The Israeli National Genetic Database*

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ABSTRACT: The Israeli National Genetic Database http//www.goldenhelix.org/israeli is a continuously updated depository on monogenic genetic disorders that are present in the various Israeli populations. It provides the means of obtaining information for clinical purposes, genetic counseling and research.

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The Israeli population includes Jewish communities that have been separated from one another for centuries, as well as several non-Jewish communities. In each of these communities certain genetic disorders have been found in a relatively high frequency. The genetic disorders that were found among Jews were compiled by the late Prof. Richard Goodman [1], and since 1998 the list is updated in a catalog that is available online (http://www.health.gov.il/genetics). In parallel, a catalog of genetic disorders in the non-Jewish population in Israel was created.

The Israeli National Genetic Database includes clinical and molecular data on genetic disorders present in the different Israeli populations as well as on the Israeli laboratories providing diagnostic services for these disorders

In 2007 the Israeli population comprised 7,243,600 citizens of whom 75.8% were Jews and 16.5% Muslim Arabs [2]. The Bedouins, most of whom live in the Negev desert, represent one-fifth of the Muslim Arabs. The other groups, which include mainly Christian Arabs and Druze, each represent less than 2% of the population. There are also some smaller ethnic groups in Israel, in particular the Circasssians, Armenians and Samaritans.

The Jewish population immigrated to Israel from most countries in the world. Although genetic differences existed among Jews in the various regions where the Ashkenazi** Jews were living, it is difficult to distinguish subgroups among them. On the other hand, most of the other Jewish communities remained geographically separated and they developed as distinct identities. Consanguineous marriages were relatively common but since the creation of the State of Israel in 1948 they became rarer in all the Jewish communities [3].

As a rule, the Arabs and Druze live in villages/tribes that were founded by a few individuals less than ten generations ago. Today, there are more than 100 entirely non-Jewish localities in Israel, most having between 2000 and 10,000 inhabitants. In several of the largest Israeli towns a large Arab population lives as a minority. In more than 20% of Arab and Druze marriages the spouses are first cousins with an additional 25% related in other ways [4]. As a result, in most of the disorders the high frequency is limited to a local community, either a village or a tribe.

In September 2006, we launched the Israeli National Genetic Database (available at http://www.goldenhelix.org/israeli) in order to improve the availability of existing knowledge on genetic Disorders in the Israeli population and their distribution in the various Israeli ethnic groups [5]. The Israeli National Genetic Database is based on the ETHNOS software, an off-the-shelf database management system that facilitates National Genetic Database development and curation [6]. In this article we present the different possible uses offered by the database, with an emphasis on its clinical relevance.

THE DATABASE

SUMMARIES

The summaries are divided into two parts, one for disorders among Jews and the other for disorders among non-Jews. For each disorder the summary includes the mode of inheritance, the Online Mendelian Inheritance in Man (OMIM) number (hyperlinked to the OMIM database http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim), a short description of the disease, its molecular basis if known, its frequency in the population, and some of the most important references (hyperlinked to the PubMed literature summary http://www.ncbi.nlm.nih.gov/PubMed/). In August 2008 the database included 428 summaries, 173 concerning disorders among Jews and 255

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** Jews of East European origin

Figure 1. The summaries page of the database

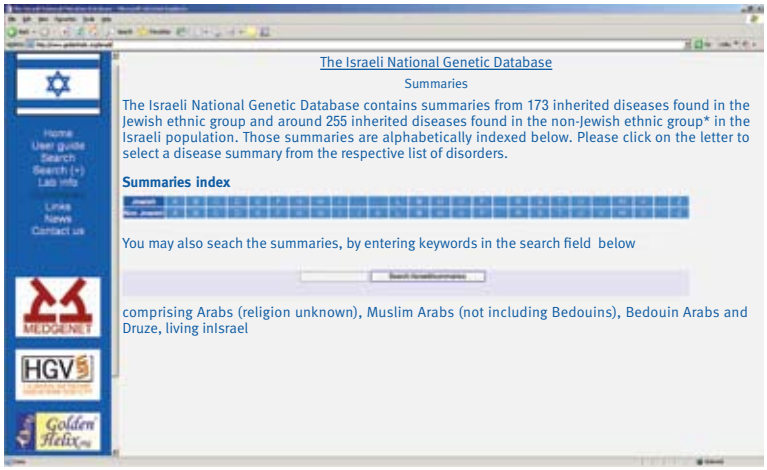
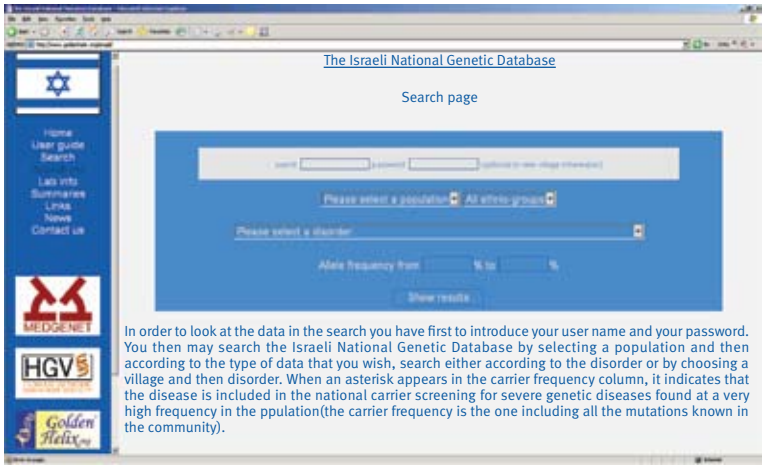


Figure 2. The search page of the database



on disorders in the non-Jewish Israeli population. Some of the disorders are present in both populations; therefore, summaries of the same disorder may be found in each part of the database, including different data on the frequency, the underlying mutations, and the references. The search for a summary is possible through two alphabetical indexes, one for each population [Figure 1].

The Israeli database is equipped with a query module based on key words that allows the user to formulate queries in the disease summaries [Figure 1]. This facilitates searching the data included in the summaries, particularly since rare diseases often have more than one name and the relevant summary may be difficult to localize. Another function it offers is searching for a specific symptom from the list of disorders that are relatively frequent in the population from which the patient originates, thereby adding a population-related differential diagnosis.

The database provides the means to obtain information for clinical purposes, genetic counseling and research

MUTATION DATA

This part of the database includes disorders in which at least one causing mutation is known. It is possible to search according to the disorder or to the population, classified as either Jews or non-Jews. The Jewish population is subdivided as Ashkenazi and non-Ashkenazi according to the country of origin, while the non-Jewish population is subdivided according to religion when it is known. Muslims are subdivided into two groups: Muslims (non-Bedouins) and Bedouins.

The total number of entries is 756 – 353 for Jews and 403 for non-Jews. Results are returned in a tabular format in which the gene and mutation(s) are given in their official nomenclature, accompanied by the allelic and carrier frequencies, where available, and the respective OMIM number, hyperlinked to the corresponding web page.

THE "SEARCH +" FEATURE

This feature was recently included in the database to enable the acquisition of information on genetic diseases that exist in each of the localities where Arabs and Druze live. In this part of the database the monogenic disorders known in each locality are included even if no molecular data are available [Figure 2]. In August 2008 there were 553 entries, but this represents the most incomplete part of the database since it depends directly on the cooperation of clinicians working in the localities. In order to protect patient privacy and to ensure anonymity, data access is provided on the basis of a username and password.

The search may be conducted according to either locality or disorder. This feature allows the acquisition of a list of the disorders known in the localities, or the distribution of a disorder in the different religions and among the different localities.

LABORATORY INFORMATION

The "Lab info" page contains relevant information on the laboratories involved in the provision of genetic services in Israel that contributed information to the database. The user can select the relevant genetic laboratory from the corresponding table, categorized by institute, department, and city. Alternatively, it is possible to select an inherited disorder from the menu, and identify which laboratory (laboratories) is (are) involved in administering this test. The information also includes the type of examination that is provided by the laboratory, such as the test determining details of the mutations examined and/or other services such as sequencing or linkage. The name of the laboratory is hyperlinked to detailed information, the name of the scientist(s) in charge including contact details, and the complete list of genetic tests offered by this center.

DISCUSSION

The Israeli population is diverse and includes Jewish communities that were separated from one another for centuries, and several non-Jewish communities isolated because of their preference to marry close relatives and the absence of inter-religious marriages. These communities are characterized by an increased frequency of many monogenic diseases. The Israeli National Genetic Database offers the means to obtain the available information for use by general physicians, medical geneticists and researchers.

The usefulness of the database is in direct relation to its completeness. In order to achieve this aim, the collaboration of users is needed – namely, that they contribute their data and correct any existing mistakes and omissions

Clinical practice is an area that can benefit enormously from the database. When a disease is relatively frequent in the population of origin of a patient, the differential diagnosis of his or her symptoms may be different from the classical one found in textbooks. For example, while most physicians identifying splenomegaly in an Ashkenazi Jew will raise the possibility of Gaucher disease early on, few know that in an Iranian Jew with hypoparathyroidism the most probable diagnosis is Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED, polyglandular syndrome). In this example, the difference in the manifestations that may be expected to occur in addition to hypothyroidism is significant and early diagnosis may allow a much more effective treatment and follow-up. The database not only enables a relevant differential diagnosis according to the origin of the patient but provides the means to reach a rapid diagnosis. The database shows that among Iranian Jews the condition is due to a unique founder mutation in the *AIRE* gene and that there are two laboratories where the test can be performed.

Another significant use of the database is genetic counseling. Knowledge of diseases that exist in the population from which the family originates allows for better understanding of the problems existing in the proband. The database is particularly useful for geneticists, since in many cases the families who come for counseling do not know which illness may be present among their relatives. By knowing which diseases are known in the community the physician/researcher can ask more precise questions about the condition present in the family. In addition, when data are available the frequency of the mutation in the community is also included. Knowledge that a disease is present in several families in a small community is essential for public health purposes and may be helpful for planning medical facilities and/or prevention programs. Indeed, information on the frequency and distribution of genetic diseases in the non-Jewish population in Israel was the basis for the initiation in 2002 of a national program for the prevention of severe genetic diseases [7]. The information about diseases included in the national program is included in the database.

Another important function of the database relates to research. The accumulated data indicate disorders that are known but not yet characterized and for which further research is needed, or a rare disorder currently under investigation and found in another locality. In addition, it allows comparative studies between different subpopulations in the Israeli population or even neighboring populations if such information is available [8]. On the basis of the ETHNOS software, many more national genetic databases have been developed [9,10], and this software is being implemented by the MEDGENET European-funded project for the development of community genetics databases in different populations (http://medgenet.tredueuno.it).

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