GENCOR

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Published in:
Netherlands Heart Hournal

Publication date:
2006

GENCOR: a national registry for patients and families suffering from a familial heart disease in the Netherlands

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Introduction. Developments in DNA-diagnostic techniques allow us to identify a significant proportion of patients with gene mutations causing familial heart diseases (arrhythmia syndromes, cardiomyopathies etc.) and to identify family members in early stages of the disease and/or even before symptoms occur. Early treatment can prevent sudden cardiac death and disease progression. However, data on long-term outcome in unselected genotyped patients are scarce due to a lack of large registries. In 2005, a national internet-based registry for familial heart diseases in the Netherlands, named GENCOR, was developed in collaboration with the Interuniversity Cardiology Institute of the Netherlands (ICIN).
Objectives. GENCOR aims to assess the prevalence of familial heart diseases in patients and families in the Netherlands and to facilitate research to improve the quality of diagnostics and therapy in familial heart diseases.
Methods. Patients who visit the (cardio)genetic outpatient clinic are informed about GENCOR and asked to consent to the storage of information about cardiac examinations, family history and DNA diagnostics from all their visits. Patient data are entered into the internet-based GENCOR database by the cardiologist or clinical geneticist in attendance. Additional information can be stored for scientific research.
Results. Four university hospitals are actively obtaining informed consent from the patients, which resulted in the inclusion of more than 300 patients. In 2006, more university hospitals will start using GENCOR and the aim is that all university hospitals will participate. Three research projects have already started using GENCOR.
Conclusion. GENCOR is already a success, regarding the number of included patients and the related research projects set up within a limited period of time. GENCOR provides easy internet-based access for authorised cardiologists, clinical geneticists and scientists throughout the country. (*Neth Heart J* 2006;14:272-6.)

Keywords: registries, genetics, hereditary, heart disease (familial)

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In the past decade the knowledge on the genetic basis of various cardiovascular diseases increased rapidly with the elucidation of several genes that may cause cardiac diseases. This resulted in an increased knowledge on the basic pathophysiology of familial heart diseases but also led to an increase in the diagnostic, prognostic and in some cases even therapeutic possibilities for the individual patient and his/her family.

Familial heart diseases can be divided into primary and secondary cardiac arrhythmia syndromes. Primary cardiac arrhythmia syndromes (or ion channelopathies) are associated with abnormalities in ion channel function, which results in

arrhythmias. Normal cardiac rhythm is dependent on the proper movement of ions mediating the action potential in each cardiac compartment. These arrhythmogenic disorders occur in structurally normal hearts and include the long-QT syndrome (LQTS), short-QT syndrome (SQTS), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), atrial standstill and idiopathic atrial fibrillation.[1,2] Secondary cardiac arrhythmia syndromes (or cardiomyopathies) are defined as 'diseases of the myocardium associated with cardiac dysfunction'.[3] There are four categories of cardiomyopathies: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and restrictive cardiomyopathy (RCM), although it is increasingly appreciated that there is a large overlap between these four categories. The cardiomyopathies manifest differently, from being symptomless to providing major health problems such as progressive heart failure or potential lethal arrhythmias.[4]

Accurate figures about the prevalence and incidence of familial heart diseases are not available for the Netherlands. There are now an estimated 5000 patients with a familial heart disease in the Netherlands and every year this number will increase by 500 patients.

Developments in DNA-diagnostic techniques allow us to identify a significant proportion of patients with gene mutations causing familial heart diseases and to identify family members with the disease in its early stages. Early treatment can prevent sudden cardiac death. However, data on long-term outcome in unselected genotyped patients are scarce due to the great lack of large registries. In 2004, the Interuniversity Cardiology Institute of the Netherlands (ICIN) took the initiative to develop a national registry for patients and families with familial heart diseases, named GENCOR (GENetic CORvitia). GENCOR is developed by analogy with CONCOR (CONgenital CORvitia). CONCOR is a national registry and DNA bank of patients with congenital heart diseases in the Netherlands. CONCOR aims to promote research into the prevalence and long-term outcome of specific congenital heart diseases and their treatment, to develop an efficient organisation structure for improvement of healthcare for these patients and to allow investigation of the molecular basis of congenital heart defects.[5]

GENCOR aims to facilitate studies into the prevalence of familial heart diseases in the Netherlands and to promote research to improve the quality of diagnostics and therapy in familial heart diseases.[6]

The purpose of this paper is to introduce this registry and to describe the design, the methodology and first results of the GENCOR registry.

Methods

GENCOR study population

Patients with primary cardiac arrhythmia syndromes (ion channelopathies) or secondary cardiac arrhythmia syndromes (cardiomyopathies) are potential candidates for the registry. Only when a mutation has been identified is the patient included in the registry. Patients with structural congenital heart defects (e.g. tetralogy of Fallot, aortic coarctation, ventricular septal defect and atrial septal defects, aortic valvar stenosis) or Marfan syndrome are excluded from participation.

Organisation

ICIN's working group on inherited cardiac diseases took the initiative to develop GENCOR. Cardiologists and clinical geneticists (with a special interest in cardiogenetics) of all the academic centres in the Netherlands are represented in this working group.

GENCOR is directed by a project group and steering committee. The project group is responsible for the inclusion of patients, project documentation and public relations. The project group consists of two cardiologists (project managers), one research nurse (project coordinator), two clinical geneticists, an IT manager and a research fellow. The steering committee supervises the GENCOR project and consists of one representative from the Departments of Cardiology and/or Departments of Clinical Genetics per participating academic centre, the project managers and project coordinator. The representatives per centre can join the steering committee, depending on the contributions made to GENCOR.

Legislation

The GENCOR registry is reported to the Dutch Data Protection Authority (CBP), which supervises compliance with legislation regulating the use of personal data. GENCOR complies with the 'Code of conduct for medical research' drawn up by the Dutch Federation of Biomedical Scientific Societies (FMWV). The laws in force in the Personal Data Protection Act (WBP) and the Medical Treatment Contracts Act (WGBO) are incorporated in this code of conduct.

The Medical Research Involving Human Subjects Act (WMO) does not apply to the GENCOR registry because the included patients are not subjected to research bounded activities and no rules of behaviour are enforced to them.

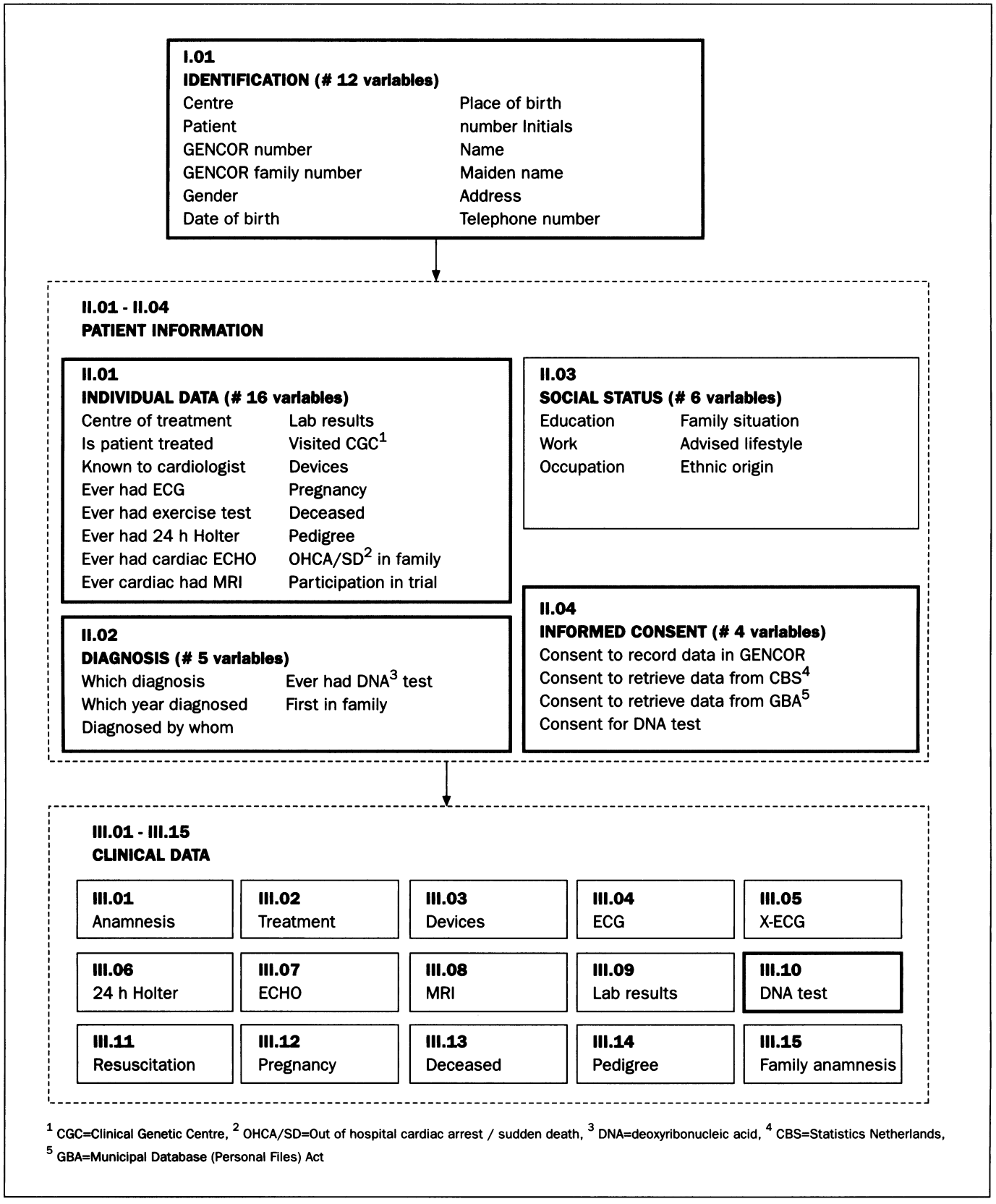
Inclusion procedure

Patients receive information about the aims and procedures of the GENCOR registry from their cardiologist / clinical geneticist during their visit to the outpatient clinic. Patients genotyped in the past receive the information at home. Patients are asked to sign a consent form and return it to the project coordinator before their data are stored in the GENCOR database.

Data storage and protection

GENCOR is an internet-based registry. Patient data are entered into GENCOR by the cardiologist or clinical geneticist in attendance. In some cases trained research nurses enter the data. The patient data are collected from patient records from the departments of cardiology and clinical genetics. Each time a patient visits the outpatient clinic additional (new) data are added to the GENCOR registry. Each patient is allotted a unique GENCOR number.

The patient data are stored in three layers. Layer 1 includes information about identification data of the patient, such as name, gender, date of birth and patient hospital number.



[1] CGC=Clinical Genetic Centre, [2] OHCA/SD=Out of hospital cardiac arrest / sudden death, [3] DNA=deoxyribonucleic acid, [4] CBS=Statistics Netherlands, [5] GBA=Municipal Database (Personal Files) Act

Figure 1. Structure of GENCOR registry.

Layer 2 includes general information about patients examination status. It is noted whether the patient has had an electrocardiogram (ECG), echocardiography, 24-hour Holter monitor or other cardiac examinations. The results of the cardiac examinations, family history and DNA diagnostics are recorded in layer 3. Each layer is made up of one or more information blocks and each information block consists of variables with respect to the subject of the block. In figure 1 the structure of the registry is presented. The blocks outlined in grey need to be filled in for every patient and serve as a 'sampling frame' for research purposes.

All collected data are stored in one central database. The database (server) was developed and is maintained at the Department of Clinical Epidemiology and Biostatistics of the Academic Medical Centre in Amsterdam. Users enter clinical data using a web application. The server is approachable through a https protocol. Users need to log on using an individual username-password combination to which authorisations are connected.

Data for research

GENCOR facilitates scientific research in two ways. Firstly, data stored in the GENCOR registry can be used for research projects. Researchers can submit their research proposals via the GENCOR website. The steering committee reviews the request and evaluates whether the privacy regulations are met. When the steering committee has approved the research proposal they give the ICIN a positive advice for delivering GENCOR data. The project group will supply the requested data. This procedure takes about three weeks.

Secondly, specific data for a study can be collected using GENCOR. It is therefore possible to add information blocks to GENCOR to store additional information. Again, the steering committee reviews the request and has to give its approval. When the advice is positive the researcher gets a temporary account to collect the data needed and analyse it.

Results

Inclusion

We started the inclusion in September 2005. The Academic Medical Centre, Amsterdam, the University Medical Centre Groningen, the Radboud University Medical Centre, Nijmegen and the University Hospital Maastricht are actively obtaining informed consent from their patients. The other university hospitals have been informed about GENCOR and are willing to participate. Currently, informed consent has been obtained from 337 patients with a familial heart disease. Table 1 provides information about the distribution of the diagnosis in the total group of patients who provided consent.

Patient characteristics

Clinical data have been entered in the GENCOR registry for 75 patients: 69 patients with HCM, four patients with DCM, one patient with long-QT syndrome and one patient with Brugada syndrome.

Research projects

Three research projects have already started using GENCOR. One study aims to optimise the care of mutation carriers of HCM, identified by presymptomatic family screening, based on risk factors for sudden cardiac death.[7] The second project is investigating an optimal strategy for ICD implantation in lamin A/C gene mutation carriers to prevent sudden cardiac death, which seems to be associated with mutations in this gene.[8-10] For both projects the required patient data are entered into the GENCOR registry. The third project is investigating whether different HCM causing mutations are related to differences in the surface ECG, allowing a more efficiently targeted DNA analysis.[11]

Discussion

GENCOR aims to establish a complete national registry of patients with familial heart diseases in the Netherlands in which long-term clinical data of patients are collected. This registry is of importance to assess the prevalence of familial heart diseases in the Netherlands and to improve the quality of diagnostics and therapy in familial heart diseases.

Dutch cooperation between the university hospitals as a result of GENCOR has already been quite successful in the identification and characterisation of gene mutations in the recent past.[12-15] Once fully established GENCOR will further improve this cooperation and facilitate DNA studies in larger patient populations.

Because GENCOR is an internet-based registry authorised users can enter patient data through a web application at any time and any place. All entered data are stored at one server. When information stored in GENCOR is needed for research projects on familial heart diseases, the researcher can immediately (after the request procedure) gain access to the complete dataset entered so far.

The distribution of the diagnoses (table 1) does not provide a proper overview of the distribution of familial heart diseases in the Netherlands. This biased view is due to the related research project on presymptomatic mutation carriers of HCM.

Table 1. Distribution of diagnoses over total population who provided consent.

Diagnosis	# of patients
LQTS	2
Brugada	1
CPVT	1
HCM	323
DCM	6
Non-compaction cardiomyopathy	1
Diagnosis missing	3
Total	337

LQTS=long-QT syndrome, CPVT=catecholaminergic polymorphic ventricular tachycardia, HCM=hypertrophic cardiomyopathy, DCM=dilated cardiomyopathy.

Conclusion

GENCOR is already a success regarding the number of included patients and the related research projects set up within a limited period of time. GENCOR provides easy internet-based access for authorised cardiologists, clinical geneticists and scientists throughout the country. It is aimed and hoped that all the cardiogenetic centres gain confidence in the concept and that all will indeed actively participate.

Acknowledgements

This registry is supported by the Netherlands Heart Foundation (NHS/2003T302) and by the Interuniversity Cardiology Institute of the Netherlands (Project 27 and Project 50). ■

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