



LodIRO: Helping Linkage Based Eye Research Go Faster

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Purpose

To describe lodIRO a freely available web interface for linkage analysis in inherited eye diseases. LodIRO is included in webIRO the common platform dedicated to linkage analysis of the Institute for Research in Ophthalmology.

Introduction

In order to isolate genes involved in diseases, geneticists use several statistical tools. They are largely used to perform linkage analysis by computing data set composed either of genetic marker alleles or SNP alleles obtained from microarray. This approach uses the logarithm of the Odd technique (LOD score) to calculate the overall likelihood that contiguous markers are linked. Computerized LOD score analysis is the best way to examine complex pedigrees for linkage between Mendelian characters¹. The amplitude of the LOD Scores depends on several factors in particular the number of members who participate to the study and others parameters generally determined in an empirical manner.

A wide variety of software capable of doing such statistical calculations is available. The main differences between them are the input data and configuration files, the accuracy and how the results are displayed.

The content of the input files is identical and only the way it is arranged differs. LodIRO was designed to overcome the creation of such individual files for each software.

LodIRO is a tool included in webIRO (fig.1), the common platform dedicated to linkage analysis of the Institute for Research in Ophthalmology. It is accompanied by other tools such as pedIRO a pedigree drawer, genIRO a data screening software that translates data files exported from sequencer machine software into input ready files for linkage analysis and snpIRO a platform dedicated to SNPs.

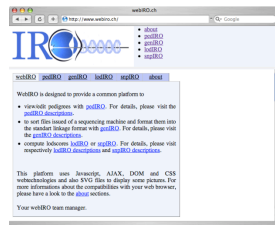


Fig. 1. The home page of webIRO.ch where lodIRO and other free tools are available.

WebIRO is freely available at the address <http://www.webiro.ch>

Material and Method

The frontends of lodIRO are HTML web pages generated with PHP executed on a server. The calculation is performed in four steps:

1. The main page consists of a per chromosome data file selection that is uploaded together with the statistical software chosen by the user to perform the analysis. The actual choice of software is limited to autoscan² and genehunter³ and will be extended to merlin⁴ and allegro⁵ in the near future.
2. The second page is the interface for the calculus settings. Common parameters have to be entered only once, independently of the software selection.
3. While proceeding to the third page the data files integrity is checked. Because the uploaded data files contain originals markers values, a by marker recoding is performed ranging from 1 to the sum of different alleles values found throughout the pedigree. Undefined values and non digits characters are set to 0 (zero).
Next, the input parameter files are created following the user manual of each separate software. Some tools are able to display graphically genetic maps of resulting LOD score calculation. For this they need a supplementary file filled with genetics inter-markers distance. This can be tricky and time consuming if performed by hand. For this reason a complementary tool was created to automatically generate this file. Based on a database that gather markers name linked to their absolute genetic position on the chromosome the relative inter-marker position is computed. If a marker is not known from the database, it will be asked to the user and added to it for future utilizations.
4. The last page is to display results.

To accelerate the calculation a dedicated home made clustering solution was developed⁶.

In order to quantify the real time improvement brought by the bundle of tools available on webIRO a family actually under study in our lab was used. The pedigree (fig.2) of this family consists of 68 members including 5 consanguinities.

The test was performed with the following settings:

- 1 family with 68 persons including 5 consanguinities.
- 24 subjects of them have DNA data available.
- 23 Chromosomes.
- 386 Markers.
- Autoscan, was selected for the analysis with its default parameter.

This represents 18'528 data to be entered and analyzed.

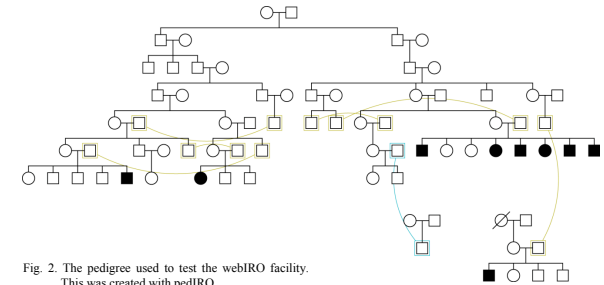


Fig. 2. The pedigree used to test the webIRO facility. This was created with pedIRO.

Results

The mean time needed to introduce the marker alleles in this family by hand is about 16 hours per chromosome (~50 data/hour) and was decreased with the genIRO program to about 2 hours for the whole genome.

The total time needed for the statistical analysis without the clustering solution was 62 hours. Improved by the clustering solution, the typical calculation time was decreased to 2.3 hours.

Conclusions

A single web interface reduces the risk of transcription errors from the DNA sequencer through the different programs and facilitates linkage analysis in inherited eye diseases. This facility is freely available to the eye disease research community through the web site <http://www.webiro.ch>.

References

1. Human Molecular Genetics 3, Tom Strachan & Andrew P.Read, Garland Science, ISBN 0-8153-4184-9
2. <http://www.helsinki.fi/~tsjuntun/autoscan/>
3. <http://linkage.rockefeller.edu/soft/gh/>
4. <http://www.sph.umich.edu/csg/abecasis/Merlin/index.html>
5. <http://www.decode.com/software/>
6. <http://comosix.sourceforge.net>