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HC Forum®: a web site based on an international human cytogenetic database

Olivier Cohen*, Marie-Ange Mermet and Jacques Demongeot

Genome Team, TIMC Laboratory, UMR 5525 CNRS-UJF, IMAG, Medical School of Grenoble, Domaine de la Merci, F38700 La Tronche Cedex, France

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ABSTRACT

Familial structural rearrangements of chromosomes represent a factor of malformation risk that could vary over a large range, making genetic counseling difficult. However, they also represent a powerful tool for increasing knowledge of the genome, particularly by studying breakpoints and viable imbalances of the genome. We have developed a collaborative database that now includes data on more than 4100 families, from which we have developed a web site called HC Forum® (http://HCForum.imag.fr). It offers geneticists assistance in diagnosis and in genetic counseling by assessing the malformation risk with statistical models. For researchers, interactive interfaces exhibit the distribution of chromosomal breakpoints and of the genome regions observed at birth in trisomy or in monosomy. Dedicated tools including an interactive pedigree allow electronic submission of data, which will be anonymously shown in a forum for discussions. After validation, data are definitively registered in the database with the email of the sender, allowing direct location of biological material. Thus HC Forum® constitutes a link between diagnosis laboratories and genome research centers, and after 1 year, more than 700 users from about 40 different countries already exist.

INTRODUCTION

Familial structural rearrangements of chromosomes represent a factor of malformation risk that could vary over a large range, making genetic counseling difficult. However, they also represent a powerful tool for increasing knowledge of the genome, particularly by studying breakpoints and viable imbalances of the genome.

Structural chromosomal abnormalities, which result from abnormal sticking following chromosomal breakpoints, concern about one couple in 200 in the general population. The difficulties in studying them, and also their potential, result from the very large number of different abnormalities, as the chromosomes involved and the location of the chromosomal breakpoints vary from one abnormality to another.

In medical practice, structural abnormalities present two kinds of difficulties:

- cytogenetic diagnosis of rearranged chromosomes
- genetic counseling with estimation of the specific risk of malformation since it can vary between ~0 and 80%

In research, structural abnormalities represent an extremely powerful tool for physical cartography of the genome, and the discovery of numerous genes has already benefited from these potentialities (Duchenne muscular dystrophy, retinoblastoma, etc.). In the future, they should also be used to approach functional genomics by studying phenotype–genotype correlation.

But the use of structural abnormalities remains very insufficient, since the cytogenetic laboratories who discover them do not know who to offer them to, and the research laboratories who need them do not know where to ask!

THE DATABASE

HC Forum® is a repository of raw data relevant to familial structural abnormalities of autosomes. HC Forum® stores data from published papers and unpublished data from genetic medical centers.

The database currently contains anonymous genealogical data on 4175 families, of which 3527 carry a reciprocal translocation and 648 carry a pericentric inversion.

The last release (August 2000) contained 15 810 different individual karyotypes, exhibiting 3363 different abnormalities.

The database also contains the international chromosomal nomenclature data (1).

HC Forum® can be accessed on the WWW at http://HCForum.imag.fr, however the access is restricted by a password, which can be requested through an online procedure.

INFORMATION TECHNOLOGY

HC Forum® is stored and maintained in the relational database management system (RDBMS) SYBASE. As the pedigree is the current tool in genetics, structuring the information in a genealogical way is of great importance to avoid any loss of information. Therefore each stored data element is linked to its familial and/or couple and/or individual relations.

Each family has a specific identification number and is characterized by the familial abnormality for which individual karyotypes represent variations of the state of the abnormality inside the pedigree.

*To whom correspondence should be addressed. Tel: +33 4 76 63 71 64; Fax: +33 4 76 63 71 74; Email: olivier.cohen@imag.fr

THE DATA

The primary types of data are the pedigree entries including familial and individual karyotypes of the abnormality. The familial data entries include the kind of abnormality with the chromosomes involved and breakpoint locations, and the mode of ascertainment. References of familial abnormalities are another primary type of entry in the database. Pedigree entries give an accession number, which is a permanent unique identifier. From these data, secondary types of data are calculated from nomenclatures and statistical models, such as physical and genetic lengths of the different segments of the rearranged chromosomes.

DATA SUBMISSION

The primary intent of HC Forum® is to be a public repository of familial structural abnormalities whatever their mode of ascertainment. Since medical data often remain unpublished, an online procedure was made available. Ideograms of chromosomes warrant the entry of the breakpoints according to the international nomenclature (1). An interactive pedigree drawing allows the entry of familial and individual data in a user-friendly submission process in which a simple click on symbols of the pedigree opens individual data windows.

A forum receives the pedigrees sent via the Internet, for anonymous exhibition and discussion. After validation, data are entered into the database and associated to the email of the sender in order to allow contact with interested users.

The administrator of HC Forum® can also enter data-providing papers or paper mail submission.

DATA QUERY/RETRIEVAL

Queries are performed from graphical exhibition of data based on ideograms of chromosomes. HC Forum® offers three kinds of information.

(i) Assistance in diagnosis by instantaneously representing the chromosome rearranged in accordance to the international nomenclature.

(ii) Assistance in genetic counseling with an estimate of risk of malformation specific to each abnormality, based on original statistical models extracted from data (2). Much information related to the meiotic behavior of rearranged chromosomes and to natural selection is provided with educational information (3–5).

(iii) Assistance for research with cartographic representations of the chromosomal breakpoint distribution (6) (Fig. 1), and of the genome segments observed at birth in trisomy or monosomy and responsible for polymalformation/mental retardation syndromes (Fig. 2). Interactive screens allow the immediate acceptance of specific information related to the data shown, such as gene content through a link to Genatlas database (7), a contact for the senders of data and references with their summary through a link to PubMed (NCBI).

The graphical views can be printed after a capture procedure.

DISCUSSION AND FUTURE DEVELOPMENT

During the first year, HC Forum® was requested about 150 000 times, by about 700 different users from 40 different countries. HC Forum® constitutes a link between genetic medical centers and genome research laboratories by providing

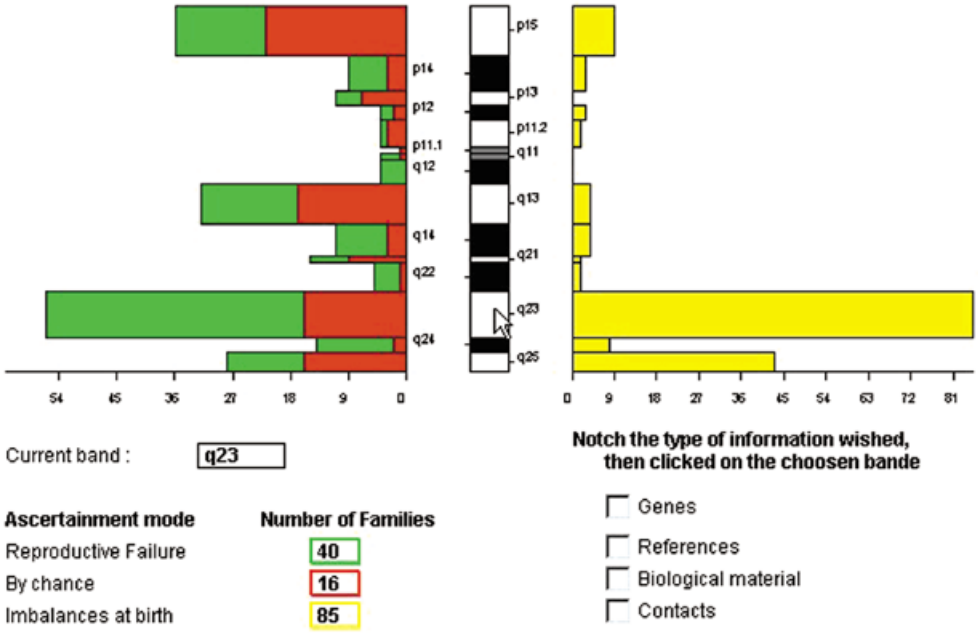

Figure 1. Example of interface showing the distribution of breakpoints from reciprocal translocations involving chromosome 11. Histograms show the number of breakages observed in each band, according to the mode of ascertainment.

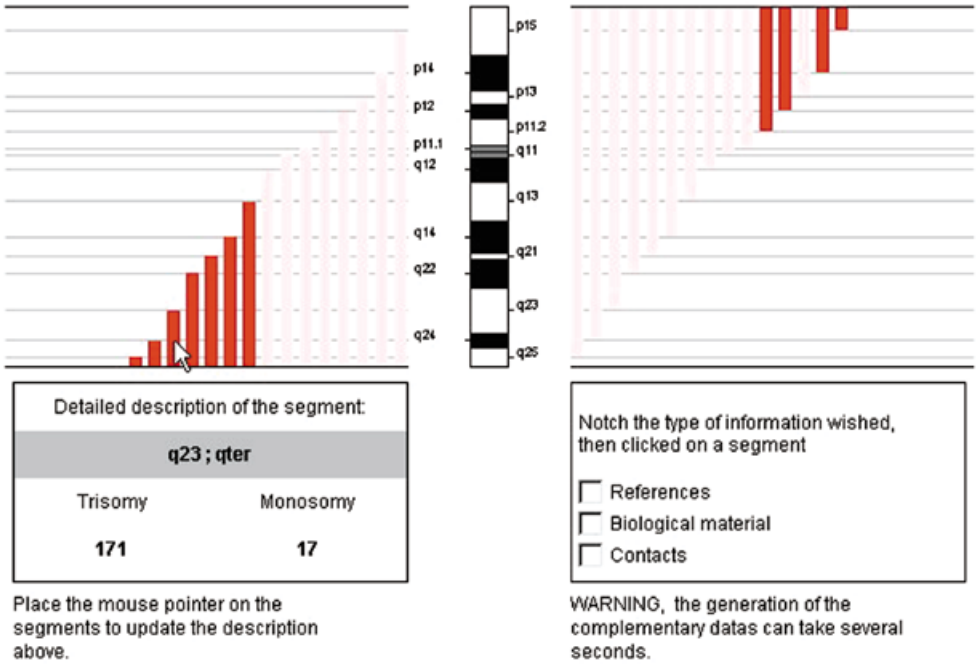

Figure 2. Example of interface showing the distribution of unbalanced regions of chromosome 11 observed at birth in trisomy and in monosomy. The size of each bar corresponds to the size of the facing chromosomal segment. It is shown in red when a given imbalance is already observed, and in pink if not.

contacts for finding biological material relating to any abnormality of interest.

Whereas genetic counseling is very difficult in familial structural abnormalities, the available statistical models are particularly helpful to inform the carriers and to define the best strategy, particularly in prenatal diagnosis or in assisted procreation.

All the patients' data are anonymously shown. Nevertheless, HC Forum® is restricted to professional use to ensure proper protection of the patients and families. Indeed, in some cases, the risk of malformation can be very high and reaches ~80%. It is not desirable from an ethical point of view that families should be informed over the web that they carry such a malformation risk without any medical support. Moreover, the aim of this site is not to replace medical genetic consultations, but to simply constitute a supportive tool for them.

Emergencies are very rare while genetic counseling is generally differed to a potential next pregnancy.

The request for a password is a 'once and for all' procedure and does not seem to constitute a real barrier to the access to information. Therefore the choice has been made to aid true protection of the patient with regard to the very weak probability that the restricted access of HC Forum® could represent an obstacle in an emergency.

In the coming update, a thesaurus of dysmorphology (8) will be available and it will be possible to associate pictures in order to enter the description of the clinical features related to the unbalanced chromosomal abnormalities.

Furthermore, an unrestricted access will be also added to HC Forum® to provide information for patients including explanations on structural abnormalities with the aim of reinforcing the prevention of malformed progeny in the family of the carriers.

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