.....	17
Manager.....	17
Curator.....	17
Creating new users.....	18
Editing users.....	18
Locking users from the system.....	18
Deleting users.....	19
Assigning curators to specific genes.....	19
Submitters.....	20
Creating new submitters.....	20
Editing submitters.....	20
Deleting submitters.....	20
Custom links.....	21
Creating new links.....	21
Editing links.....	22
Deleting links.....	22
Modules.....	23

Installing modules.....	23
Enabling or disabling modules.....	23
Uninstalling modules.....	24
Available LOVD modules.....	24
Mutalyzer module.....	24
ShowMaxDBID.....	25
reCAPTCHA.....	25
System logs.....	26
What is logged by LOVD.....	26
Authorization events and errors.....	26
General events.....	26
General errors.....	28
Installation and upgrade events.....	28
Viewing and searching through the logs.....	29
Removing log entries.....	29
Uninstalling LOVD (database administrator only).....	30
<b>LOVD Gene configuration area.....</b>	<b>31</b>
Gene settings.....	31
Custom variant columns.....	32
Curating variants.....	33
Download or import variants.....	34
Advanced edit features.....	35
Find & Replace.....	35
Copy Column.....	36
<b>Gene homepage.....</b>	<b>37</b>
News feed.....	37
<b>Variant and patient data.....</b>	<b>38</b>
Viewing and searching variant and patient data.....	38
Gene-specific variant listings.....	38
Unique variants.....	38
All contents.....	38
Variants with no known pathogenicity.....	39
System-wide variant listings.....	39
Based on patient origin.....	39
Submitter variant listing.....	39
Advanced options.....	40
Sorting.....	40
Advanced search terms.....	40
Column hiding.....	40
Submitting variant and patient data.....	41
Adding variant data.....	41
Adding patient data.....	41
Finalize submission.....	42
Editing variant data.....	43
Editing patient data.....	44
Deleting variant or patient data.....	45
Deleting variant data.....	45
Deleting patient data (deletes the whole submission).....	45
Downloading data to text files.....	46
Importing text files.....	47
Database statistics (Summary tables).....	50
<b>Submitters.....</b>	<b>51</b>
Registering a new account.....	51
Keeping your account up to date.....	51
Keeping track of your submissions.....	51

<b>LOVD Scripts.....</b>	<b>52</b>
Enabling the scripts.....	52
Making the genbank and refseq directories writable.....	52
GenBank File Uploader.....	53
Reading Frame Checker.....	53
Reference Sequence Parser.....	53
Input formats Reference Sequence Parser.....	53
<b>Use of HTML within LOVD.....</b>	<b>55</b>
<b>Updating LOVD.....</b>	<b>56</b>
<b>Keeping your data secure.....</b>	<b>57</b>
Built-in security measures.....	57
Protection against SQL injection.....	57
Protection against Cross-site scripting (XSS).....	57
Password protecting data manipulation forms.....	57
What you can do to protect your data.....	58

## Introduction

LOVD stands for Leiden Open (source) Variation Database. LOVD is designed to provide a flexible, freely available tool for gene-centered collection and display of DNA variations.

LOVD was developed approaching the "LSDB-in-a-Box" idea for the easy creation and maintenance of a fully web-based gene sequence variation database, that is platform-independent and uses PHP and MySQL open source software only. The basic gene-centered and modular design of the database follows the recommendations of the Human Genome Variation Society (HGVS) and focuses on the collection and display of the DNA sequence variations but it is extendable with clinical data with minimal effort. The open LOVD set up also facilitates functional extensions with scripts written by the community.

The development of (then nameless) LOVD started in late 2002, while it was first officially released in January, 2004. Before that LOVD was only in use by the [Leiden Muscular Dystrophy pages](#), as a not-so-modular system with lots of characteristics specific for that website only. With the official release of LOVD in 2004 the system had become much more dynamic and customizing LOVD was made easy mostly by editing text-files.

In 2004, LOVD became available under the open source license GPL and with the 1.1.0 release most of the text-files had been replaced by online forms so customisations can be performed through the web interface. Early in 2005 the LOVD article was published, and in 2005 the development of LOVD was more targeted at improving the ease of use of the system.

In 2006 the development of LOVD 2.0 started after the decision was made to rewrite all of LOVD from scratch to be able to include a long list of upgrade suggestions that were hard to implement in LOVD 1.1.0. Aimed at modularity and data redundancy, LOVD 2.0 was meant to be a more flexible and more powerful successor of the popular 1.1.0 version and soon it received the interest of LOVD users eager to try out the all-new version.

LOVD 2.0 reached alpha stage in November 2006 after which a select group of enthusiastic LOVD users started testing the database software. With more features being added and bugs fixed rapidly, LOVD 2.0 reached beta stage in April 2007, after which more and more users started to upgrade their 1.1.0 databases to 2.0. Finally, in October 2007 LOVD 2.0 reached the stable stage but even now LOVD 2.0 is continuously improved. Every last Friday of the month, a new release is available from the LOVD website.

## Installing LOVD

Installing LOVD is a "piece of cake". If you just want to try out LOVD to play around with it a bit, we recommend using the [LOVD local install CD](#), which we currently have available for Windows. This LOVD local install CD will install LOVD and all necessary software on your computer in just a few minutes with virtually no effort. This CD requires roughly 200MB free space on your hard drive. For production environments (you intend to publish LOVD on your institution's server) we recommend a manual install, for which you may require help from your system administrator.

### **Before you install**

LOVD is a web-based software project. Therefore, installation requires a correctly set-up webserver running PHP 4.2.0 or higher and MySQL 3.23.33 or higher. LOVD has been extensively tested with the Apache webserver, but any webserver able to run PHP scripts should suffice. See the FAQ about [software needed](#).

A suitable server with the necessary software installed is available at virtually all (academic) institutions and countless (commercial) hosting providers.

Before installing LOVD, be sure you have the required credentials for connecting to the MySQL database. You need a hostname, username, password and a database name to be able to install LOVD. If you are installing LOVD on a remote server, be sure to have the FTP username and password to be able to copy the necessary files to the server.

### **Download & Extract**

To download LOVD, go to [the LOVD website](#) and click on the 'Download' tab. You can download LOVD in two formats; GZIPPed TARball and ZIP archive. The first format is common for Unix and Linux systems while the ZIP archive is popular on the Windows platform. Usually you will be able to open both formats.

Download the file of your choice and save it to your hard drive. Now extract the file using GZIP/TAR or ZIP to the desired location. On a server, common directories may be /var/www on Unix or Linux servers, or C:\htdocs on a Windows server.

### **Pre-install Setup**

You will need to rename the standard config file config.ini-lovd to config.ini and edit it in, for example, a basic text editor. This is absolutely mandatory, because you will need to enter the MySQL hostname, database name, username and password here.

Please go through the entire config.ini file to determine if you need to change any of the other settings.



A .htaccess file is put in the root directory of your LOVD installation protecting the .ini file. This will prevent the .ini file from being viewed on Apache HTTP servers (if configured properly), the most commonly used webserver. If you use Apache, please check that your version and configuration support this feature. Make sure you have the .htaccess file into your LOVD directory, on Unix and Linux systems it's a hidden file so it can be missed easily. For the .htaccess file to work, you need to have "Limit" and "Options" enabled in Apache's "AllowOverride" setting. If you use a different webserver, make sure to configure it to deny access to the config.ini file. LOVD will access the .ini file through the filesystem.

More information about .htaccess files:

<http://httpd.apache.org/docs/2.0/howto/htaccess.html>

More information about AllowOverride:

<http://httpd.apache.org/docs/2.0/mod/core.html#allowoverride>

## **Install process**

To install LOVD on a remote webserver, upload the LOVD directory with all the files to the webserver by, for instance, FTP. If you install LOVD on your own computer, you do not need to follow this step.

Next, point your web browser to the directory where you've uploaded the LOVD files. LOVD will tell you it's not installed yet, and include a link to the install directory.

LOVD will first check a few requirements. Both the PHP and MySQL versions will be checked, to make sure your LOVD will function properly on your webserver environment. Also, LOVD will check if your config.ini file has been hidden.

Installing LOVD consists of only 5 simple steps and will take only a couple of minutes, or less.

## **Administrator account details**

Fill in the database administrator data to install LOVD. The database administrator will be the first user registered with LOVD and has full access to all of LOVD's functionalities. The database administrator is the only user capable of creating manager accounts. Curator accounts can also be created by managers.

Most of the form is pretty straight forward, but I will highlight these two fields:

**Number of entries per page:** To save time to build up the variant table, the variant listings will be split into separate pages. Here you can specify the maximum number of variants you want to see on each page.

**Allowed IP address list:** An IP address is an address a computer is known by on the network. To help prevent others to try and guess the username/password combination, you can restrict access to the database administrator account to a number of IP addresses or ranges. This also means you need to be very careful with this setting, as being too restrictive may lock you out of your account. The default, unrestricted, value is \*.



The database administrator is the absolute owner of the LOVD installation. Not only is he/she the only one that can uninstall LOVD from the database using the uninstaller, but he/she will also be able to create, edit or delete all user accounts in the system and (depending on the settings) receive submission and registration notifications.

After completing the database administrator account details, click the "Continue" button at the bottom. LOVD will apply a simple username and password quality check. If the provided details are OK, click the "Next >>" button.

The next step is to create all necessary LOVD database tables. LOVD will now generate tables for genes, users, submitters, patients, settings, modules, logs, etc. Also some default settings will be loaded and the database administrator account will be created. This can take a while and although LOVD will show the progress of the installation, some browsers may just show an empty screen for a couple of seconds. Please be patient until LOVD is finished installing itself. When everything is done, click the "Next >>" button.

## Configuring LOVD system settings

The final form in the installation process is completing the initial configuration of the LOVD system settings. These settings can be changed after installation at any time through the LOVD setup.

The only setting that cannot be changed at a later time, is the install lock, which is checked by default. Setting the uninstall lock will prevent uninstallation of LOVD by the database administrator. The only way to remove this lock is directly through the MySQL database backend.

For more information on the options of the LOVD system settings, see the LOVD system settings section of the manual.

After filling in the form, click "Continue". LOVD will now register the LOVD system settings and inform you of the result. Then, click "Next >>". Almost done!

## Configuring LOVD modules

LOVD has a modular setup that can be taken advantage of through the LOVD module system. For more information on modules, see the modules section of the manual.

LOVD comes with standard modules. They are pre-packaged with LOVD and are installed in this step of the LOVD installation. The LOVD module installation is fully automatic, so no action on your part is required. LOVD will inform you of the module installation status, after which you can just click the "Next >>" button to complete the LOVD installation. Click the "Continue to Setup area >>" button to be forwarded to the LOVD setup area. The button to create a new gene will be highlighted, as a suggestion of your next step!



## LOVD Setup

All system-wide settings and other system-wide options can be viewed and changed in the setup area. The setup is only available for managers and the database administrator and can be accessed by clicking on the 'Setup' tab in the menu. If you do not see a 'Setup' tab, you first need to log into the system with a manager or administrator account.

The options available in the LOVD setup are accessible through the setup main page, but also through the quick navigation bar directly below the navigation tabs. It allows you to quickly navigate to other setup options without having to go through the setup main page. Some options may not be available, depending on the status of your LOVD installation. Also, some statistics of the database contents are shown, like date of installation, number of registered users and variant counts, separated by status.

### **LOVD system settings**

The LOVD system settings form allows you to change global settings, such as the installation's displayed name, settings on statistics and security and some modifications to the disease and detection technique fields.

#### **General system settings**

These settings are used to somewhat update the LOVD behaviour to your needs.

**Title of this LOVD installation:** This title will be shown on the top of every page, above the menu tabs. The default value is "LOVD - Leiden Open Variation Database".

**Database location:** The database location is displayed in the public area and in emails sent by LOVD. It's commonly set to a laboratory name or a website name. If it's not specified, LOVD will use the (autodetected) website name LOVD has been installed on.

**Database URL:** This is the URL with which the database can be accessed by the outside world, and is not necessarily the URL you are using right now to access the database. The URL will also be used in emails sent by LOVD. This field is mandatory if you select the "Include in the global LOVD listing" option. If you click the "check" link, LOVD will try to predict the value. The "check" option will also verify any value entered in this field.

**LOVD email address:** This email address will be used to send emails from LOVD to users. LOVD needs this address to make sure that emails from LOVD arrive, to prevent problems with spam filters. Although strictly speaking this email address does not need to exist, we recommend that you use a valid address to make sure that bounces of emails sent from LOVD (to submitters or curators) are still caught by someone.

**Forward messages to database admin:** With this setting enabled, LOVD will forward messages to the database administrator about submitter registrations, submissions, and such.

**Enable 'My Submissions':** 'My Submissions' is a new feature that allows submitters to quickly gather a list of submissions they've made to the database and make changes to them. Changes made by submitters will be reported to the curators by email.

**Enable searching through hidden entries:** Enabling this feature allows the public to find the number of entries in the database (including hidden entries) matching one or more search terms on a specified set of columns. This feature will only mention the number of variant entries matched, without showing them.

## Global LOVD statistics

Your LOVD installation can send some general information on your installation back to us. We use this information to see how popular LOVD is, which versions of LOVD are currently in use, to see what type of software is used to run LOVD and to construct the public list of LOVD installs.

**Send signature:** This allows LOVD to send us a randomly generated 32 character text string that helps us keep your LOVD install apart from others, so we can reliably determine the number of LOVD installations world wide. We cannot use the signature to identify you.

**Send statistics:** When this setting is enabled, LOVD will collect some general statistics and send this to us. This is the number of submitters, genes, patients and variants in your system.

**Include in the global LOVD listing:** On our website, we keep a list of public LOVD installations. If this setting is enabled, your LOVD installation will send us your installation's name, the URL and the available gene databases. If you change this setting, please allow one day for the setting to take effect.

## Security settings

This allows you to turn some LOVD security measures on or off.

**Use cookies for user authentication:** Cookies are small text files stored on your computer that help a website identify you. LOVD uses this to keep you identified after you log into the system. If this setting is disabled, LOVD will include a so-called session id in the URL, to keep track of the authenticated users. However, this is much less secure because including the session id in the URL may expose this session id in log files on your computer or on proxy servers. This may allow others to hijack your user's accounts. So leaving this option set is highly recommended.

**Use SSL only to access LOVD:** SSL is a secure protocol allowing for encryption of data sent between you and LOVD. When you record sensitive patient information in LOVD, you should enable this setting, as the patient information can otherwise be 'sniffed' off the network. If you do not record sensitive information, enabling SSL is still recommended.

**Hide non-public entries from the unique variant listing:** If you turn this off, information on non-public variants will be included in the unique variant listing. If visitors click the non-public variant, a message is printed that the data is hidden. This setting does not effect the safety of the patient data.

**Lock curators after 3rd failed login:** With this setting enabled, curators (and managers) will be locked out of the system after they have provided the wrong password three times. A manager or, in the case of a locked manager, the database administrator needs to unlock the user's account once it's locked.

**Lock submitters after 3rd failed login:** With this setting enabled, submitters will be locked out of the system after they have provided the wrong password three times. A manager or the database administrator needs to unlock the submitter's account once it's locked.

**Allow locked users to retrieve a new password:** If a curator, manager, or submitter has lost his/her password, enabling this "I forgot my password" feature allows them to receive a unlocking code in their email with which they can unlock their account and choose a new password.

## Legend settings

These settings are used to create a more detailed legend. Also, the lists of phenotypes and techniques are used to create selection lists on the variant submission form.

**List of possible diseases associated with mutations in the available genes:** Specify a list of phenotypes that are used in this LOVD installation. This list will appear on the full legend and will allow a submitter to select a phenotype from the list. If no phenotypes are specified, the submitter will need to fill in the phenotype in a common text field.

**List of available detection techniques:** Specify a list of detection techniques appropriate for the genes configured in this LOVD installation. By default, a full set of detection techniques has been put in this list already. This list will appear on the full legend and will allow a submitter to select the used detections technique(s) from the list. If no techniques are specified, the submitter will need to fill in the technique in a common text field.

## **Gene databases**

Before you can enter variant or patient data, you'll need to create at least one gene in LOVD. Through the setup area, you can create, edit and delete genes. Curators can also edit the genes after they've been created. Emptying genes (removing all associated variant and patient data) and managing its variants is done through the configuration area.

### **Creating new genes**

Probably the first thing users want to do after installing LOVD, is creating a gene database. Then you can start adding variant and patient information to LOVD. After installing, you are forwarded to the setup area and LOVD will highlight the link to the create gene database form.

After clicking this link, you are first asked for the HGNC ID, to pre-fill the form fields. In case you don't have the HGNC ID or rather want to enter all the information yourself, just leave the field empty and press "Continue" to continue to the create gene database form. This form allows you to set a lot of gene-specific settings. The top part, "General information", is mostly mandatory to fill in. Only the "Date of creation" is optional. The entire bottom part of the form is optional.

### **General information**

This part describes the bare essentials of the gene information; the gene name, gene symbol and chromosome location. Also the date of creation can be filled in; if you leave it empty it will default to today's date.

### **Links to information sources (optional)**

Lots of optional information you can add about your gene, especially links to other resources such as Entrez Gene, OMIM, HGMD, GeneTests or any website you want. These links will be displayed on the gene homepage in the public area.

New in LOVD 2.0 is the option to add a GenBank file to the gene. You can provide a GenBank ID, or upload your own genbank file in the LOVD genbank directory. LOVD can use this GenBank file for some optional functionalities, such as the Mutalyzer module for nomenclature checking. As a contrast, the reference sequence is the gene's sequence formatted for display by human users. For genes with a properly configured transcript reference sequence, LOVD will map the variants to the genome and will add links to the Ensembl, NCBI and UCSC genome browsers to the gene homepage, generating an overview of the variants in the database which have been mapped to the genome. You can choose which version of the Human Build (hg18/Build 36.1 or hg19/GRCh37) to map to.

### **Customizations (optional)**

LOVD allows you to adapt the gene homepage by adding citation references, headers, footers, notes and a disclaimer. The header and footer will also be shown on the variant listings.

### **Security settings**

Using the following settings you can control some security settings of LOVD. It allows you to control whether or not the public can also make downloads of your gene's variants, and whether or not you want your public data to be indexed by the [WikiProfessional](#) concept web.

## Editing genes

Both curators and managers can edit a gene's settings. Managers however, also have an overview of all genes added to the system, accessible via the Setup area. This overview shows general information on all genes, including the number of variants. Selecting one of the genes allows a manager to view all of this gene's information.

To edit a gene's settings, curators go through the configuration area using the "Edit gene database" link, managers can also go through the setup area, using the "Edit gene" link from the gene's detailed view.

The form itself is similar to the creating new genes form.

## Emptying genes

Both curators and managers can delete all variants from a gene database with the "Empty gene database" feature. Patients with variants only in this gene's database will be deleted also! Patients with variants also in other genes, will not be deleted but they will lose the variants that were in this database. The gene database itself and its settings will remain untouched.

To empty all variants from a gene's database, go to the configuration area and click the "Empty gene database" link.

## Deleting genes

Only managers can delete gene databases from LOVD. Below the gene's detailed view, click the "Delete gene" link. To complete the removal, you will need to fill in your password twice.

Please note that besides the loss of all variants within this gene database, also all patients that will have no variants left, will be deleted. So a patient with only variants in the deleted gene will be removed, but a patient who also has variants from other genes, will remain but will of course lose the variants from the removed gene.

## **Custom columns**

The data you can store on your variants and patients in LOVD 2.0 allows for great flexibility. All standard LOVD columns can be edited and removed, except for the HGVS recommended columns, which can only be edited but not removed.

Besides this default set of selected columns which are added to the variant and patient tables by default, LOVD also comes with a set of columns that have not been added to the variant or patient tables yet, but can be added with a click of a button. Additional columns can be created to suit your every need.

### **Variant vs. patient columns**

Custom columns are either of the variant or the patient type. Variant columns can be added to genes, while patient columns can only be added to the system-wide patient table. Therefore, managing variant columns is done via the configuration area, while patient columns and the general custom column actions can be reached through the setup area.

However, some column settings are global. For instance, the way a column is represented on the submission forms and the type of data going in to the field, is a system-wide setting and can therefore only be edited by a manager through the custom column default settings. Therefore, if you seek to edit a column characteristic that you can't seem to be able to edit on the display settings form, make sure you check out the column's default settings also.

### **Managing patient columns**

To add a pre-configured column to the patient table, click the "Add unselected pre-configured custom patient column" link in the setup area. You will get a list of patient columns that are available, but not yet added to the patient table. Click the column you wish to add, and confirm using your password.

Custom columns that already have been added to the patient table can be edited, resorted or removed (the latter only in case it's not a HGVS standard column). These options are available from the "Manage selected custom patient columns" link in the setup area.

The overview shows the selected patient columns which have been added to the patient table and some settings like the column header, column width and the form type.

To change the order in which the patient columns are shown in the variant overviews, click the "Change column order" button. A new window will pop up where you can move columns around by selecting one and using the up or down buttons next to the list. Click the "Change column order" button to save the changes and close the window.

Clicking on one of the entries in the overview will provide a detailed view and links to manage the custom column.

### **Edit column display settings**

You can make changes to the custom column, mostly the appearance. If you're unsure what the fields mean, check out the creating new columns section.

### **Reset column to current defaults**

This will reset the column to the default settings, forgetting all your changes you may have made to the column's appearance. Please note that you can edit the default settings, too.

### **Delete column from patient table**

Columns that are not HGVS standard, can be removed from the patient table. Please note that any data you have stored in a column will be lost permanently if you remove it from the patient table.

## Creating new columns

Using the "Create new custom column" link from the setup area you can create a new variant or patient custom column, which will be inactive unless you explicitly add it to either a variant table or the patient table.

### Column name and descriptions

**Category:** Select if this column is a patient or variant column. You can't change this value later on!

**Column ID:** Choose a simple unique name for your column, consisting of only letters, numbers and underscores. Subcategories must be divided by a slash (/), such as "Phenotype/Disease". Do *NOT* add 'Patient/' or 'Variant/' here.

**Column heading:** This will appear above the column on the variant listings and on the legend. In principle, this is free text, but try to keep it short, because a long name will increase the width of the column.

**Description on form:** If you think this field may require some explanation on the submission form about what to put in there, you can add a description here.

**Description on short legend:** Describe the meaning of the column in short. This will appear in the short legend, below the variant tables.

**Description on full legend:** Describe the meaning of the column. You can be more elaborate here. This text will be shown on the full legend.

### Data settings

There are two ways to define the data type of your custom column. The recommended way is to use the data type wizard, which will fill in the MySQL and the form type values. Only if you really know what you're doing, you can edit the MySQL data type and the form type directly.

To use the data type wizard, you first need to select what type of field you want to create for your custom column:

**Basic form style:** Select what type of field you want to create:

- *Text/numeric input field* for a standard input field allowing textual or numerical free text input.
- *Integer input field* for a standard input field allowing only whole numbers.
- *Decimal input field* for a standard input field allowing only numbers with a certain number of decimals.
- *Large multi-row textual input field* for a large text field with multiple rows, allowing large amounts of text to be filled in.
- *Drop down list (one option selected)* for a drop down list with a set of options of which the user must choose one value.
- *Selection list (multiple options selected)* for a selection list where the user can select one or more options (like the detection technique list).
- *Date input field* for a standard input field allowing for dates (year, month, day), optionally also storing time (hours, minutes, seconds).
- *On/off checkbox* for a simple checkbox allowing only a yes/no answer.

The next page shows you some additional options that depend on the type of field you've chosen:

**Column name on form** (all field types): The name the column will have on the submission form.

**Width on form** (all input fields and text area): The input field width on the form, in number of characters.

**Maximum input length** (text and integer input field types): The maximum number of characters allowed to be filled in. If a user tries to enter more characters in your field, an error is issued.

**Regular expression pattern** (text input only): For advanced users, you can enter a full regular expression pattern (PHP's Perl-compatible regular expression syntax), including the / delimiters and possible modifiers. Using this, you can force a certain format for the input.

**Number of digits before the decimal point** (decimal field only): The maximum number of digits allowed before the decimal point. This practically limits the maximum value of the field.

**Number of digits following the decimal point** (decimal field only): The maximum number of digits allowed at the right of the decimal point. This limits the maximum precision of values in the field.

**Allow only positive values** (integer and decimal fields): Select this to allow only positive whole numbers to be entered.

**Also store time** (date field only): Select this to also store time (hours, minutes, seconds) in this date field.

**Height on form** (text area and multiple selection list): The height of your field on the submission form, in lines.

**Provide "-- select --" option** (drop down list only): Adds a "-- select --" option to the list of options, that will be selected by default. If this option is not set, the first option of the list will be the default selected option.

**Provide "select all" link** (multiple selection list only): Adds a "select all" link, which allows the user to select all available options in the list with one click of a button.

**List of possible options** (both list types): Enter the options available for this field, one options per line. If you want to use abbreviations, use: Abbreviation = Long name, like "DMD = Duchenne Muscular Dystrophy".

**Default value** (all input fields except text area): A default value that will appear in the field for new submissions.

When you click the "Finish" button, the data type wizard will fill in the "MySQL data type" and "Form type" fields for you.

### Column settings

**Standard for new genes:** This controls whether new variant columns that you create will be added to newly created genes by default or not. All variant columns with this option set, will be added to the variant tables of newly created genes.

**Mandatory field:** With this option selected, users can't leave your column empty.

**Show contents to public:** With this option selected, only authorized viewers can see the contents of this column.

**Show field on public forms:** This option controls whether or not submitters can submit a value for this column.

**Include in search form:** This option controls whether or not this column shows on the special search overview that allows the public to find the number of entries in the database (including hidden entries) matching one or more search terms on a specified set of columns.

### Editing custom column default settings

After a custom column is added to a variant table or the patient table, part of the settings can be edited by curators or managers. But the default column settings are stored separately and cannot be edited by curators for three reasons:

- Variant columns can have different appearance settings per gene.
- Curators can modify some basic settings, but do not have permissions to edit the more advanced settings.
- If a column's settings are screwed up for whatever reason, they can be reset to default settings which can be defined by a manager.

Because of this separation of settings, by default not all changes you make will take effect if the column has also been added to a variant table or the patient table, because some changes are overridden by the local display settings of that column. Changes to some advanced options do take effect immediately, like the MySQL data type and form field type. You can do two things to apply all of your changes also to selected columns;

- You can (one by one) reset a selected column to the (new) default settings, to easily apply your changes to a selected column in a variant table or the patient table.
- You can have your changes applied immediately by overriding all local display settings, by selecting the checkbox "Apply changes to patient table where this column is active" in case of a patient table or "Apply changes to all genes where this column is active" in case of a variant table. This checkbox will only appear if the column has actually been added to any of the tables.

If you wish to change the default order in which variant columns appear in future gene databases, click the "Manage all custom column default settings" link in the setup area and click the "Change default column order (for new genes)" button.

### **Edit column default settings**

To edit the custom column default settings, click the "Manage all custom column default settings" link in the setup area, select the column of interest and click the "Edit column default settings" link. The fields on this form are explained in the creating new columns section.

### **Edit column ID (columns created by users only)**

For columns which have been created by users of LOVD, you can change the column ID (the name the column is referenced by the system, such as "Variant/DNA") or move the column from the Patient to the Variant side or vice-versa, only if the column is currently not in use in the Patient table or any of the Variant tables. Click the "Manage all custom column default settings" link in the setup area, select the column of interest, click the "Edit column ID" link and complete the form.

### **Deleting custom columns**

Custom columns created by users of LOVD can also be removed permanently from the system, for instance if they were for testing purposes only or if they are no longer needed. First, you need to make sure the column is no longer active in any of the Variant tables or in the Patient table. Then click the "Manage all custom column default settings" link in the setup area, select the column of interest, click the "Delete column" link and confirm with your password.

### **Downloading custom column data to text files**

To share custom column specifications with other LOVD installs, LOVD supports exporting the custom column default settings to a text file, which you can import back into a different LOVD installation.

In the setup area, click the "Download all LOVD custom columns" link. We *do not* recommend you to edit this file.

### **Importing custom columns from text files**

LOVD supports importing custom columns from tab delimited text files, generated by the download custom columns feature available in the setup area. We *do not* recommend you to edit this file.

The first line should contain the version number and data type definition. If you do not include this line, LOVD will not accept your file. The line should say something like:

```
### LOVD-version 2000-150 ### Columns ### Do not remove this line! ###
```

LOVD will only import the custom columns from the file which are not already in the system. No comparison is performed between the columns already in LOVD and the columns in the file, LOVD just checks if the column IDs are present in the database or not.



## **Authorized users**

Besides the public access to LOVD and users registering themselves as a submitter to add new variants to the database, the users who are setting up LOVD and curating the variants are all authorized LOVD users who need to have their account created by others. The authorized users come in three levels; the database administrator of which there is only one, managers, and curators.

The database administrator has full access to LOVD and can create managers and curators. Managers have access to almost everything, except uninstalling LOVD and creating other managers. Curators do not have access to the setup area and are restricted to the genes they are appointed to.

## **User levels**

Creating, editing and deleting users is only possible with users with a lower level than you. So when you are a manager, you can create, edit and delete curators only. The database administrator can create, edit and delete managers and curators.

## **Database administrator**

The database administrator is the first user within LOVD; this account is created during the installation of LOVD. After installation, the administrator can create other users (managers and curators) in the system, if desired. The administrator has full access to all areas and settings of LOVD. The administrator is also the only user who can uninstall LOVD, provided the uninstall lock has not been set at LOVD installation.

When the "Forward messages to database admin" setting in the LOVD system settings is enabled, the database administrator will receive copies of submitter registrations and variant submissions.

## **Manager**

A manager has access to almost everything the database administrator has access to. However, the manager is not able to create new managers or to edit existing managers. Also, a manager cannot uninstall LOVD even if the uninstall lock is not in place.

A manager can only be created by the administrator and often assists the administrator or takes over the customisation of LOVD for the curators.

## **Curator**

A curator only has access to the gene databases he or she is appointed to. Also the database administrator or a manager can act as a curator, so no separate accounts are required. But the curator user level is very useful for allowing users access to certain genes while access to LOVD system-wide settings and such is restricted.

You can set an authorized user as a gene curator by editing the user's account and selecting the relevant genes in the "Curator for" field.

## Creating new users

LOVD allows a total number of 255 users. You can create a new user by clicking on the "Create a new authorized user" link from the setup area.

If the user is to be a curator, the email address that's filled in will be shown on the gene's homepage and will be used to sent variant submission notifications to.

If the curator is actually also of the curator user level, be sure to assign one or more genes to this user otherwise the curator will be rejected access to the LOVD gene configuration area.

Most of the form is pretty straight forward, but I will highlight these four fields:

**Username:** LOVD requires the username to be 4 to 20 characters and starting with a letter followed by letters, numbers, dots, underscores and dashes only.

**Password:** LOVD requires the password to be at least 4 characters long, containing at least one number or special character.

**Number of entries per page:** To save time to build up the variant table, the variant listings will be split into separate pages. Here you can specify the maximum number of variants you want to see on each page.

**Allowed IP address list:** An IP address is an address a computer is known by on the network. To help prevent others to try and guess the username/password combination, you can restrict access to the database administrator account to a number of IP addresses or ranges. This also means you need to be very careful with this setting, as being too restrictive may lock you out of your account. The default, unrestricted, value is \*.

## Editing users

If you wish to edit your own account, please use the "Your account" link on the top right-hand side of the screen, which leads directly to your account overview.

From the setup area, click the "Manage authorized users" link. This shows a list of the authorized users, sorted by default by the user's level and name.

The Status column provides a quick view of the user's status:

- The user is locked.
- The user is currently logged in.
- The user is currently logged off.

Deleted users show at the bottom of the list and are greyed out.

Select the user you wish to edit, to continue to the user's detailed view. Below the user details, click on the link "Edit user". When editing your own account, this link is named "Update your registration". The form is similar to the creating new users form.

Please note that the "New password" fields are optional when editing a user, you only have to fill them in when changing the password for the user.

## Locking users from the system

As a manager, you can lock curators out of the system. The database administrator can also lock managers. A user is automatically locked if the wrong password is used three times to log into his/her account, provided this security setting is enabled (see LOVD system settings), but this lock can also be enabled by clicking the "Lock user" link below the user's detailed view. If the user is already locked, the link is named "Unlock user".

The "Lock user" and "Unlock user" links are very quick ways to deny or allow access to LOVD, although this can also be accomplished through the edit user form.

Users who are logged in, can also be booted out of the system. If a user is logged in, a link is added named "Force user log out". This will destroy the user's session and force the user's log out. Locking the user essentially also causes the user to be booted out of the system the next time the user performs an action, although in that case it's not possible for the user to log back in until the account is unlocked.

## Deleting users

Deleting a user in LOVD is a non-permanent action. Since the user may have created or edited variants, patients, custom columns, custom links etc, permanently deleting the user from the system may leave some references in the database broken. Therefore, deleting a user only disables the user's account and removes the user as a curator from the genes he or she was a curator for, but does not permanently remove the account. A deleted user can therefore be 'revived' by editing the user and unchecking the 'deleted' checkbox.

If the user is the only curator for one or more genes, and you delete the user, you inherit the curator rights on these 'orphaned' genes. If you want to prevent this, make sure the gene has at least one other curator.

From the user's detailed view, a link named "Delete user" is available if the user has not already been deleted and you have the correct rights on the user account. After clicking that link, you need to confirm deleting the user with your password. Also, if you will take over any genes, this is reported on this confirmation form.

## Assigning curators to specific genes

All genes in LOVD should have at least one curator, to send the new submission notifications to. All curator-level users should have at least one gene to curate, otherwise they will not be able to access the configuration area.

Please note that a curator for a gene is not necessarily a user with the curator user level. A manager, or even the database administrator, can be appointed as a gene curator so that small LOVD installations can be configured and curated by one user account.

Curator-level users will not be able to switch to any gene other than the genes in their allowed list. Managers and the database administrator will have unrestricted access to all genes. If multiple users are assigned curator for a gene, all those users will receive the submission email.

To assign genes to curators, edit the user you wish to assign a gene to. At the bottom of the form is a list of available genes. Select the gene(s) you want the user to be curator for in the list "Curator for". To select all genes, click the "Select all" link next to the gene list.



To select a few genes, you can use the Ctrl and Shift keys on your keyboard. Holding the Ctrl key while clicking on an entry allows you to select or deselect this entry. You can select a range of list entries by selecting the first of the range, then holding Shift and clicking the last of the range. On a Macintosh, use the Command key in stead of the the Ctrl key.

Besides assigning genes to curators, managers and the database administrator can also assign curators to genes, which may be a faster method depending on your specific situation. Please note that you can only assign or remove curators from a gene database if your user level is higher than that of the user you wish to assign/remove.

From the setup area, click the "Edit genes" link. This will show a list of all genes in this installation. Then, click the gene you'd wish to assign curators to. Below the gene's detailed information, click on the link "Add/remove curators". There you can select/deselect the gene's curators. The resulting form enables you to add or remove curators.

After completing this form, you are forwarded to the page where you can sort or hide curators from the list of curators on the gene's home page and on the top of the screen. You can also access this page from the "Sort/hide curator names" link next to the "Add/remove curators" link on the gene's detailed view.

To sort the curators active for this gene, simply move your mouse over the icon on the left of the curator name, and click and drag the name up or down. To hide a curator, simply deselect the checkbox on the right of the name. Don't forget to click the "Save" button to save the new sort order!

## Submitters

LOVD allows users to register themselves as submitters which allows them to submit new variant and patient data to the database. Depending on the LOVD system settings, submitters are also able to edit the data they have submitted previously.

Besides self-registering and maintaining their own accounts, submitters can also be managed by LOVD authorized users, who can create, edit and delete submitter accounts.

### Creating new submitters

LOVD allows a total number of 65535 submitters. Submitters can create accounts for themselves, or you can create one for them. To create a new submitter, click the "Create a submitter" link from the setup area.

One submitter account can hold multiple email addresses, since a submitter account is usually shared among multiple people from one institute. In the "Email address(es)" field, you can enter as many email addresses as you like, one email address per line. In the event of a new submission, all added email addresses will receive a notification with the submission data.

### Editing submitters

From the setup area, click the "Manage submitters" link. This shows a list of the authorized users, sorted by default by the submitter's country and name.

The Status column provides a quick view of the submitter's status:

- The submitter is locked.
- The submitter is currently logged in.
- The submitter is currently logged off.

Deleted submitters show at the bottom of the list and are greyed out.

Select the submitter you wish to edit, to continue to the submitter's detailed view. Below the user details, click on the link "Edit submitter". The form is similar to the creating new submitters form. Please note that the "New password" fields are optional when editing a submitter, you only have to fill them in when changing the password for the submitter.

### Deleting submitters

Deleting a submitter in LOVD can be both permanent and non-permanent. Since the submitter may have created or edited variants and patients, permanently deleting the submitter from the system may leave some references in the database broken and is therefore only possible with submitters not linked to any patients. Deleting a submitter disables the submitter's account, but leaves the account dormant. A deleted submitter can be 'revived' by editing the submitter and unchecking the 'deleted' checkbox.

From the submitter's detailed view, a link named "Delete submitter" is available if the user has not already been deleted. After clicking that link, you need to confirm deleting the submitter with your password. If the submitter is already deleted and has no associated submissions, the account can be permanently deleted by clicking the "Permanently delete submitter" link.

## Custom links

LOVD offers the custom link feature to quickly create links to external sources. By default, LOVD comes with a set of custom links allowing curators to quickly create links to entries in the online databases DbSNP, GenBank, OMIM and Pubmed, without actually having to know how to create links in HTML. You need access to the setup area to create new custom links to other external data sources. The curator can easily add custom links to the variant and patient data using shortcuts on the submission forms.



If you wish to add new custom links, or edit existing ones, you will need a basic knowledge of the internet markup language HTML. Custom links allow curators to put a text like '{PMID15977173:Fokkema et al}' in a certain column and get it replaced by a link to an article on PubMed, in this case the LOVD article: '<A href="http://www.ncbi.nlm.nih.gov/pubmed/15977173" target="\_blank">Fokkema et al</A>', which will be interpreted as '[Fokkema et al](http://www.ncbi.nlm.nih.gov/pubmed/15977173)'.

References are used to pass on information necessary for building the link, e.g. a PubMed ID. These references are defined in the link pattern and then specified in the replacement text, and are indicated by numbers surrounded by square brackets, like '[1]' or '[2]'.



**Example:** the PubMed custom link.

*Pattern:*

```
{PMID[1]:[2]}
```

Links to abstracts in the PubMed database.

[1] = The PubMed ID.

[2] = The name of the author(s).

*Replacement text:*

```
<A href="http://www.ncbi.nlm.nih.gov/pubmed/[1]" target="_blank">[2]</A>.
```

## Creating new links

When creating a custom link, you'll need to determine what the constant and dynamic parts are of the link you wish to point to. The dynamic parts will be the references that you will define. To create a new custom link, click on the "Create a new custom link" link in the setup area.

**Link name:** Fill in a short title that will make curators recognize what the custom link is for.

**Pattern:** Choose a pattern that curators need to use for LOVD to recognize the custom link. This pattern should always start with a '{' and end with a '}'. Between these braces only letters, numbers, spaces, some special characters (;,\_,-) and references ([1] to [99]) may be used. The custom link pattern must be between 3-20 characters long. Two or more references directly after each other must be separated by at least one character to keep the two apart.

**Replacement text:** Fill in the (HTML enabled) text that should replace the entire pattern. It is intended to be a HTML link, but can actually be anything. You need to use the same number of references that you used in the pattern, but a specific reference can be used twice or more in the replacement text.

**Link description:** Provide a short description about this link. What will it point to, what is supposed to be used for which reference?

**Active:** You can enable or disable a custom link using this checkbox. When it's disabled, the custom link patterns will not be replaced.

**Active for columns:** Select for which columns you want this custom link to be activated.



To select a few columns, you can use the Ctrl and Shift keys on your keyboard. Holding the Ctrl key while clicking on an entry allows you to select or deselect this entry. You can select a range of list entries by selecting the first of the range, then holding Shift and clicking the last of the range. On a Macintosh, use the Command key in stead of the the Ctrl key.

## Editing links

For an overview of the available links, click the "Manage custom links" link on the setup page. Clicking the custom link entry of interest shows a detailed overview including the menu options to manage the custom link. To edit a custom link, click the "Edit custom link" menu item.

This form is in every way similar to the create new custom link form.

## Deleting links

When deleting a custom link, it is permanently removed from LOVD. When this link is still in use, the field will show the pattern instead of the replaced text. If you want to temporarily disable a custom link, you can do so by editing the custom link and deselecting the "Active" option.

To permanently delete a custom link, click the "Delete custom link" menu item on the custom link's detailed overview and provide your password for confirmation.

## Modules

LOVD has a modular setup that can be taken advantage of through the LOVD module system. Currently, it is only possible to modify forms within LOVD using the module system. There hasn't been put much development time into getting a very advanced module system available, because of lack of time and because so far very few developers outside our group have expressed interest in modifying LOVD themselves to fit their specific needs. Still, being able to modify LOVD forms with very little code, has already been proven quite useful in the modules that exist right now.

One of the major advantages of the modules is that they can be turned on and off at will. As such, you can always turn a module off if you choose not to need it anymore. If you're sure you will never use it anymore, you can also choose to uninstall it, after which LOVD also removes the settings stored by the module. Uninstalling a module does not remove it from the LOVD installation, you can always re-install it without the need to restore files from backup.

Currently, LOVD comes with three modules, all developed within our own team:

**Mutalyzer nomenclature checker module** - modifies the variant submission form to allow the DNA change value to be checked with the Mutalyzer software on a remote server.

**ShowMaxDBID** - modifies the variant submission form for curators to help them apply the DB-ID field.

**reCAPTCHA** - modifies the submitter registration form to protect it against fake registrations by spam bots.

## Installing modules

During the installation of LOVD, all available modules are installed automatically. Only if you have uninstalled a module or upgraded your LOVD installation with an update that included a new module, you'll need to install it before you can use it.

To have LOVD scan for modules added after installation of LOVD, click the "Scan LOVD install directory for new modules" link from the Setup area. You will see a warning, explaining that you need to know that the modules are from a trusted source. Basically: use your common sense here, just like you would when you run a program on your computer, downloaded from the web. Don't just include a module in LOVD if you're not familiar with it's source.

After clicking "Next >>", LOVD will search the modules directory for modules that are not already installed. LOVD will inspect the new modules and query them to verify if they respond properly. If everything is found to be OK, LOVD will report which modules have been installed.

Please note that newly installed modules are not yet enabled.

## Enabling or disabling modules

LOVD modules can be enabled and disabled by will. Newly installed modules are not yet activated, so you'll need to activate them.

To activate or deactivate a module, click the "Manage installed LOVD modules" link from the Setup area. All installed modules are listed, and the "Active" column indicates whether or not the module is currently activated.

When you click one of the module entries, you'll see the detailed information including the decoded module's settings. If the module is activated, simply click the "Disable module" link. If the module is already disabled, click the "Enable module" link. The changes are applied immediately.



Remember, disabling a module does not reset the module's settings. If you really want to completely reset a module, uninstall and reinstall it.

## Uninstalling modules

If you're sure you're never going to use a module anymore, you can uninstall it to remove it from the system. Also, if you wish to completely remove a module's settings in order to reset it, you'll need to uninstall it (and reinstall it afterwards).

To uninstall a module, click on the "Manage installed LOVD modules" link in the Setup area, and select the module you wish to uninstall. Then, select the "Uninstall module" link.

To reinstall the module, see installing modules.

## Available LOVD modules

These are the modules included with LOVD. Of each of the modules, the functionality is described in detail.

### Mutalyzer module

The [Mutalyzer software](#) was developed to guide researchers in using the correct HGVS nomenclature for their variants. LOVD helps by connecting to the Mutalyzer module from the submitter form, to allow both submitters and curators to check their nomenclature.

For Mutalyzer to work correctly, a GenBank file is necessary.

You can upload a GenBank file to LOVD, after which it can be used by the Mutalyzer module and for the LOVD Reference Sequence parser.

You can also upload one through the Mutalyzer GenBank uploader or even have Mutalyzer [generate one for you](#), after which you can configure LOVD to use the Mutalyzer GenBank ID by editing the gene's settings.

Also filling in a valid NCBI NG or NC accession number in the "GenBank file name or ID" field in the gene settings, will enable the Mutalyzer module to check your variants.

### Using the Mutalyzer module

Once the module is enabled, the variant submission form for every gene which has a GenBank file associated to it, will include a button "Check variant with Mutalyzer 2.0" directly below the "DNA change" field. Fill in a value in the "DNA change" field, and click the button. A new window will pop up, where the results of the query to the Mutalyzer service will appear.

### Mutalyzer stores your GenBank files

Mutalyzer saves all GenBank files in the GenBank file cache. Currently, the cache size is sufficient and no files are removed.

In a future version of Mutalyzer, the GenBank file cache will be cleaned up automatically, when the GenBank file cache is nearly full. In this case, the files which have not been used for the longest period of time will be removed. The clean up may include files with a Mutalyzer GenBank ID, which are generated in the following cases:

1. You have a GenBank file uploaded to LOVD, or
2. You have uploaded a GenBank file into Mutalyzer, and have supplied LOVD with the generated Mutalyzer UD identifier

### Troubleshooting

In the future, the automatic cache clean up may result in breaking the link between Mutalyzer and your gene database in LOVD if the Mutalyzer module has not been used for a long period of time. To fix this, do *either* of the following:

1. Don't download a GenBank file, but configure LOVD to use an official NCBI GenBank ID, or
2. Uninstall and reinstall the Mutalyzer module. Reinstallation may take some time, as the module is contacting Mutalyzer to generate new ID's for every gene's GenBank files.

Fortunately, it is unlikely that this will happen to an active database.



### **ShowMaxDBID**

This module is useful for curators, as it mentions the first free DBID value on the variant submission form and allows curators to quickly insert it into the DBID field. Do this by clicking the link "copy to field".

### **reCAPTCHA**

This module is an implementation of a [CAPTCHA](#) functionality in the submitter registration form, used to block fake submitter registrations done by spambots or similar programs. CAPTCHA stands for "**C**ompletely **A**utomated **P**ublic **T**uring test to tell **C**omputers and **H**umans **A**part". It is a technique nowadays used widespread over the internet to protect data entry forms, such as registration forms or contact forms, to be filled in by computers by presenting a question that is regarded currently not possible for a computer to answer. This could be a simple mathematical equation or, more often used, a distorted image that contains text.

This module is based on the [reCAPTCHA project](#) that is currently the recommended standard of the CAPTCHA method. It combines a CAPTCHA test with the digitalisation of books, by using the answers given by human beings using reCAPTCHA modules all over the world, to solve words which could not be digitized properly.

## System logs

System logs were introduced in LOVD 2.0 to allow authorized users to keep track of events in LOVD. This can be for security purposes, to follow each other's progress when working together, or to track down errors in the case something went wrong.

The logs are initiated when LOVD is installed and they can be accessed using the "System logs" box on the LOVD Setup area.

## What is logged by LOVD

LOVD logs four types of events: authorization events and errors, general events, general errors, and installation and upgrade events. In case the event or error was triggered by an authorized user, the username of this user is also logged.

## Authorization events and errors

This list stores both successful and unsuccessful login attempts. When a user's account has been locked, this log shows you from what IP address the login attempts have been made. Also, it shows you if users provide a password or not. Brute-force attempts to hack into LOVD are quickly uncovered using these logs.

<i>Event</i>	<i>Caused by</i>
AuthError	Unsuccessful attempt to log into LOVD. Shows IP address, hostname, username, and the length of the provided password.
AuthLogin	Successful attempt to log into LOVD. Shows IP address, hostname, username, and the length of the provided password.

## General events

General events are logged to show a user's activity, to allow collaborating users to track each other's activities or to check what happened to a certain variant or patient entry.

<i>Event</i>	<i>Caused by</i>
ColAdd	A custom column has been added to a variant table or the patient table. In case the column has been added to a variant table, the gene is also displayed.
ColCreate	A new column has been created from the setup area.
ColEdit	A column's display settings or default settings have been edited.
ColRemove	A selected column has been removed from a variant table or the patient table. In case the column has been removed to a variant table, the gene is also displayed.
ColReset	A selected column's display settings are reset to the default settings.
ConfigEdit	Successfully edited LOVD's system settings.
FreeEditFNR	Successfully ran Find & Replace. The column and the selected genes where Find & Replace was performed on are also logged.
GeneCreate	Successfully created a new gene.
GeneDrop	Deleted a gene and it's variants.
GeneEdit	A gene's settings have been edited.
GeneEmpty	All of a gene's variants have been removed.
LinkCreate	A new custom link has been created. If the link also has been added to any columns, this is mentioned in separate log entries.
LinkDrop	A custom link has been deleted.
LinkEdit	A custom link has been edited. If the link also has been removed from or added to any columns, this is mentioned in separate log entries.
ModuleDisable	Successfully disabled a module (turned off).
ModuleEnable	Successfully enabled a module (turned on).
ModuleScan	LOVD scanned for new modules, successfully recognized one and installed it.
ModuleUninstall	Successfully uninstalled (removed) a module.
PatientDrop	A patient and all of it's variants have been deleted.
PatientEdit	A patient has been edited, by an authorized user or a submitter, or submitted changes have been accepted by an authorized user.
SelfEdit	A user has successfully edited him/herself. When a user selects or deselects him/herself as a curator, this is also logged.
SubmitNew	A new submission has been added to LOVD. The gene, internal patient ID and internal variant ID are also displayed. This log entry could also mean that a new variant has been added to an existing patient.
SubmitterAssign	A submitter has been assigned to a patient, or removed from a patient.
SubmitterCreate	A submitter account has been created by an authorized user.
SubmitterDrop	A submitter account has been deleted from the system. This is a non-permanent action.
SubmitterEdit	A submitter account has been edited by an authorized user.
SubmitterPurge	A previously deleted submitter account has been permanently deleted from the system.
SubmitterRegister	A submitter has registered him/herself.
UserBoot	An authorized user that was logged in, has been thrown out of the system by an authorized user with a higher level.
UserCreate	A new authorized user has been created by an authorized user with a higher level. When this user is selected as a curator, this is also logged.
UserDrop	An authorized user has been deleted from the system by an authorized user with a higher level. This is a non-permanent action.
UserEdit	An authorized user has been edited by an authorized user with a higher level. When this user is selected or deselected as a curator, this is also logged.
UserLock	An authorized user has been locked out of the system by an authorized user with a higher level.
UserUnlock	An authorized user's account has been unlocked by an authorized user with a higher level.
VariantDrop	A variant has been dropped from a patient. If this was the patient's only variant, the patient entry is also deleted.
VariantEdit	A variant has been edited by either an authorized user or a submitter who owns the variant's patient entry.
VariantImport	Variant and patient information has been loaded into the database. The number of new patient and variant entries are reported.

## General errors

Whenever an unrecoverable error occurs, LOVD logs the error and stops processing. When it's a database error, LOVD tries to log the error to a file.

In principle, during any database event, an error can occur. This is then logged under the name of the event, so any of the above event names can also be found in the error log. In the below table you can find the event names that appear exclusively in the error log. If you find any other event name in the error log, see the above table.

<i>Event</i>	<i>Caused by</i>
CheckUpdate	There was an error while reading the answer of the upstream server to see if there is an update available, or the current version seems newer than the one available.
CURRDB::Lib	An error occurred in a function from the CurrDB class. This is caused by a bug in LOVD.
EmailNotify	An error occurred while sending an email notification to a user who edited his/her own account, a submitter sending in new information, a curator of a gene which has received a new submission, or the database administrator.
HackAttempt	Someone tried to access information or trying to edit or delete information while not being authorized. This error can only be caused if someone is actively modifying the URL to access LOVD.
LibInit	An error occurred in a function from inc-lib-init.php. This is caused by a bug in LOVD.
LibList	An error occurred in a function from inc-lib-list.php. This is caused by a bug in LOVD.
NoCurrDB	The CurrDB class has been initiated without receiving a gene symbol. This is caused by a bug in LOVD.

## Installation and upgrade events

During installation of LOVD, a few log entries are added to the Install log to show the progress of the installation. Also, after each upgrade, LOVD will add an entry stating from which version and to which version it has been upgraded.

<i>Event</i>	<i>Caused by</i>
Step2	LOVD has successfully registered the system status, the variant pathogenicities and the variant statuses, and created the database administrator account.
Step3	LOVD successfully stored the system settings.
Step4	LOVD successfully installed the available modules.
Step5	Successfully completed the installation.
Upgrade	LOVD has been upgraded successfully. This entry also reports from which version LOVD was upgraded, which version it has been upgraded to, and how many queries are performed during the upgrade.
UpgradeError	LOVD has found that the database backend is newer than the LOVD files. This can only be caused by retrieving LOVD files from backups without restoring the database. Since this can cause severe problems with the data within LOVD, LOVD will only work if you restore the correct LOVD files.

## Viewing and searching through the logs

To browse the system logs, click the "View, search and delete system logs" link from the setup area. The system log overview shows you which logs are available, how many entries are logged and the dates of the first and last log entry.

Select one of the available system logs (auth, error, event or install). You can sort the log entries on date or event name. For a full list of event names, see what is logged by LOVD.

The log can be searched on date, event name and the log entry text. Use the fields in the blue search box on the top left side of the screen.

## Removing log entries

To remove a single log entry or a range, first select the log you wish to remove entries from. Every line contains a red cross. Clicking this red cross will immediately remove the entry from the system log.

You can also remove log entries older than a certain number of days. For that, use the red box on the top right-hand side. Fill in a number in the "Delete entries older than" field, and press the "Delete" button. This will remove all log entries in the selected system log older than the number of days filled in.



Please note that when using this functionality, LOVD will ignore any search terms you have entered. All log entries older than the specified number of days will be removed, even if they do not match your search terms and if they are therefore not currently shown on your screen.

To empty an entire system log, click the checkbox "Delete all entries in log" and click the "Delete" button. This will also remove the system log from the system log overview, until it contains a new log entry.

### ***Uninstalling LOVD (database administrator only)***

Only the database administrator can uninstall LOVD, provided the uninstall lock has not been set when LOVD was installed. The uninstall lock is set within the MySQL database and can only be removed by directly accessing MySQL. Uninstalling LOVD can also be done by using MySQL directly, and removing all LOVD tables.

To uninstall LOVD and remove all data stored in LOVD, go to the setup area and click on the "Uninstall LOVD" link. This link is only available if the uninstall lock is disabled. You will need to fill in the database administrator's password twice to complete the uninstallation process.



Once you have uninstalled LOVD, you have lost all variant and patient information. If you wish to keep them, make sure you download all data!



Please note that the LOVD uninstaller will not remove the LOVD files itself, just the database tables that it has created during install and use. Thus, to completely remove LOVD from the system, also remove the files from the server.

## LOVD Gene configuration area

The configuration area is the default starting place for authorized users and can be accessed by clicking the 'Configuration' tab in the menu. If you do not see a 'Configuration' tab, you first need to log into the system with a curator, manager or administrator account.

From here curators can get a quick status overview of the currently selected gene, quickly curate all uncurated entries, perform special "find and replace" actions on all variants, configure what kind of data is stored about the variants, change gene settings, and download and import variant and patient data.

The options available in the LOVD gene configuration area are accessible through the configuration area main page, but also through the quick navigation bar directly below the navigation tabs. It allows you to quickly navigate to other configuration options without having to go through the main page. Some options may not be available, depending on the status of your selected gene.

Since the configuration area is gene specific, you'll need to switch to the gene you wish to work on. To switch to a different gene, select the green "Switch gene" icon next to the currently selected gene name above the menu tabs on the top of the screen, and select the gene you'd like to work on.

### **Gene settings**

Unlike in LOVD 1.1.0, also curator-level users can edit their gene's settings, so that curators can modify their gene's appearance without the need for a manager to help them out. The customizations include adding links to external sites from the gene homepage, setting a GenBank file and reference sequence and adding disclaimer, notes and page header/footer.

To edit your gene's settings, switch to that gene and click the "Edit gene database" link. The form is similar to the creating new genes form.

### **Custom variant columns**

To add a pre-configured column to the variant table, click the "Add unselected pre-configured custom column" link in the configuration area. You will get a list of variant columns that are available, but not yet added to the gene's variant table. Click the column you wish to add, and confirm using your password.

Custom columns that already have been added to the variant table can be edited, resorted or removed (the latter only in case it's not a HGVS standard column). These options are available from the "Manage selected custom columns" link in the configuration area.

The overview shows the selected variant columns which have been added to the gene's variant table and some settings like the column header, column width and the form type.

To change the order in which the variant columns are shown in the variant overviews, click the "Change column order" button. A new window will pop up where you can move columns around by selecting one and using the up or down buttons next to the list. Click the "Change column order" button to save the changes and close the window.

If you wish to change the default order in which variant columns appear in future gene databases (only available to Managers and up), click the "Change default column order (for new genes)" button next to the "Change column order" button.

Clicking on one of the entries in the overview will provide a detailed view and links to manage the custom column.

#### **Edit column**

You can make changes to the custom column, mostly the appearance. If you're unsure what the fields mean, check out the creating new columns section.

#### **Reset column to current defaults**

This will reset the column to the default settings, forgetting all your changes you may have made to the column's appearance. Please note that only managers and the database administrator can edit the default settings.

#### **Delete column from gene**

Columns that are not HGVS standard, can be removed from the variant table. Please note that any data you have stored in a column will be lost permanently if you remove it from the variant table.



## ***Curating variants***

As a curator, your most important job is to keep the variants in your gene database(s) up to date and to curate new entries submitted to the system. New entries sent in by submitters are always hidden from the public view until you publish the entry. This also works the other way around, you can unpublish entries previously publicly available. Of each variant entry, you control whether it's visible to the public or not. The patient information will be hidden from the public if none of all associated variants are public.

You will always have full access to the variants in your gene database and the connected patients, provided these patients aren't also connected to a gene you do not have access to. To edit those patients, you'll need at least a manager account.

To curate entries one by one, use one of the two links that are displayed in the configuration area that point to the variant overviews; "View all uncurated entries in the ... gene database" shows all newly submitted, non-public and marked entries and the "View all entries in the ... gene database" link shows all entries, whether or not they are public.

More about the different ways to view and search the variant listings in viewing and searching variant and patient data.

From any of these two overviews, if you click on a variant entry, you will see a detailed overview of the patient and variant information, possibly including information about other variants found in the same patient.

The detailed overview provides you links to curator tasks provided you have access; editing the patient information, quick-curating or editing the variant information, adding a new variant to the patient, deleting a variant or removing the whole submission (all patient and variant data) all in once.

Also available from the configuration area is the "Curate all" option, that quick-curates all marked and non-public entries in the gene database. Only entries that are filled in completely will be published, other entries will be left.

## ***Download or import variants***

From the configuration area, there are two options to download data from LOVD. The most commonly used option is available from the "Download all variant and patient data" link. It downloads all variant and patient data (public and non-public data) in the standard LOVD import format, which can be imported back into LOVD directly. Not only can this file be used as a backup for your variant and patient data, for instance if you accidentally deleted the wrong entry or the wrong column, it can also be used to make large parallel changes to LOVD entries using spreadsheet software such as OpenOffice.org Calc or MS Excel.



Please NOTE that spreadsheets are well known for introducing errors in importing/exporting text files, due to automatic interpretation of the values. When using a spreadsheet program to edit a downloaded file, format all cells to "Text" **before** importing/pasting the downloaded data.

Also some cases have been reported where MS Excel removed contents of large text fields (> 255 characters).

For more information on how to import variant and patient information, see importing text files.

The other option to download variant data is the central repository format, available from the "Download the variant data for central repositories" link. The form allows you to select which gene(s) you wish to download the variant data from and set some filter options. Curator-level users will only be able to select the genes they control from the list, manager-level users and the database administrator can select any gene.

The central repository format is designed for limited data exchange with other databases, such as genome browsers. The format contains the gene name, the DNA field, the DBID to facilitate linking back to the LOVD database entry, and possible DbSNP and OMIM ID's associated with the variant entry.

## Advanced edit features

LOVD 1.1.0 used to contain a feature called "Free edit", which allowed you to modify data in a certain column of all records at once. LOVD 2.0 comes with two such features; Find & Replace allows you to search for a pattern in a certain field and replace this pattern with a different value, Copy Column allows you to copy or move the contents of a certain column and add it to, or overwrite, an other column's contents. You can apply these advanced edit features directly from the search overview, allowing you to quickly apply this feature to the set of entries on your screen.

### Find & Replace

This feature, in LOVD 1.1.0 known as "Free edit", can be used to update large numbers of variant and patient records all at once. The find & replace form guides you to define which genes would you like to work on, which text you want to search for in what column, where in this field you want to have the search text match and which text it should be replaced by if it matches. This works for one field at a time only, so you can not set a certain reference for all mutations causing a certain phenotype, for instance. What you can do, is change all commas in a field to decimal dots, fix common typing errors, or replace a reference with a different one in all entries.



Be extremely careful when using this function since misuse can empty an entire field in the database. It would be wise to do a download of the database first for backup purposes.

In the configuration area, click the "Find & Replace" link.

**Select genes:** Select which genes you want to apply this find & replace on. If you perform find & replace on a patient column, only the patients that have variants in the selected genes will be edited.

**Apply find & replace to:** Select the field you want to work with. This drop-down list shows all custom columns available in LOVD; if you select a column that is not enabled for the gene(s) you want to apply the find & replace to, no changes are done to the database.

**Match type:** Select how you want to search the selected field for the search value:

- *Field value is...* the search string should match the field's contents exactly.
- *Field contains...* the search string can be found anywhere within the field's value.
- *Field starts with...* the field's value should start with the search string.
- *Field ends with...* the field's value should end with the search string.
- *Field contains anything* - obviously, in this case you do not need to provide a search string.

**Find text:** Fill in the search string that you wish to have replaced by the replace string.

**Replace text:** Fill in the replace string, the text value that you want to use to replace the matched search string with.

If all fields are filled in correctly, LOVD will first notify you about the number of entries that matched your find text and ask you if you want to continue. After your confirmation, LOVD will do the find & replace and notify you of the number of matched entries and the number of replaces performed.

Find & replace does not have an undo. So be extremely careful with what you do. If you make an error while using the form, you may lose important data from the selected column.

## Copy Column

This feature can be used to copy or move certain values from one specific column to another. The copy column form guides you to define which genes would you like to work on, which columns you want to copy values from, which text you want to search for in that column, where in this field you want to have the search text match and which field you want to have the value copied to. You also have to choose whether you want to overwrite the existing value or to append the copied value to the existing value, and you can choose to delete the copied value in the copied from field (move the value). This works for two columns at a time only, the column you want to copy from and the column you want to copy to.



Be extremely careful when using this function since misuse can empty an entire field in the database. It would be wise to do a download of the database first for backup purposes.

In the configuration area, click the "Copy Column" link.

**Select genes:** Select which genes you want to apply this copy column on. If you perform copy column on a patient column, only the patients that have variants in the selected genes will be edited.

**Copy values from:** Select the column you want the values copied from. This drop-down list shows all custom columns available in LOVD; if you select a column that is not enabled for the gene(s) you want to apply copy column to, no changes are done to the database.

**Match type:** Select how you want to search the selected field for the search value:

- *Field value is...* the search string should match the field's contents exactly.
- *Field contains...* the search string can be found anywhere within the field's value.
- *Field starts with...* the field's value should start with the search string.
- *Field ends with...* the field's value should end with the search string.

**Find text:** Fill in the search string that you wish to match the column you want to copy. Please note that the entire contents of the column will be copied, not just the part matching your "Find text".

**Copy value to:** Select the column you want the values to be copied to.

**Append or overwrite:** Choose between appending to or overwriting the existing value.

**Move the copied field:** Tick this box to delete the values in the column you copied from.

If all fields are filled in correctly, LOVD will first notify you about the number of entries that matched your find text and ask you if you want to continue. After your confirmation, LOVD will do the copy column and notify you of the number of matched entries and the number of updated entries.

Copy Column does not have an undo. So be extremely careful with what you do. If you make an error while using the form, you may lose important data from the selected column.

## Gene homepage

LOVD automatically generates a gene homepage for every gene created within LOVD. On this homepage you can find general information on the gene, including links to a list of all PubMed references in the database and a RSS feed subscription link for updates of the gene, combined with links to graphical displays and utilities, the sequence variant tables, links to search forms and links to other external resources.

The "Graphical displays and utilities" table provides links to summary tables, to the Reading Frame Checker, and to external/genome browsers (UCSC, NCBI). The summary tables show statistics on all sequence variants in the database, including graphs on the distribution of variants over the gene and the different variant types. The Reading Frame Checker generates a prediction of the effect of whole-exon changes. The UCSC Genome browser will show the variants in this database as a custom track, so you will have an overview of the variants in relation to their position in the gene. The normal view will show the variants labeled with the DNA change, the compact view without these labels. The NCBI Sequence Viewer will show a distribution histogram of variants from this database. This feature is only available if the gene's transcript reference sequence ID has been filled in in the gene database settings.

If the gene database contains variants, LOVD shows a third table titled "Sequence variant tables". It contains links to three different overviews, which are described in detail in the *Viewing and searching variant and patient data* section. Optionally, a download link is also added to the table, with which you can download all of the variant and patient information in the database. The unique sequence variants listing shows all unique sequence variants in the database, but no patient data. The complete sequence variant listing will show all variants in the database in combination with the patient data associated with them. The listing of variants with no known pathogenicity shows all variants that do not appear to have any pathogenic effect on the patient.

Also links to search forms are provided on the gene homepage if the gene database contains data. A fourth table shows four or five links, depending on the database settings. The first three links (type of variant, simple search, advanced search) provide search forms with increasing number of fields. The results of your search will be displayed in the 'full database search' variant listing, where you can add more search terms if you like.

The variant listing based on patient origin only works if origin fields have been enabled. If enabled, you can create an overview of all variants and patients from a certain geographical or ethnic origin. More information on this overview can be found in the *Viewing and searching variant and patient data* section.

And finally, if enabled, an option is presented to search through all (including hidden) data to return the number of entries matching your search terms. This overview allows you for instance to quickly check if a certain variant is already included in the database (even if it's not yet public) or the amount of entries associated with a certain reference.


The "Links to other resources" table can contain any number of links to external sources, as configured by the gene's curator(s). Examples of external sources that LOVD can link to easily are Entrez Gene, OMIM, UniProtKB, HGMD, GeneCards and GeneTests.

## News feed

You can use the "Subscribe to updates of this gene" Atom feed subscription link on the gene homepage to subscribe to the update feed of the database. Using an Atom compatible feed reader, you can receive information about additions or updates to the database. This news feed is provided both gene-specific and system-wide. The link to the system-wide news feed should be shown in your browser's address bar if your browser supports it.

## Variant and patient data

LOVD stores the variant and patient data separately. Each gene has its own list of variants. Therefore, you first need to select a gene before you can view any variant and patient information. So if you enter a LOVD database website, you first need to select a gene to look at. If this LOVD installation contains only one gene, you are forwarded automatically. Selecting a gene forwards you to the gene's homepage.

At any time, you can switch to a different gene by clicking on the green icon on top of every page:  Clicking the icon will show a drop-down list allowing you to select an other gene database. You will be forwarded to a similar page in the other database. For example: when viewing all disease-causing substitutions in one gene, using this way to switch genes will show you all disease-causing substitutions in the gene you selected.

The gene homepage will show you some general information on the gene, including the number of variants and patients stored in the database and external links with more information about this gene. All these links can be configured by the gene's curator.

### **Viewing and searching variant and patient data**

The variant and patient listings are available from the Variants tab. There are three different gene-specific variant listings, of which two can have the advanced search capabilities enabled. There are also two system-wide variant listings.

#### **Gene-specific variant listings**

##### **Unique variants**

When you click on the Variants tab and you have a gene selected, the default overview is the unique variant listing with search fields enabled. It is also accessible through the gene's homepage, through the link "Unique sequence variants", which leads to the same overview but without the search fields enabled. This overview shows all variant fields, but no patient information. Also, information on pathogenicity is not shown. Variants that are found multiple times are shown only once, including the number of times it has been found. By clicking on a variant, you are guided to the full contents of the selected variant. If the top search bar is enabled, you can type search terms for that particular column. After typing in a search term, either press enter or click outside the field.

This overview supports these advanced options: sorting, advanced search terms, column hiding.

##### **All contents**

This complete overview can be reached through the "View all contents" submenu item just below the menu tabs or the gene's homepage, through the "Complete sequence variant listing" link. This overview shows all information on the variants and associated patients in a large table. Variants that are found multiple times, are not grouped. The pathogenicity information is always shown as the first column. Also, the variant columns are always shown first, after which the patient columns are shown. Although the order of the variant and patient columns can be set by an authorized user, variant and patient columns can not be mixed in this overview.

The "Full database search" submenu item just below the menu tabs enables the top search bar, in which you can type the search terms for that particular column. After typing in a search term, either press enter or click outside the field.

This overview supports these advanced options: sorting, advanced search terms, column hiding.

### Variants with no known pathogenicity

From the gene's homepage, a link named "Variants with no known pathogenicity" leads to a list of variants that do not appear to have any pathogenic effect. Variants with an unknown effect are left out of this overview. This overview is based on the unique variant listing and clicking on a variant will therefore show all variant information including the associated patient(s).

This overview supports these advanced options: sorting, advanced search terms, column hiding.

### System-wide variant listings

#### Based on patient origin

If any of the Patient/Origin fields are enabled, LOVD allows you to search through all genes in the database based on the Patient/Origin columns. The standard LOVD origin columns are Patient/Origin/Geographic (geographic origin), Patient/Origin/Ethnic (ethnic origin) and Patient/Origin/Population (population). If you wish to add any columns to search on, create a new patient column and make sure the column ID starts with "Origin/".

To reach the variant listings based on patient origin, select the "Variant listing based on patient origin" submenu item under the Variant tab, or click the "Based on patient origin" link on a gene homepage in the "Search the database" table.

This overview supports these advanced options: sorting, advanced search terms (on origin fields only), column hiding.



You may get this error: "There are no Patient/Origin columns enabled. Therefore this overview is non functional."

That means that none of the Patient/Origin fields have been added to the patient table yet. Three Patient/Origin columns are available by default, but they are not added to the patient table by default. See Managing patient columns.

### Submitter variant listing

The "my submissions" feature allows submitters to gather a list of variants they've submitted to the LOVD database installation. It is available for submitters and the public if the "my submissions" setting has been enabled in the LOVD system settings, otherwise it's only available for authorized users. Also this overview is system-wide, meaning the overview allows you to select which genes you want to show the variants of.

Submitters can access this overview by clicking on "your submissions" on the top right of the screen. You can also go through the Submitters tab, and then click the "My submissions" sub menu item.

This overview supports these advanced options: sorting, column hiding.

## Advanced options

The LOVD variant overviews support a range of advanced options. Not all options are available from all variant overviews.

### Sorting

Sorting is available on all variant overviews and allows you to sort the data on whatever column you wish. The column currently sorted on has a darker blue background color than the other columns.

Two arrows indicate which direction the values on sorted on:

- ▼ The values are sorted low to high (standard).
- ▲ The values are sorted high to low (reversed).

To sort on a certain column, click on the column header or on the arrows. If that column is already selected to sort on, the sort order will be swapped.

LOVD uses an algorithm that interprets the values of the Variant/Exon (if available) and Variant/DNA fields to facilitate proper sorting. The result of the algorithm is stored in a sort column, which LOVD uses by default to sort on. If sorting on any field other than Variant/DNA, LOVD will sort secondarily on this sort column.

### Advanced search terms

LOVD allows boolean search terms, meaning you can construct complex queries with AND, OR and NOT logic. All search terms are treated as AND by default. OR is indicated with a pipe '|' with no spaces around it and NOT is indicated by an exclamation mark '!', not followed by a space. If you enclose two or more words in double quotes, LOVD will search for the combination of those words only exactly in the order you specify.

Note that search terms are *case-insensitive* and that wildcards such as \* are treated as normal text!

#### Examples:

Search terms	Field	Result
>	Variant/DNA	Show only substitutions
A>T T>A	Variant/DNA	Show only A to T or T to A substitutions
c.328 >	Variant/DNA	Show only substitutions at position c.328
p.(Arg X)	Variant/Protein	Show only arginine to stopcodon changes
Asian	Patient/Origin/Ethnic	Shows "Asian", but also "Caucasian" entries
Asian !Caucasian	Patient/Origin/Ethnic	Shows "Asian", but no "Caucasian" entries
Asian African !Caucasian	Patient/Origin/Ethnic	Shows "Asian" or "African", but no "Caucasian" entries
"South Asian"	Patient/Origin/Ethnic	Shows "South Asian", but no "South East Asian" entries

### Column hiding

The variant overviews can be personalized by hiding columns that you don't need. Especially the full overview including the patient data can get quite wide and to prevent a lot of horizontal scrolling, you can hide the columns you're currently not interested in. These settings will be stored in a cookie on your computer, so that the next time you return to LOVD the settings will remain. The link on the detailed entry view to temporarily unhide all columns does not influence the stored settings.

On the column headers of variant overviews that support this feature, there is a little red icon (✖) that you can click to hide the column. The column will disappear, and leave a narrow column with an arrow (↗). If several columns next to each other were hidden, only one arrow will be shown. Clicking on this arrow will show a selection list of the hidden columns, where you can choose the columns which you want to be restored. Use the link "Hide Specific Columns" to show a selection list where you can choose which (additional) columns to hide, and "Hide all columns" to show only the DNA column. To restore all columns all at once, click the "Unhide all columns" link.

Since LOVD v.2.0-23, the hidden columns are also hidden in the detailed view of the variant, in the patient data table, the variant data table and the listing of all variants reported in the selected patient. The hidden fields can be shown by clicking on the "show all fields" link on the top of the page, or by clicking on an arrow in one of the hidden columns of the entries overview at the bottom of the page. As mentioned on the page, this will not influence your configured display settings.



## Submitting variant and patient data

Unlike LOVD 1.1.0, both submitters and curators now use the same submission form to submit variant and patient data. The differences between submitting as a curator compared to submitting as a submitter:

- Curators can also fill in non-public fields
- Curators can directly publish the variant entries
- Curators can directly assign a submitter to the patient entry

Since in LOVD 2.0 variant data has been split from patient data, the submission is now a multi-step process where variant data is entered separately from the patient data. To start the submission process, click the "Submit" tab. You'll need to be logged in to start the submission process.

The first step of the submission process is to select the gene the variant you are about to enter, is found in. Select the gene you're submitting to and click the "Select gene database" link. You're shown the submission overview, where you can see the data you entered. Currently, it's empty. Whether you start with adding variant or patient information, does not matter.

## Adding variant data

It's easy to check if the variant you're about to enter, already exists in the database. Just click the "Using an existing variant »" button in the "Sequence variant data" section. This will open a pop-up where you can enter the variant name (i.e. 'c.11G>A'). The field will autocomplete your input. You can also double click on the field, and it will show you a list of variants already in the database (if any). After you filled in or selected the variant's name, press "Review variant data". If the variant already existed, the variant submission form is filled in for you. Review all fields and click "Add variant data" when you're done.

If the variant is not in the database yet, just click the "Add variant data »" button on the submission overview and you'll get an empty variant submission form that you can fill out. Once you're done, click the "Add variant data" button and you'll be forwarded back to the submission overview.



If you want to submit a homozygous mutation, you only have to fill in the variant form once. Just select "Both (homozygous)" for the "Variant allele" field and LOVD will create two variant entries for you.

Once you've added variant data to your submission it'll show up in the submission overview. You can keep adding variant data until you're done. If you want to add variant data from a different gene, first complete this submission and then add those other variants to your patient entry in a new submission process.

You can also remove added variant data by clicking the small red mark at the right side of the variant entry.

## Adding patient data

You can add only one patient per submission. If you want to add one or more variants to an existing patient, you'll need the patient's internal reference ID. You can find it in the header of the patient data table in the detailed view, or you can just click the "Add new variant to patient" link below the patient data table in the detailed view, which will forward you into the submission process, and will fill in the patient information for you.

For adding a new patient, use the "Add new patient data »" button, and fill out the patient data submission form.

## Finalize submission

Once you have the patient data filled in and have added at least one variant, the "Finalize submission" button will be enabled. Once you click this button, the data will be stored in the database and the curator(s) and you will receive a copy of your submission through email. If you are a submitter, your submission will be public once the curator publishes (curates) your findings.

### ***Editing variant data***

Variant data can be edited by authorized users that have access to the gene containing the variant (appointed curator, manager or the database administrator) or, if the "my submissions" setting has been enabled, also the submitter owning the connected patient can edit the variant information.

To edit the variant information, go through any of the available variant listings and find the variant you're looking for. Click the variant (if you were on the unique variant listing, you'll need to click again to select the variant belonging to the correct patient) to go to the detailed view. Below the variant data table, click the "Edit variant" link. The form to edit a variant is similar to the variant submission form.

In case a submitter edits the variant information, the curator(s) connected to the variant's gene will be notified of the changes and the variant status will be put back to marked in case the variant was already public. However, if nothing is changed by the submitter, nothing is updated in the database and the curators are not notified.

If you just wish to curate (publish) the variant without making any changes, use the "Curate variant" link below the variant data table. You will then only need to go through the form in case the entry is not ready for publishing (i.e. empty mandatory fields).

### ***Editing patient data***

Patient data can be edited by authorized users that have access to the gene(s) containing the patient's variant(s) (appointed curator, manager or the database administrator) or, if the "my submissions" setting has been enabled, also the submitter owning the patient can edit it's information. However, if the patient has variants in more than one gene, curator-level users can only edit the patient if they are appointed to all of the patient's genes.

To edit the patient information, go through any of the available variant listings and find the patient you're looking for. Click the patient or one of the connected variants to go to the detailed view. Below the patient data table, click the "Edit patient" link. The form to edit a patient is similar to the patient submission form.

In case a submitter edits the patient information, the curator(s) connected to the patient's variant's gene(s) will be notified of the changes. However, if nothing is changed by the submitter, nothing is updated in the database and the curators are not notified.

### ***Deleting variant or patient data***

Variants can be deleted from a patient one by one, until the patient has no variants left in which case the patient record will be deleted also. If a patient is deleted, all variant data connected to the patient will be deleted automatically.

### **Deleting variant data**

Variant data can only be deleted by authorized users that have access to the gene containing the variant (appointed curator, manager or the database administrator).

To delete the variant information, go through any of the available variant listings and find the variant you're looking for. Click the variant (if you were on the unique variant listing, you'll need to click again to select the variant belonging to the correct patient) to go to the detailed view. Below the variant data table, click the "Delete variant from submission" link and confirm with your password.



Remember that deleting a patient's last variant will also remove the patient entry!

### **Deleting patient data (deletes the whole submission)**

Patients can only be deleted by authorized users that have access to the gene(s) containing the patient's variant(s) (appointed curator, manager or the database administrator). However, if the patient has variants in more than one gene, curator-level users can only delete the patient if they are appointed to all of the patient's genes.

To delete the complete submission, go through any of the available variant listings and find the submission you're looking for. Click the entry to go to the detailed view. Below the patient data table, click the "Delete complete submission" link and confirm with your password.

### ***Downloading data to text files***

Besides the two download options in the configuration area, LOVD also supports to download a subset of a gene's variant and patient data. Authorized users always have access to this, all other users will only be able to download the data if the gene's curator enabled this feature in the gene settings.

If this feature is enabled or you are an authorized user, the unique and full variant listings will have a disk icon below the data table. Clicking this disk creates a download file in LOVD import format. In case you provided search terms, only the results will be included in the download file. Also the order in the downloaded file is equal to the order of the entries on the screen.

If you're downloading from the unique variant listing, only the variant columns are presented in the downloaded file. The columns and entries you are not authorized to see, will also be left out of the downloaded file.

## Importing text files

For curators, managers and the database administrator, LOVD supports importing your variant and patient information from tab delimited text files, data preferably enclosed by double quotes. These can be taken from a LOVD download, or saved from a spreadsheet program such as OpenOffice.org Calc or MS Excel. You do not need to send the file to the server using FTP, as was done with LOVD 1.1.0. The exact list of columns needed is dependent on your LOVD configuration. If you're unsure, make a full download of your gene in the configuration area.

To import new data, click on the 'Configuration' tab in the menu and find the "Import new variant and patient data" link.



Please NOTE that spreadsheets are well known for introducing errors in importing/exporting text files, due to automatic interpretation of the values. When using a spreadsheet program to edit a downloaded file, format all cells to "Text" **before** importing/pasting the downloaded data.

Also some cases have been reported where MS Excel removed contents of large text fields (> 255 characters).

If you're converting your own spreadsheet data to LOVD format, please read the following notes carefully. Always start out with a LOVD download file, so you have the correct headers!

1. The first line should contain the version number and is very important in versions 2.0-04 and up, but should be left out in older versions of LOVD. If you do not include this line, LOVD will assume it's an old import format, and will alter the pathogenicity settings. The line should say something like:

```
### LOVD-version 2000-150 ### Variants/Patients ### Do not remove this line, unless importing in versions before 2.0-04 ###
```

2. The second line contains the column names and is essential. LOVD looks at these column names to check if all required columns are present. The order of the columns does not matter.
3. If there are mandatory columns missing from the import file, you get a warning and nothing is imported.
4. If non-mandatory columns are missing, the column value will remain empty for the imported variants.
5. Columns which are present in the file, but not in the database, are **ignored**. The names of these columns will be mentioned after a successful import.
6. The ID\* columns, such as ID\_allele\_ and ID\_pathogenic\_, contain numeric references representing values that will appear on the screen. The meaning of the (often numeric) values of these columns are listed below:

```
ID_allele_ (optional)
0 => Unknown
1 => Parent #1
2 => Parent #2
10 => Paternal (inferred)
11 => Paternal (confirmed)
20 => Maternal (inferred)
21 => Maternal (confirmed)
```



**Please note that the below values for pathogenicity have changed as of LOVD version 2.0 build 04.** If you're importing anything in an older version of LOVD, do not use these values, but scroll down for the older values.

ID\_pathogenic\_ (optional)

This should contain two numbers; the first for the reported pathogenicity and one for the concluded pathogenicity.

1 => No known pathogenicity  
3 => Probably no pathogenicity  
5 => Unknown  
7 => Probably pathogenic  
9 => Pathogenic

So 95 means a mutation is supposedly pathogenic, but this has not been proven.

All options are:

11 => -/-  
13 => -/-?  
15 => -/?  
17 => -/+?  
19 => -/+  
31 => -?/-  
33 => -?/-?  
35 => -?/?  
37 => -?/+?  
39 => -?/+  
51 => ?/-  
53 => ?/-?  
55 => ?/?  
57 => ?/+?  
59 => ?/+  
71 => +?/-  
73 => +?/-?  
75 => +?/?  
77 => +?/+?  
79 => +?/+  
91 => +/-  
93 => +/-?  
95 => +/?  
97 => +/+?  
99 => +/+



**If you're importing in LOVD 2.0-03 or earlier, use this list of pathogenicity values and make sure there is no version code on top of the imported file.**

```
0 => No known pathogenicity
1 => Pathogenic
9 => Unknown
```

All options are:

```
00 => -/-
01 => -/+
09 => -/?
10 => +/-
11 => +/+
19 => +/?
90 => ?/-
91 => ?/+
99 => ?/?
```

```
ID_status_ (optional)
1 => Submitted
4 => Non public
7 => Marked
9 => Public
```

ID\_variantid\_

This contains the internal variant ID (numeric). If your database is empty, you can start counting from 1. If variants are equal, you can copy all variant fields including the variant ID in the file. If a variant is already in the database, use that variant ID. The import script will then check if the data in the file equals the data in the database.

ID\_patientid\_

This contains the internal patient ID (numeric). If your database is empty, you can start counting from 1. If the patient has more than one variant, you can copy all patient fields including the patient ID in the file. If a patient is already in the database, use that patient ID. The import script will then check if the data in the file equals the data in the database.

ID\_submitterid\_ (optional)

The submitter ID of the submitter who's submitted this patient.

ID\_variant\_created\_by\_ (optional)

ID\_variant\_edited\_by\_ (optional)

The user ID of the user who's created and/or edited this variant data.

ID\_patient\_created\_by\_ (optional)

ID\_patient\_edited\_by\_ (optional)

The user ID of the user who's created and/or edited this patient data.

7. Date fields (variant\_created\_date\_, variant\_edited\_date\_, patient\_created\_date\_ and patient\_edited\_date\_; all optional) should contain a date in the format YYYY-MM-DD HH:MM:SS (2007-05-21 11:57:31).

8. You can then import the file back into LOVD through the configuration area (Configuration > Import new variant and patient data). You don't need to send the file through FTP, like in LOVD 1.1.0.



### ***Database statistics (Summary tables)***

A summary of the database statistics can be reached through the "Database statistics" submenu item under the Variants tab, or the "Summary tables" link from the gene homepage.

In the first table, the numbers of variants are shown per exon (and intron, depending on the values in the Exon column). Next to the numbers are horizontal bars showing the relative percentage of variants in this exon or intron. If the Reference Sequence parser has been run using a GenBank file, LOVD knows the actual lengths of the exons and introns, and the percentages are compensated using these exon and intron lengths. LOVD tries to interpret exon values as much as possible to group them together.

The bottom three tables represent the numbers of variants at DNA, RNA and Protein levels, given as absolute numbers and as percentages (bars), categorized according to variant types (e.g. substitutions, deletions). The variant types are links, clicking on them will give you an overview of all those variants counted. Please note that the number of variants shown can deviate from the numbers shown in the database statistics tables. Reasons for these differences can be that a variant is reported more than once (see # Reported field) or a homozygous variant (shown only once but counted twice).

The DNA variants table also displays the number of variants per section of the gene (5' start, coding region, introns, 3' stop). These numbers are always calculated based on textual interpretation of the DNA field. Please note that the values "c.=" and "c.0" in the DNA field are not counted as variants.

## Submitters

Submitters are often clinicians collecting patient and variant information and willing to share this information with others. LOVD allows users to register themselves as submitters which allows them to submit new variant and patient data to the database. Depending on the LOVD system settings, submitters are also able to edit the data they have submitted previously.

The public list of submitters, available from the Submitters tab, automatically shows all submitters in the database, sorted on country and city.

### ***Registering a new account***

You can create a submitter account for yourself, and start submitting variant and patient information immediately after. To create a new submitter account, click the "Register as submitter" link from the top right-hand side of the screen. Alternatively, select the "Submitters" tab and click the "Register as submitter" submenu item.

To be able to share one submitter account with a few colleagues, you can add as many email addresses as you like in the "Email address(es)" field, one email address per line. In the event of a new submission, all added email addresses will receive a notification with the submission data. When you're done, click the "Create submitter account" button and you will receive a notification email with the registered data.

### ***Keeping your account up to date***

It is important to keep your account up to date. You are listed on the public list of submitters and the email addresses associated with the account will receive copies of the submission information. To view or update your account details, click the "Your account" link on the top right-hand side of the screen. This will show you all account details. To update your account, select the "Update your registration" link below the data table and complete the form. All email addresses will receive an account update.

### ***Keeping track of your submissions***

Especially in larger installations with multiple genes and multiple submitters, you can easily lose track of all your submissions. If the "Enable 'My Submissions'" system setting is enabled, LOVD supports a full listing of all your submissions. If you're logged in as a submitter, it's available from the "Your submissions" link from the top right-hand side of the screen. Alternatively, you can find it through the "Submitters" tab, the "Variant listings" submenu item. Remember, if the "Enable 'My Submissions'" setting is turned off, this overview is not available to submitters. It is always available for authorized users.

If this overview is enabled, submitters can also edit previously submitted data. For more information, see editing variant data.

## LOVD Scripts

Besides modules, that modify LOVD's behaviour, LOVD is also extended with scripts that behave quite separate from LOVD. LOVD currently comes with two such scripts, the GenBank File Uploader and the Reference Sequence Parser.

The public is encouraged to help extend LOVD with such useful scripts. If you are a programmer and you have written a script that you think is of use to other LOVD users, please [contact us](#). Maybe we can add it to the next LOVD releases.

### Enabling the scripts

LOVD comes with a couple of useful scripts, allowing you to perform some extra tasks related to LOVD. Since these scripts need to have writing permissions on some of the LOVD directories, you need to perform some actions before you can use them.

LOVD's GenBank File Uploader requires the genbank directory to be writable, the Reference Sequence Parser requires a writable refseq directory, and if you want it to generate GenBank files for you, it also requires a writable genbank directory.

### Making the genbank and refseq directories writable

Your LOVD package comes with two (empty) directories called 'genbank' and 'refseq'. As explained above, these directories need to be made writable so that the LOVD scripts can access these folders. Below we will explain how to do that on Unix/Linux systems. If your LOVD is installed on a different server (Windows, Macintosh), please contact the person responsible for that server in order to make the directory world writable.



#### For advanced users

It is actually more secure to do a 'chgrp' on the folder to the user running the webserver, than to make the directory world writable. If you don't know which user the webserver runs as (i.e. 'www-data' or 'httpd'), you will need to do a 'ps' to find out which user that is, or consult the webserver configuration. After that, make sure the groupbit has been set to 7 (rwx). This way, the scripts work without having to make the directories world writable.

### Using the commandline

1. Log in to the server using SSH, telnet or any non-graphical (S)FTP client.
2. Move into the directory LOVD is placed using the 'cd' command.
3. Type in 'chmod 777 genbank refseq'.
4. Check if the scripts are still generating an error. If not, you're done.

### Using a graphical (S)FTP client

Of course, there are so many different FTP clients that I can't write a exact manual on how to change rights on a folder. This will describe a generally used method.

1. Log in to the server using your favorite (S)FTP client.  
(FTP is a protocol used to transfer files to or from the internet. If you have uploaded your LOVD files to a server, you can use the same program you used then.)
2. Move into the directory LOVD is placed (usually by double clicking on the folder names).
3. Right click on the folder 'genbank', this will bring up a menu.
4. Select 'chmod' if it is an option. Otherwise, click 'Properties' and look for the folder permissions/rights.
5. Fill in '777' as the new value.
6. Repeat steps 3-5 for the 'refseq' directory.
7. Check if the scripts are still generating an error. If not, you're done.

## **GenBank File Uploader**

LOVD uses GenBank files containing your genes' sequences for some optional functionalities, such as creating a reference sequence and the mutation check Mutalyzer module. If you want LOVD to use your GenBank file, you can use this script to upload your GenBank file to LOVD. If you have no GenBank file associated with your gene yet, this script will automatically configure LOVD to use the uploaded GenBank file. For the uploader to work, you will need to make the genbank directory writable.

The form is rather straight forward. You have to select a gene, for which you will upload a GenBank file. This implies that for new genes, you first need to create the gene, and only then you can upload the GenBank file. You can choose to have the uploaded file renamed to a standard name, such as DMD.gb for the DMD gene, or to retain its original name. If you already have a GenBank file for the selected gene, you can choose to delete it or to have it overwritten by the uploaded file.

When you upload a new GenBank file for a gene that does not have a GenBank file associated with it yet, LOVD will automatically configure the gene database to use this new GenBank file.

## **Reading Frame Checker**

The Reading Frame Checker allows you to quickly generate a prediction of the effect of whole-exon deletions and duplications on the RNA translation. Amongst others, the script will check if the given deletion or duplication is in-frame or out-of-frame. It will also generate the HGVS name of the given mutation.

The Reading Frame Checker is only available for your gene database if you have once run the Reference Sequence Parser, because the Checker needs to know exon and intron information from your gene that the Reference Sequence Parser takes out of the GenBank file. Once available, it is also linked to from the gene homepage, in the "Graphical displays and utilities" table.

## **Reference Sequence Parser**

The Reference Sequence Parser allows you to create coding DNA reference sequences for the genes in your database. For it to work, you will need to make the refseq directory writable. If you also want the script to generate a GenBank file for you, you'll also need to make the genbank directory writable.

### **Input formats Reference Sequence Parser**

The Reference Sequence Parser accepts specific input formats for each step. Step 1 requires a GenBank file, and will generate the formats for steps 2 and 3 automatically, so starting at this step is recommended.

Step 2 requires the genomic sequence formatted to provide the positions of the upstream sequence, exons, introns, downstream sequence and the start of the translation.

Step 3 requires the coding DNA sequence formatted to provide the positions of the exon borders and the start of the translation.

All formats are case-**ins**ensitive. It does not matter whether you use capital or non-capital nucleotides.

### **Input format for step 1**

Step 1 requires a valid GenBank file, uploaded into the 'genbank' directory. You can upload GenBank files with the GenBank File Uploader. Preferably, the GenBank file contains only your gene of interest and only one transcript is defined. If more than one transcript is defined, you will have to fill in the appropriate transcript\_id and protein\_id. If you do not fill in both fields, the first mRNA and CDS fields appearing in the file and associated with this gene will be selected.

Step 1 will create the correct format for step 2, so this is the recommended step to start out with.

**Input format for step 2**

*UPSTREAM<EXON>INTRON<EXON>INTRON<EXON>INTRON (...etc...) <EXON>DOWNSTREAM*

Make sure you include the starting point of the translation by putting a '|' in front of the 'a' of the 'atg' starting codon. If you started at step 1, this is done for you automatically.

Example:

```
ccccccc<gggggg|at>ttttttt<gggggggg>aaaaaaaa
```

will parse:

- 'ccccccc' as the upstream sequence.
- 'ggggggat' as exon 1, with the translation starting at the 'a'.
- 'ttttttt' as intron 1.
- 'gggggggg' as exon 2.
- 'aaaaaaaa' as the downstream sequence.

Step 2 will create the upstream sequence, intronic sequences and the downstream sequence, as well as exon lengths tables in html and text format, in which the exon start and end positions (in c. and g. numbering) and exon and intron lengths are provided. These are all saved in the refseq directory. Step 2 will also create the input for step 3 for you. Optionally, you can also have it create a file in GenBank format. You will then have to fill in the appropriate transcript\_id, protein\_id and db\_xref numbers. The created file will meet the minimum requirements for uploading in [Mutalyzer](#).

**Input format for step 3**

*EXON;EXON;EXON; (...etc...) ;EXON*

Make sure you include the starting point of the translation by putting a '|' in front of the 'a' of the 'atg' starting codon. If you started at step 1 or 2, the same start codon is used.

Example:

```
gggggg|at;gggggggg
```

will parse:

- 'ggggggat' as exon 1, with the translation starting at the 'a'.
- 'gggggggg' as exon 2.

Step 3 will create the coding DNA sequence including the translation and save it in the refseq directory.

If your gene does not have a reference sequence configured yet, this script will automatically add the created coding DNA reference sequence to the gene homepage.

For examples on how these reference sequences will look like, take a look at the reference sequences [www.DMD.nl](http://www.DMD.nl), such as the [CAPN3 reference sequence](#).

## Use of HTML within LOVD

LOVD allows very limited use of HTML, in contrast with LOVD 1.1.0. HTML stands for HyperText Markup Language, and is the language used to create webpages. HTML allows you to define markup in headers, footers, notes and other information.

It is restricted to authorized users only, and not in any variant or patient fields. The reason for this restriction is that allowing HTML input also allows Javascript code insertion, which in turn allows a security thread referred to as XSS, or Cross-site scripting. Javascript code inserted by a submitter may, amongst other things, lead to the theft of a curator's account information.

These forms allow HTML input:

- System settings form
- Create and edit genes
- Create and edit custom columns
- Change custom column display settings
- Create and edit custom links

There are so many books and websites about how to write HTML, that explaining HTML here, even the basics, is useless. In stead, I will provide a couple of links that may help you find your way in HTML.

[World Wide Web Consortium \(W3C\)](#)

The W3C is responsible for the definition of HTML standards and provide full documentation on all HTML versions, however they provide quite technical reading.

[Introduction to HTML HTML Tutorial](#)

By Ian Graham, author of the "HTML Sourcebook".  
By W3Schools.

Please note that when using HTML in LOVD, you do **not** need to declare or close the <HTML>, <HEAD> or <BODY> tags, since LOVD will do this.

## Updating LOVD

At least once every month, a new LOVD build is released. Currently, this is at the first Monday of the month. An update may contain bug fixes, new features, new custom columns, module updates and such. Therefore, each update has a priority setting to indicate how important it is to update your LOVD installation to the new release.

Depending on whether or not LOVD has found that there is an update available, an update icon appears at the bottom right-hand side of the screen:



There is an update available.



There is no update available.



There was an error while checking for updates.

If you are logged in as an authorized user, you can click the update notification icon for more information on the status of the update. If an update is available, detailed information is presented:

**Last checked for updates:** Shows the date LOVD last checked for a new update.

**Latest version:** Shows the detected update.

**Release date:** The date this update has been released.

**Priority level:** Shows how important the LOVD developers consider this update. Can contain 'Optional', 'Common', 'Suggested', 'Recommended', 'Important' or 'Critical', with increasing priority.

**Release info:** Information on the changes that have been done in this release. Please note that this is usually only a very short list of updates. A more elaborate description can always be found in the [news section](#) of the LOVD website, and the full list can be found in the [LOVD changelog](#).

### If you choose to upgrade LOVD, follow these steps:

1. **Download the new build.** Either using the direct link to it from the update window, or from the website.
2. **Unpack the new build** and overwrite the LOVD files.
3. If you're working from your local machine, **upload the updated files** to your webserver.
4. **Log into LOVD.** This is an important step. If you are already logged in, perform some activity, like clicking on the Home tab. LOVD will then upgrade the database tables to make sure the database backend has the same version as the files. Skipping this step may result in serious errors occurring.
5. **You're done!**

## Keeping your data secure

LOVD contains several important security measures to protect your data from unauthorized access. This page explains IT experts what kind of security measures are implemented in LOVD, but it also shows what you as a LOVD user can do to protect your data.

### ***Built-in security measures***

After a public request on a programmer's internet forum a LOVD installation had been subjected to various attacks and hack attempts. Furthermore, the source code has been security audited by three different software packages to ensure no security holes were left open.

Some of the security risks LOVD protects you against, are displayed below.

### **Protection against SQL injection**

SQL injection is the process of including unwanted SQL database commands into a database through the manipulation of online web forms. SQL injection can be used for, amongst other things, unauthorized modification of database contents or unauthorized access to the administrator account.

### **Protection against Cross-site scripting (XSS)**

Cross-site scripting is a vulnerability where malicious users can include Javascript code into webpages, through entering a script in web forms, or including code in variables which are being printed on the web page. This can, for instance, be used to forward a user unnoticed to a different site.

### **Password protecting data manipulation forms**

To prevent manipulation of your variant or patient data when your computer is used by someone else while you are logged into LOVD, all data manipulation forms are password protected. Before the form can be submitted and processed, your password is required to confirm the changes.



## ***What you can do to protect your data***

A chain is only as strong as the weakest link. Even with all the effort we have put into making LOVD as safe as possible, some weak links may still exist. Read this section to learn about how to protect LOVD further.

1. **Choose your password carefully and protect it.** Even though LOVD does include a password quality check, please take care in choosing a password that can not be guessed by others and you don't use for other systems as well. Also, don't write it down on a sticky note stuck near your computer.
2. **Don't leave your computer unattended while logged in.** This will give anyone who uses your computer in your absence access to the data stored in LOVD. Also, don't leave your computer unattended if you're not logged in but had your browser remember your password for you. Once you're done using LOVD, log out.
3. **Use cookies.** Make sure the "Use cookies for user authentication" setting in the LOVD system settings is enabled. Disabling it, allows others to hijack someone's user account more easily.
4. **Use SSL.** Ask your systems administrator to enable SSL (https) on the server your LOVD is installed on, and enable the "Use SSL only to access LOVD" option in the LOVD system settings. This encrypts any data exchange between you and LOVD, such as your password and sensitive patient information.
5. **Don't allow access to your LOVD files or the database to other users on the server.** If there are other users on the server you have LOVD hosted on, make sure they cannot access the LOVD directory or get access to the same database LOVD stores its information in.
6. **Verify LOVD modules.** Modules for LOVD introduce new code in LOVD that can be malicious. Don't install a LOVD module unless you're sure it's from a trusted source.