

## The Genetic Family History

# The pedigree, taken to heart

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*All heart disease is not the same.*

*Taking a targeted family history can help to reveal genetic predispositions to sudden cardiac death (SCD) and identify family members at risk.*

Sudden cardiac death (SCD) affects more than 460,000 North Americans each year. SCD occurs when the heartbeat ceases suddenly, also known as cardiac arrest. Often, there is no prior warning or known heart disease in the individual. A common misperception is that heart attack, sudden cardiac death, and cardiac arrest are all the same condition. In fact, a heart attack damages the heart muscle, which may or may not lead to cardiac arrest. The term cardiac arrest means that the heart stopped, but it does not describe the underlying cause.

Tragic at any age, sudden death is particularly poignant when it occurs in young people. Cardiac events are known to account for 30% of sudden deaths among youths age 14-21 years; however, the average age at which SCD occurs is 60. Both men and women can be affected. Statistics from the Centers for Disease Control and Prevention show that SCD among young women has increased by 30 percent in the last decade, a finding associated with risk factors such as smoking and high blood pressure.

SCD may result from a genetic predisposition or secondary environmental factors. Inherited, familial SCD conditions are less frequent than sporadic, isolated incidents of SCD. Familial SCD may be difficult to recognize, but medical records, autopsy reports, and family history screening can provide clues to a diagnosis. A medical family history is an important tool for identifying individual at risk for SCD who may benefit from preventive screening and treatment.

### Heart conditions predisposing to SCD

Cardiomyopathy refers to an abnormality of the heart muscle, which can be genetic or environmental. There are many types of genetic cardiomyopathy, many of which are relatively rare. In general, cardiomyopathies cause the heart to enlarge or the walls to thicken, and the symptoms relate to the heart's inability to pump efficiently. In addition to genetic causes, infections and alcohol can also damage the heart muscle and cause cardiomyopathy.

Another type of heart problem is arrhythmia, or an abnormality of the heartbeat in either the rate or rhythm. Arrhythmias are very common, especially as we age. Many types of arrhythmia are benign, such as the racing pulse you get from too much coffee or a roller coaster ride. Other types of arrhythmia, especially those in which the upper and lower chambers of the heart are not beating in synchrony, can cause fainting and even sudden death. Arrhythmias that occur with exercise, especially swimming, or after sudden loud noises such as fire alarms, might be related to a genetic condition called long QT syndrome. Symptoms of palpitations and fainting often lead to a referral to a cardiologist, and a variety of investigations are necessary to make a diagnosis.

Recently, at numerous academic medical centers, cardiology and genetic teams have established collaborations to help evaluate not just individuals, but families, with the goal of early diagnosis and treatment of SCD. Genetic testing is available for some conditions on a clinical or research basis. These teams may involve cardiologists that specialize in different diagnoses (heart failure or arrhythmia) as well as different age groups (pediatric or adult). Cardiologists provide treatments that include combinations of medication, surgery, exercise, and implanted devices. Medications can help the heart beat more efficiently and help control the abnormal heart beats. For some types of heart conditions, such as long QT syndrome, avoiding certain medications can prevent dangerous rhythm disturbances.

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# New family history tools further the science and art of medicine

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The American Medical Association (AMA) is committed to promoting the science and art of medicine and the betterment of public health. To facilitate understanding of the genetic basis of disease and integration of emerging molecular techniques into clinical practice, the AMA has developed the Genetics & Molecular Medicine website ([www.ama-assn.org/go/genetics](http://www.ama-assn.org/go/genetics)). The site provides easy-to-understand educational material on a variety of topics (e.g., stem cells, pharmacogenomics, gene therapy, and genetic testing) for people not familiar with genetics. It also contains numerous links to Web-based resources for individuals seeking more detailed information about these rapidly evolving fields. Physicians, genetics professionals, and patients will find this site an excellent place to explore current trends in medical genetics and identify recent advances in genetic research.

Genetics is often perceived as a highly specialized field that has little practical application in routine clinical medicine. To help dispel this myth, a portion of the Genetics & Molecular Medicine website is devoted to a description of one of the most basic yet powerful genetic tests available to a clinician: the family medical history

([www.ama-assn.org/ama/pub/category/2380.html](http://www.ama-assn.org/ama/pub/category/2380.html)). A variety of educational resources are provided to assist physicians and their patients in identifying trends that may indicate increased risks for certain inheritable diseases. One of the newest resources available on this site is a recently released AMA educational pamphlet titled *Family Medical History in Disease Prevention* ([www.ama-assn.org/ama1/pub/upload/mm/464/family\\_history\\_bklt.pdf](http://www.ama-assn.org/ama1/pub/upload/mm/464/family_history_bklt.pdf)). This booklet emphasizes the importance of early identification in treatment and prevention of such disorders as heart disease, diabetes, and certain cancers. It also highlights various non-medical issues associated with family medical history (e.g., genetic discrimination) and contains a listing of Web-based directories for locating nearby genetics laboratories and clinics, medical geneticists, and genetic counselors. A free hard copy of this booklet can be obtained by sending an e-mail request to [srt@ama-assn.org](mailto:srt@ama-assn.org). An electronic version is available on the website as well.

In addition to these educational resources, a number of easily accessible forms are provided on this site to help individuals gather and organize information for a family medical history. For parents, questionnaires are avail-

able to assist in collecting details needed for prenatal genetic screening and pediatric clinical genetics assessment. For adult patients, a family history form and instructions for generating a family medical history tree (pedigree) are provided. Information collected in these forms is meant to improve communication between a physician and patient and to help promote a sense of partnership in health care management.



## The Pedigree, taken to heart continued from page 1

Pacemakers and implantable defibrillators can also help a heart to beat more efficiently or correct an abnormal rhythm. Depending on the type of heart condition, there could even be specific recommendations about exercise and participating in sports.

### Tips for taking a targeted family history

Both dominant and recessive inheritance patterns have been described in association with SCD. The variable age at presentation and variable penetrance of cardiac disorders adds complexity to interpretation of the family history. Try to determine specifics about the type of heart disease present in the family, and whether it is congenital or acquired. For example, an individual might remember if a relative had heart surgery, or recall a description of symptoms. Note the age at onset of

symptom. Ideally, you should obtain medical records and autopsy reports for the most accurate diagnostic information. Pay attention to any deaths in the neonatal period, such as sudden infant death syndrome (SIDS). Clarify the cause of deaths by accidents, especially by drowning. Even near-drowning episodes may reflect an underlying heart rhythm disturbance. Ask if anyone in the family has ever experienced blackouts, fainting spells, or seizures. It is also helpful to clarify if the SCD occurred in an individual who had significant exposure to alcohol or prescription drugs. As always, it is important to ascertain if there is any consanguinity in the family.

The take-home message is that there are many different types of heart conditions, many of which are quite common. It is rare to take a family history and NOT find

someone with some type of heart condition. However, a few questions can help to distinguish between coronary artery disease, congenital heart disease, problems related to the heart valves, arrhythmias, or heart disease related to other illnesses. Taking a family history is the necessary first step in identifying a hereditary predisposition to SCD, and in recognizing family members at risk who may benefit from early screening or treatment.

**For more information** about sudden cardiac death, see [www.americanheart.org](http://www.americanheart.org) and [www.heartandstroke.ca](http://www.heartandstroke.ca). For more information about familial cardiomyopathy and long QT syndrome, see GeneClinics Reviews at [www.genetests.org](http://www.genetests.org).

# Shaking the family tree:

## States hope family history data will bear fruit for public health initiatives

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A positive family history for a disease, which reflects the consequences of genetic susceptibilities, shared environment, and common behaviors, is a risk factor for almost all chronic diseases and is increasingly being promoted as a tool for addressing many diseases of public health importance. In response to the increased emphasis on using family history in both clinical and public health settings, some state public health departments have begun to develop plans for collecting information about family history through population-based surveillance systems. For example, public health departments in Michigan, Minnesota, Oregon, and Utah plan to include family history questions on the 2005 Behavioral Risk Factor Surveillance System (BRFSS).

The BRFSS, an ongoing telephone survey conducted in all states, is the primary source of information on the health-related behaviors of adults. Public health professionals use BRFSS data for numerous purposes, including: identifying emerging health issues, documenting health trends (such as the alarming rise in the prevalence of obesity among U.S. adults in recent years), comparing health behaviors across states, and measuring progress toward health goals. The BRFSS survey consists of standard core questions developed by the Centers for Disease Control and Prevention, as well as state-specific questions to gather data on behaviors and risk factors that are of particular interest to individual states.

Family history data collected through such population-based surveys may contribute to answering the following important questions:

### What proportion of adults . . .

- have a family history of a given disease (e.g., diabetes, heart disease, certain types of cancer)?
- have actively collected health information from relatives for the purpose of developing a family health history?
- have had a health care provider discuss their risk for disease based upon family history information?



- perceive themselves to be at high risk for a given disease based upon family history?
- have made changes in lifestyle to reduce risk of a given disease based upon family history information?

### The answers to such questions may be useful for:

- assessing the prevalence of a positive family history of disease,
- monitoring trends in prevalence,
- gauging public awareness of family history as a risk factor for disease,
- tracking provider practices regarding the collection of family history information,
- understanding how family history contributes to patients' perceptions of risk, and
- investigating beliefs about the ability to modify risk by changing lifestyle factors (such as smoking, diet, and exercise habits).

Public health programs could use such data for planning campaigns to increase public awareness about family history or to promote the collection and use of family history in healthcare settings.

The University of Washington Center for Genomics and Public Health is one of three

centers funded by the Centers for Disease Control through the Association of Schools of Public Health to integrate advances in genomics into public health practice. Recently the center developed a working group to coordinate efforts between states that are interested in collecting data on family history through population-based surveillance systems. One goal for the working group may be to facilitate development of a standard set of questions for recommendation to other states interested in collecting data on this topic.

For more information about these efforts, or if you would like to share your experience using family history questions in population-based surveys, please contact Sarah Raup at the University of Washington Center for Genomics and Public Health, at 206-616-0684, or raup@u.washington.edu. To learn more about the University of Washington Center for Genomics and Public Health, please visit: [www.uwcgph.org](http://www.uwcgph.org).

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# Family history tools

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The American Medical Association (AMA) has several online family history tools that are available at no charge. Tools include a pamphlet (Family Medical History in Disease Prevention), a pocket guide (Family Medical Information Pocket Guide), and three family history questionnaires (Prenatal Genetic Screening Questionnaire, Pediatric Clinical Genetics Questionnaire, and Adult Family History Form). You can access these tools directly at <http://www.ama-assn.org/ama/pub/category/2380.html>, or through the Genetics & Molecular Medicine main page at <http://www.ama-assn.org/ama/pub/category/1799.html>.

grandchildren are overlooked, so you should specifically inquire about these family members. If you or a member of your staff administers this form, consider adding a note or brief explanation for patients about what types of health problems might be significant (e.g., heart disease, early cancers, dementia). In addition, patients should receive this form well in advance of an appointment so they can flesh out details such as family members' ages, health status, or cause of death.

When using any pre-packaged tool, it is a good idea to consult any published practice guidelines and supplement the tool with additional questions where appropriate. You can perform a quick search for existing guidelines by visiting the National Guideline Clearinghouse at [www.guideline.gov](http://www.guideline.gov).

In the *Family Medical History in Disease Prevention* pamphlet (8 pp.) readers will find fast facts about the importance of the family history in medical practice, practical information about how to gather and interpret a family history, and a list of resources. The Family Medical Information Pocket Guide (2 pp.), which lists the basic steps to generating a pedigree and provides a sample pedigree, is included in this pamphlet. The pocket guide would be most useful to a health professional who has some prior experience or training in drawing a pedigree. However, a professional or layperson with no experience drawing pedigrees could easily follow the instructions and create a useful draft.

Using the *Prenatal Genetic Screening Questionnaire* (3 pp.), you or your patient can record a basic medical history, family history, and pregnancy history through a series of "yes/no" questions. Space is provided to construct a pedigree and make notes; however, an example is not included, so you may want to reference the Pocket Guide for a model pedigree. Online users can learn more about highlighted genetic conditions by

linking from this questionnaire directly to the websites for Online Mendelian Inheritance in Man or GeneTests. Both sites are excellent resources as their content is authored by experts, is peer reviewed, and is updated periodically, but they are likely to provide more detail than you need.

On the *Pediatric Clinical Genetics Questionnaire* (6 pp.), space is provided to record a patient's pregnancy history, birth history, developmental history, growth history, pedigree, physical exam, assessment, and plan. In order to take advantage of the "pedigree" and "physical exam" sections, health professionals will need pedigree-taking skills and some knowledge of dysmorphology. Patients who self-administer this form should be advised to skip the "physical exam" section and possibly the "pedigree" section. Instructions to this effect are provided on the questionnaire.

The *Adult Family History Form* (7 pp.) prompts the interviewer or patient to list health information about the patient and certain family members. You or your patient could create a draft pedigree using the responses on this form. However, the patient's children and

# Famous and fascinating **family histories** for the classroom

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With the family history gaining attention as a screening tool that has broad application, there will be more opportunities to advocate use of pedigrees in practice with healthcare providers. Certainly, educators must convey the technical aspects of symbols, nomenclature, red flags, and recurrence calculations, but as we think about engaging our audiences, we should remember that the truly interesting part of any family history is the family itself. Ideally, the family history used for teaching should have a compelling story that makes audiences care. It is the human side of the story that captures interest and illustrates the impact that genetic conditions can have on a family over time as their stories unfold.

Drawing from a bank of professionally obtained family histories is a fine option, but we should take care to protect the privacy of those families. Consider instead the many benefits of using famous families in your teaching. There is ample evidence in the media that the masses are interested in the lives of famous people, and all of us can quickly generate a mental list of famous people with a known or suspected genetic condition: the British royal family, the Hapsburgs, Abraham Lincoln, Henri Toulouse-Latrec, Woody Guthrie, Flo Hyman, Gunnar Esiason, and so on. The number of advocacy organizations that include a list of "famous people with [diagnosis]" indicates the power-

ful normalizing effect this approach can have, and for better or worse, there is generally plenty of available public information from which to build a family history.

Perhaps the most commonly used famous family history in teaching is that of hemophilia in the descendants of Britain's monarch Queen Victoria and her husband, Prince Albert. Simply compiling the pedigree and evaluating inheritance, however, overlooks an opportunity to explore the devastating personal and political consequences associated with the transmission of hemophilia through the royal houses of Britain, Russia, and Spain. The most tragic story is that of Tsar Nicholas and Tsarina Alexandra of Russia. Alexandra, or Alix as she was known to her family, was the granddaughter of Queen Victoria. Under tremendous pressure to produce a male heir after bearing four daughters, Alix finally gave birth to Tsarevich Alexis. But the long-awaited heir was born with hemophilia. Although the disease was already recognized in Queen Victoria's family and its inheritance described, the family avoided the truth of Alexis's excessive bleeding as long as possible. Recognizing that a tsar must be free of physical defect, Alix and Nicholas concealed his condition and became increasingly isolated.

*Alix was grief stricken: 'she hardly knew a day's happiness after she realized her boy's fate.' As a newly diagnosed hemophilia carrier she dwelt morbidly on the fact that she had transmitted the disease (Stevens, 1999).*

Alexis's diagnosis ultimately opened the doors to the infamous Rasputin, a

mystic who gained influence over the Russian royal family as a result of his abilities to soothe the pains Alexis suffered. This influence grew into political influence and ultimately contributed to Russia's entry into World War I and to the Russian Revolution. Russia's provisional government eventually asked Tsar Nicholas to abdicate in favor of Alexis. After consulting the family physician about his son's future, however, and being advised that Alexis was "at the mercy of an accident," Nicholas refused to endanger Alexis. He instead abdicated in favor of his brother, who also abdicated. Nicholas, Alix, and their five children were ultimately executed.

The Russian royal family's story is a dramatic example, but the audience will readily appreciate the underlying common human feelings of denial, grief, stigmatization, desperation, and parental protective instincts that may be associated with any genetic diagnosis. The attempts to identify the family's remains also provide a further opportunity to use their pedigree to organize and make sense of DNA-based results (Gill, 1994), and it is especially instructive with respect to mitochondrial inheritance.

The British royal family provides another instructive example. Look back just two generations from Queen Victoria and you will find "Mad King George III." In retrospect, variegate porphyria is a likely diagnosis for George III and some descendants of Queen Victoria (Rohl et al., 1998). Tracing such symptoms as "bouts of colic," "bilious attacks," and "flying gout" is a wonderful opportunity to use the family history and pedigree to establish a pattern of inheritance. It also

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## The Genetic Family History

This newsletter is made possible by members of the Family History Working Group, contributors, the NCHPEG staff, and funding from the National Human Genome Research Institute, the Office of Rare Diseases, and the Health Resources and Services Administration. The goals of this thrice-yearly, online publication are to help educators and providers learn about the role of the genetic family history in health care, and to facilitate access to family history resources for use in teaching and clinical practice.

### CONTACT US

Please send your comments, questions, or any materials you would like to submit for the next newsletter to Erin K. Herrick, NCHPEG Project Director (e-mail [ekherrick@nchpeg.org](mailto:ekherrick@nchpeg.org), phone: 410-583-0600, fax: 410-583-0520), or to Robin Bennett, Chair of the NCHPEG Family History Working Group ([robinb@u.washington.edu](mailto:robinb@u.washington.edu)).



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serves as a springboard to some interesting conversation about society's impression of mental illness. Had George III been diagnosed with porphyria, would people have been more tolerant of his bouts of madness, or would he have automatically been deemed unfit to be king? In hindsight, do our impressions of his leadership change in the face of such a diagnosis?

Woody Guthrie's biography (Klein, 1980) provides a more contemporary example of a genetic disorder. Woody's own words describe his mother's experience with Huntington disease, his misinformation that the condition was not "pass-onable," and the frustrations of misdiagnosis even with a known familial risk.

*Face seems to twist out of shape. Can't control it. Arms dangle all around. Can't control them. Wrists feel weak and my hands wave around in odd ways. I can't stop. All these docs keep asking me about how my mother died of Huntington's Chorea. They never tell me if it's pass-onable or not. So I never know. I believe every doctor ought to speak plainer so us patients can begin to try to guess partly what's wrong with us. If it's not alcohol which has me, I wonder what it's going to be (Klein, 1980).*

Ultimately, he realizes that he too will fall victim to the disease that took his mother. Of his seven children who survived childhood, two are known to be affected with Huntington disease. Many of the details that make these and many other famous families so compelling are readily available on the internet or in the medical literature. I hope these brief accounts stimulate you to continue your search for ideal teaching families and that you find the search as fascinating as I have.

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