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Familial cancer database: a clinical *aide-mémoire*

Rolf H. Sijmons[1] and Gerard T. N. Burger[2]
[1] *Department of Medical Genetics, University of Groningen, Groningen, The Netherlands;* [2] *Department of Pathology, Sazinon Foundation, Hoogeveen, The Netherlands*

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Abstract

Cancer is associated with a wide range of hereditary disorders. Recognizing these disorders in cancer patients may be of great importance for the medical management of both patients and their relatives. Conversely, recognizing the fact that cancer may develop in patients already diagnosed with a particular hereditary disorder may be important for the same reason. We have developed a stand-alone interactive computer program, Familial Cancer Database (FaCD), to assist the clinician in making a genetic differential diagnosis in cancer patients as well as in becoming aware of the tumour spectrum associated with a particular hereditary disorder. The program tries to match tumour and non-tumour features observed in patients and their families with any of the more than 300 disorders presently contained in its database and provides a clinical synopsis with literature references for each of these disorders. FaCD is offered free of charge in support of the Familial Cancer and Prevention project of the UICC Cancer Epidemiology and Prevention program. The software is primarily aimed at health care professionals with at least a basic knowledge of clinical cancer genetics, and can be downloaded from the internet (at http://facd.uicc.org).

Introduction

As a result of recent clinical and basic research on hereditary disorders, there has been a vast increase in knowledge on hereditary aspects of cancer [1]. Cancer has been reported as a feature of more than 200 hereditary disorders [2]. These disorders include the human cancer syndromes, associated with high life-time risks of developing cancer, as well as the much larger group of hereditary disorders associated with a smaller increase in cancer risk. The recognition of a hereditary nature of cancer in patients by their physicians may have major implications for both treatment and cancer prevention, not only for those patients, but also for their families [3]. From a different clinical perspective, recognizing the fact that tumours may be part of the clinical spectrum of hereditary disorders already diagnosed, may lead to early detection or prevention of those tumours.

Some hereditary tumour syndromes are well known and easily recognized by the majority of physicians, e.g. the classical phenotype of familial adenomatous polyposis. Others are less well known and may therefore be incorrectly left out of a genetic differential diagnosis. A similar problem applies to oncological aspects of hereditary disorders already diagnosed in non-cancer patients. In some, the fact that cancer may complicate the disease is well known, e.g. in von Recklinghausen disease or Beckwith-Wiedemann syndrome. In others, it is not. Moreover, it may be difficult for physicians to keep an overview of cancer-associated hereditary disorders, because new data on these disorders are continuously being published, which leads to new clinical classifications and diagnostic criteria. With this in mind, we set out to develop a computer program, which should be easy to update, to assist the physician in recognizing hereditary disorders in cancer patients as well as in recognizing the possibility of cancer developing in their patients already diagnosed with a hereditary disorder.

Materials and methods

A list of established or presumed hereditary disorders associated with tumour development was compiled from the literature by consulting the following sources:

Correspondence to: R.H. Sijmons, Department of Medical Genetics, University of Groningen, A. Deusinglaan 4, 9713 AW Groningen, The Netherlands; Tel: +31-50-363-2925; Fax: +31-50-363-2457; E-mail: r.h.sijmons@medgen.azg.nl

McKusick's on-line catalogue of hereditary phenotypes (Online Mendelian Inheritance in Man, OMIM, found at www.ncbi.nlm.nih.gov/Omim), a catalogue of human genes predisposing to neoplasia (ONCO-MIM) [4], textbooks on hereditary cancer [5–14], as of 1994, weekly searches in Current Contents on Diskette, additional searches in Medline, and literature references found through the previously mentioned sources. The same was done for congenital anomalies (not necessarily hereditary) and constitutional chromosomal abnormalities (e.g. Down syndrome) associated with cancer, because these disorders are considered in a clinical genetic differential diagnosis as well. All disorders thus identified were stored in a set of relational databases, written in Microsoft Access 1.1 (© Microsoft Corporation, Redmond, WA, USA). Although the emphasis of this database is on malignant tumours, hereditary disorders which feature (multiple) benign tumours with a potential risk for malignant transformation were included as well. For each of the disorders included in the database, information was stored on 9 items: name, synonyms, mode of inheritance, associated genes, McKusick number, tumour spectrum, non-tumour features, a clinical summary and references. Inclusion criteria for these items were as follows. The McKusick number, mode of inheritance and genes involved were taken from OMIM, updated from more recent literature if available. In cases of doubt with regard to modes of inheritance, as expressed by the catalogue and/or the literature, a question mark was added to these entries in the database.

Tumours associated with the included disorders were labelled with regard to the strength of those associations. Tumours which, based on epidemiological data or molecular studies, were significantly associated with a particular disorder were labelled 'certain'. In many of the rare disorders where no such statistical or molecular data were available, we included tumour types shared by all or the majority of patients reported with that particular disorder. As a general rule, we also included tumours with a relatively early age at diagnosis. In cases of doubt, associations with those particular tumour types were labelled 'possible'. Of the non-tumour features, only those that are most characteristic for each disorder, according to textbooks and review articles, were included. The clinical summary contains a general description of the disorder, mentioning available diagnostic criteria and risk figures. References were included to support the clinical summaries, in particular with regard to oncological and genetic aspects.

The graphical user-interface to access the contents of the database was written in Microsoft Visual Basic Pro 3.0 (© Microsoft Corporation, Redmond, WA, USA) in conjunction with TrueGrid 2.1 Pro (© Apex Software Corporation, Pittsburg, PA, USA). System requirements to run Familial Cancer Database were kept modest: IBM compatible personal computer with a 80486 (or higher) processor, at least 4 megabytes of internal memory (RAM), a mouse, SVGA screen and the Windows 3.1, 95 or 98 operating system (© Microsoft Corporation, Redmond, WA, USA). The program was named Familial Cancer Database (FaCD) and its practical aspects were tested in the clinic by a panel representing the various medical disciplines involved in the diagnosis and treatment of cancer patients and of patients with hereditary disorders (see acknowledgements). The panel's feedback was used to refine the database contents and the user-interface. The medical contents of the database were not systematically subjected to external review.

Results

At the time of submission of this paper, the database contained information on 317 disorders, approximately 90 % of which were established or presumed hereditary disorders, the others being congenital anomalies and constitutional chromosomal aberrations. The interface was programmed to present four main options to the user: 'Find Syndromes', 'Browse Syndromes', 'Browse References' and 'Browse Chromosomes/ Genes'. The first two options are the key features of the program. An on-line help function was implemented, explaining all the features of the program, its limitations and providing general information on hereditary disorders and hereditary cancer.

The 'Find Syndromes' option allows the physician to draw up a search profile choosing from 455 different benign and malignant tumour types and 450 non-tumour features (e.g. immune deficiency) using an organ-oriented interface (Figure 1). Because we wanted the program to be able to deal with family histories when those had not yet been verified and therefore possibly would be less detailed in describing the specific tumour types, several broad search terms were included. Examples of these are gastrointestinal cancer, brain tumour and uterine tumour. On running the search profile, the program tries to match it with the disease profiles stored in the database and lists the result (Figure 2). This list, including the search profile, can be printed for use as a check-list in a patient's file. The details of the listed disorders can subsequently be viewed (Figure 3). For each of the tumour types listed in the search profile, the user may choose to have the program search for disorders certainly or possibly featuring that tumour in its tumour spectrum ('wide' search mode) or only certainly doing so ('narrow' search mode).

In the 'Browse Syndromes' option, the disorder of interest to the user can be selected from an alphabetical listing of all disorders included in the database and can subsequently be viewed for details (Figure 3). This section of the program is aimed at the user who wants to look into possible oncological aspects of a particular hereditary disorder which he or she has already diagnosed in a patient, or at the user who wants to read updated practical 'facts and figures' of a particular disorder for use in genetic counselling.

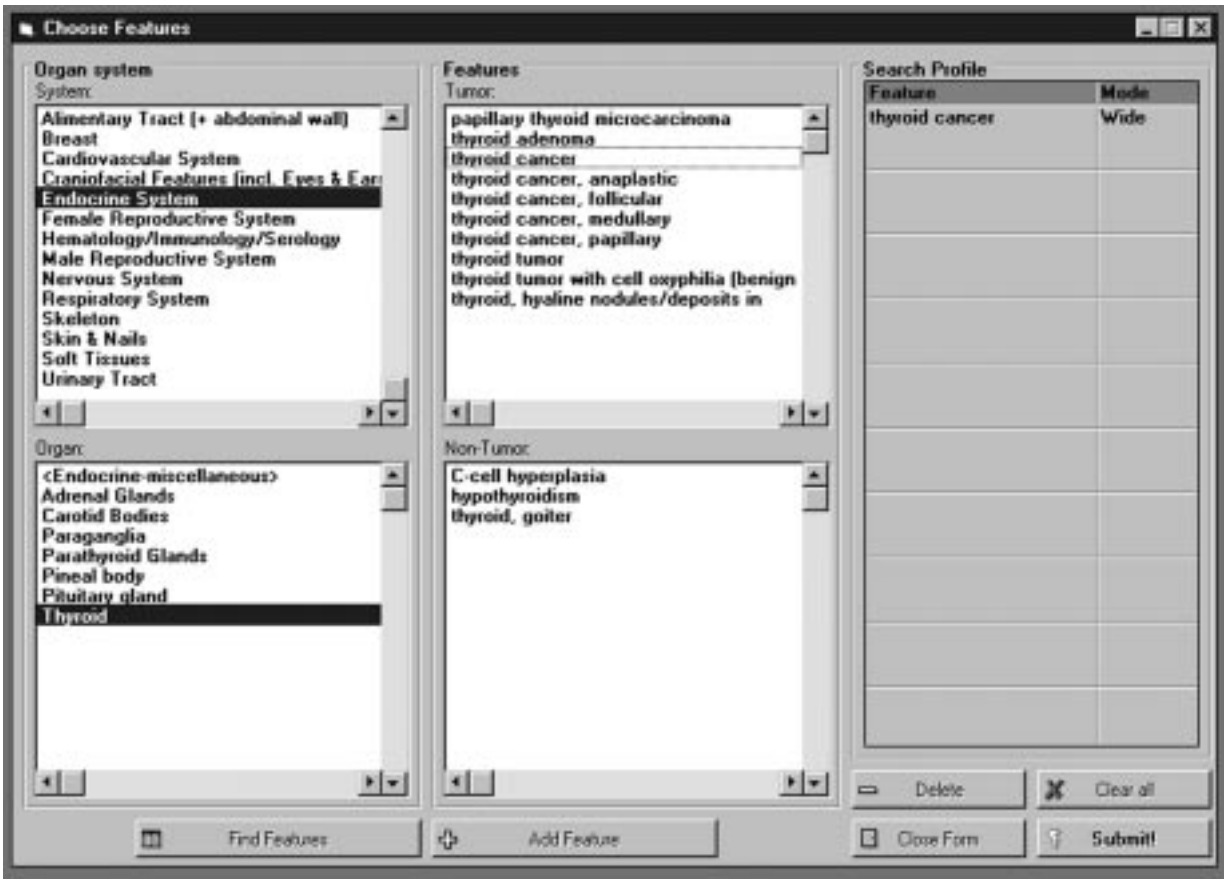

Figure 1. The user can compose a search profile refelecting the features observed in a patient and his or her relatives, by selecting the appropriate tumour and non-tumour features from the organ-oriented listings in this screen. The software will try to match this selection with the profiles of the disorders stored in its database. In this example, the software will search for disorders *certainly or possibly* associated with (any type of) thyroid cancer. The result is shown in Figure 2. The user may change the search mode in the search profile from 'wide' to 'narrow' in order to search for disorders which are *only certainly* associated with thyroid cancer.

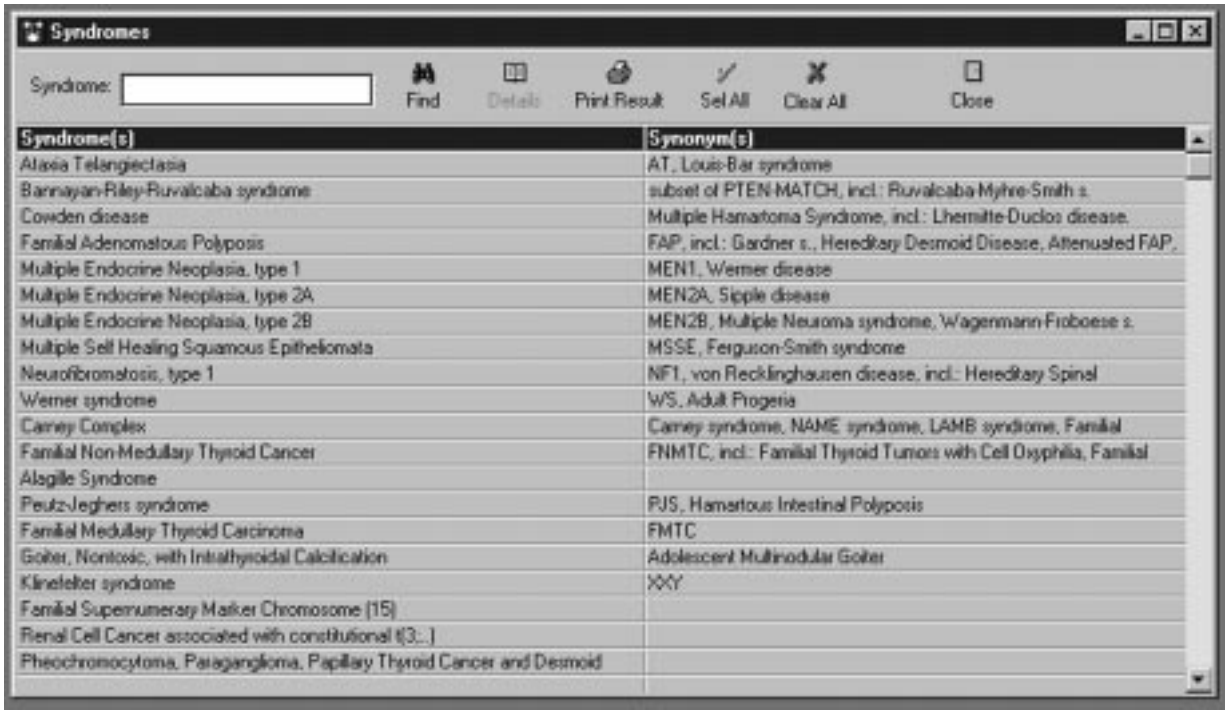

Figure 2. This screen displays the disorders associated (possibly or certainly) with thyroid cancer as found by the software after the user submitted the search profile shown in Figure 1. Details from each of these disorders can be viewed on screen and printed, an example of which is shown in Figure 3. The search profile together with its search result can be printed as well, e.g. for use as a check-list.

Name: Alagille Syndrome

---> Mode of Inheritance: AD

---> Genes:
JAG1, located on 20p12

---> McKusick number(s): 118450

---> Tumor Spectrum:
hepatocellular cancer
thyroid cancer, papillary (possible feature)

---> Non-Tumor Features:
bile ducts, paucity of intrahepatic
chin, triangular
embryotoxon posterior
eyes, deeply set
frontal bossing / prominent forehead
hypertelorism
midface, flat/hypoplastic
nose, long straight
philtrum, short
pulmonary artery stenosis
vertebral anomalies

---> Comment:
Hallmarks of this disorder are: paucity of intrahepatic bile ducts leading to cholestasis, (peripheral) pulmonary artery stenosis, vertebral arch defects, poor linear growth, a characteristic facies and embryotoxon posterior in the eye[1]. Hepatocellular cancer has been reported in a number of cases[3,4,6] and papillary thyroid cancer in one case[2]. This syndrome is caused by germline mutations in the human Jagged1 gene (JAG1)[5]

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---> Date Last Edited: 16 Dec 1998

Figure 3. Example of a clinical details screen. The remark '(possible feature)' after a feature's name means that the association of this feature with the syndrome is presently uncertain.

In the 'Browse Chromosomes/Genes' option, the user can select a specific chromosomal area and view the cancer associated genes located in that area. Also, the disorders associated with any of the more than 300 genes included in the database can be viewed. This section might be useful to physicians confronted with a constitutional structural chromosomal abnormality in a cancer patient or family, although we also strongly recommend checking the much larger gene list found at www.ncbi.nlm.nih.gov/Omim in those cases. Finally, the 'Browse References' option allows the user to search the more than 2000 references in the database by name of the first six authors.

Discussion

We have developed a computer program (FaCD) to help clinicians to orientate themselves on the possible hereditary aspects of tumours in their patients, as well as on oncological aspects of hereditary disorders already diagnosed in their patients. Because knowledge of these aspects rapidly changes, the use of software offers an advantage over printed literature as it can be more readily updated and redistributed (e.g. through the Internet). For orientation purposes, our software also offers advantages over on-line computerised literature searches because it presents information in a review format and contains many references not found by computerised searches, e.g. older literature, articles with relevant information not listed in title, abstract or keywords which are therefore not recognized by the search engines, and book references which are often not

included in electronic literature databases. Online Mendelian Inheritance in Man (OMIM) is a very valuable and updated source of information on hereditary disorders in a review format. However, it is not specifically focused on oncological aspects of these disorders (the ONCO-MIM version is focussed on these aspects, but cannot be searched online). Our program has of course limitations as well. The user needs a computer and (basic) knowledge of computers to use the software. Therefore, depending on the circumstances, consulting textbooks or other printed sources may be more convenient. Also, the present version of our program does not contain any illustrations and because of its focus on the genetic differential diagnosis of tumours, it does not discuss clinical management of disorders and covers only the most characteristic non-oncological aspects.

A limitation for any type of review on hereditary disorders, congenital anomalies and constitutional chromosomal abnormalities stems from the fact that for many of these disorders and for a wide range of tumours, there is no solid evidence yet that these tumours are truly part of the phenotype. We have explicitly labelled uncertain associations as 'possible' in the database and the user may choose to have the program search only for certain ones. Still, we are aware of the fact that deciding on the strength of association of a tumour type with a particular disorder in the absence of statistical or molecular proof is often arbitrary.

The clinical value of searching databases as well as printed literature does not depend on the data contained in those sources alone. The skill of the user in selecting good 'search handles' from the various features observed in a patient and family is important as well. Selecting tumours or features less suggestive of a hereditary cancer predisposition, e.g. a case of lung cancer diagnosed in a 70-year-old heavy smoker from a family with early-onset ovarian cancer, may very well devaluate the search results. Although the on-line help-function of the program gives general hints on selection and discusses modes of inheritance, the user should have at least a basic knowledge of clinical cancer genetics to make good use of the program.

FaCD is primarily aimed at physicians and genetic counsellors working in familial cancer clinics and in departments of medical genetics, oncology (surgical and medical disciplines), pathology and paediatrics. To determine the practical value of the program and allow it to further mature, it needs to be tested by a large group of users from various medical disciplines over some longer period of time. We intend to perform an user survey once this group is sufficiently large. FaCD is presently offered free of charge in support of the Familial Cancer and Prevention project of the UICC Cancer Epidemiology and Prevention program.[1] The software and an illustrated user's manual can be downloaded from the Internet after registration (at http://facd.uicc.org). The authors welcome comments on all aspects of the program at facd@medgen.azg.nl and will continue to update, refine and expand it as warranted from users' feed-back and scientific, clinical and technological developments.

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Note

1. The contents of this paper and the Familial Cancer Database are solely the responsibility of the authors and do not necessarily reflect the official views of the UICC.

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