ARTICLE

Contribution of Mendelian Disorders to Common Chronic Disease:
Opportunities for Recognition, Intervention, and Prevention

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Recognizing Mendelian disorders should improve health care for persons with strong familial risks for common chronic diseases. The Online Mendelian Inheritance in Man (OMIM) database was reviewed to identify Mendelian disorders featuring 17 common chronic diseases, including 9 cardiovascular conditions, diabetes, and 7 common cancers. Mendelian disorders were selected if any one of the 17 diseases was reported in more than two families manifesting in adulthood. Patterns of chronic diseases and modes of inheritance associated with these Mendelian disorders are described. The GeneTests/Reviews database and other websites were reviewed to determine availability of genetic testing and management and prevention recommendations for the selected disorders. Of 2,592 (OMIM) entries reviewed, 188 Mendelian disorders were selected. Most (67.7%) are autosomal dominant disorders. Almost half (45.8%) feature combinations of the chronic diseases under study. At least one gene is known for 68.8% of the selected disorders, and clinical genetic testing is available for 55% of disorders. Guidelines for management and prevention are available for 33.9% of these, ranging from recommendations for supportive care to guidelines for managing affected persons and screening relatives. Significant clinical heterogeneity exists for Mendelian disorders that might present as strong family histories of common chronic diseases. Recognition of the different combinations of diseases within a pedigree, including mode of inheritance and heritable disease risk factors, facilitates diagnosis of these Mendelian disorders. Genetic testing is available for most disorders, which can further clarify the genetic risk, and for some, recommendations for management and prevention are available. However, evidence-based guidelines are needed. Published 2004 Wiley-Liss, Inc.†

KEY WORDS: family history; Mendelian disorders; chronic disease; disease prevention

INTRODUCTION

Family history is an important risk factor for many common chronic diseases of adulthood. Family history represents complex interactions of genetic, environmental, cultural, and behavioral factors. Familial risk can be stratified into different risk categories (e.g., average, moderate, high) by considering the number of affected relatives and their degree of relationship; the ages at disease onset; the occurrence of associated diseases; and, in some circumstances, the sex of affected relatives [Scheuner et al., 1997]. A person with the highest familial risk for a common chronic disease might have a Mendelian disorder associated

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Grant sponsor: Career Development Award sponsored by the Association of Teachers of Preventive Medicine and the Centers for Disease Control and Prevention (MTS).

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DOI 10.1002/ajmg.c.30008

with a spectrum of conditions typically occurring at earlier ages of onset.

A person with the highest familial risk for a common chronic disease might have a Mendelian disorder associated with a spectrum of conditions typically occurring at earlier ages of onset.

These Mendelian disorders can be recognized by identifying specific patterns of disease in a pedigree, such as colon and endometrial cancer from hereditary nonpolyposis colon cancer (HNPCC), and single-gene disorders that affect important risk factors for these diseases, such as familial hypercholesterolemia associated with premature cardiovascular disease. For persons suspected of having Mendelian disorders, genetic evaluation should be considered, including pedigree analysis, risk assessment, genetic counseling and education, discussion of available genetic testing, and recommendations for risk-appropriate screening and prevention [Scheuner and Gordon, 2002].

The purpose of this study is to review the known Mendelian disorders associated with common chronic diseases of adulthood that could be identified with family history screening. Patterns of chronic diseases and modes of inheritance associated with these Mendelian disorders are described, as are availability of genetic testing and guidelines for management and prevention.

METHODS

The Online Mendelian Inheritance in Man (OMIM) database was queried for 17 common chronic diseases of adulthood (Table I). The diseases in this study were considered because they represent a substantial public health burden [American Heart Association, 2002; American Cancer Society, 2003]; family history is an important risk factor [King et al., 2002]; and, for many, early detection and preventive interventions are available [Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001; Diabetes Prevention Program Research Group, 2002; Smith et al., 2002; Straus et al., 2002; Walsh and Terdiman, 2003]. The OMIM database is a catalog of human genes and genetic disorders created by Victor McKusick and now available on the World Wide Web by the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/Omim). As of April 23, 2003, 14,365 entries existed, including 10,658 for established gene loci, 1,291 phenotype descriptions, and 2,416 other entries.

TABLE I. Common Chronic Diseases of Adulthood Queried in the Online Mendelian Inheritance in Man Database

Coronary artery disease
Myocardial infarction
Stroke[a]
Sudden death
Arrhythmia
Aneurysm
Arteriovenous malformation
Cardiomyopathy
Thrombosis
Diabetes
Breast cancer
Ovarian cancer
Uterine cancer
Prostate cancer
Colon cancer
Kidney cancer
Thyroid cancer

[a]Includes thromboembolic stroke and subarachnoid and cerebral hemorrhage.

OMIM entries were selected if they 1) described clinical disorders or phenotypes with known or suspected modes of inheritance, 2) featured at least one of the 17 common chronic diseases presenting in adulthood, and 3) were reported in more than two families. Although hereditary kidney cancer caused by translocation between chromosomes 3 and 8 (MIM 603046) has been described only in two families, it was included because additional evidence suggests that a tumor suppressor gene involving the translocation breakpoint is responsible for the phenotype [Gemmill et al., 1998, 2002]. Because genetic heterogeneity characterizes many Mendelian disorders, the different types of a disorder were characterized as distinct disorders if the phenotype or mode of inheritance varied depending upon the gene involved (e.g., autosomal dominant (AD) dilated cardiomyopathies, X-linked (XL) dilated cardiomyopathy, and autosomal recessive (AR) dilated cardiomyopathy). Conversely, if different types of a disorder had similar phenotypes and mode of inherit then the different types were represented by only one disorder (e.g., cerebral cavernous hemangiomas 1, 2, and 3). Although the disorders of HNPCC (MIM 114500) and Lynch cancer family syndrome (MIM 114400) are cataloged separately in OMIM, for this study they were considered one disorder. Knowledge of a gene or genes associated with each selected disorder or phenotype also was documented, because this could influence the availability of genetic testing. OMIM entries describing susceptibility loci only were not selected.

The availability of genetic testing, including DNA-based tests (e.g., direct DNA analyses, fluorescence in situ hybridization, and linkage) and biochemical testing (e.g., analytes and enzyme assays) for each selected disorder, was determined by querying the GeneTests database (http://www.genetests.org). GeneTests is an online publication for physicians and other health care providers that includes descriptions of inherited disorders and genetic testing used for diagnosis, management, and genetic counseling of patients and families. GeneTests data are acquired passively, i.e., submitted by laboratories and clinics that want to be included. The entries are written by expert clinicians and molecular pathologists/geneticists, peer-

reviewed by two or more experts, and frequently updated.

The availability of management guidelines for the selected Mendelian disorders in this study was determined by searching GeneReviews in the GeneTests database and policy statements of the American College of Medical Genetics, American Society of Human Genetics, and National Society of Genetic Counselors, and review of evidence-based clinical practice guidelines by searching the term *genetics* in the electronic databases of the National Guidelines Clearinghouse and the Agency for Healthcare Research and Quality, which includes the U.S. Preventive Services Task Force. The quality of the evidence for interventions identified for the selected Mendelian disorders was not assessed.

RESULTS

In searching the OMIM database for the 17 chronic diseases in this study, 2,592 entries were reviewed. Of these, 188 met the selection criteria. (For a complete listing of selected Mendelian disorders, their OMIM entries, mode of inheritance, number with known genes, availability of testing, and recommendations for management and prevention, see Appendix 1.) The majority of these disorders feature cardiovascular conditions and diabetes (n = 156), and 35 feature one or more of the cancers under study. Three disorders feature cancer and cardiovascular conditions: the von Hippel-Lindau syndrome (MIM 193300) features kidney cancer, cerebellar hemangiomas, and stroke; generalized juvenile polyposis with pulmonary arteriovenous malformation (AVM) (MIM 175050) features colon cancer and AVM; and tuberous sclerosis (MIM 191100) features kidney cancer and arrhythmia.

Most (67.7%) of the 188 selected Mendelian disorders are associated with AD pattern of inheritance. Nearly all of the hereditary cancer syndromes have AD inheritance, except for XL hereditary prostate cancer (MIM 300147) and ataxia telangiectasia (MIM 208900) caused by *ATM* gene mutations, which has AR inheritance. However, the latter was selected because women who are heterozygous for *ATM* mutations have an increased risk for breast cancer. AD, AR, and XL modes of inheritance were described for 58.3%, 28.8%, and 5.8% of the cardiovascular diseases and diabetes disorders, respectively. Multifactorial (MF) inheritance has been proposed as the mode of inheritance for the abdominal obesity-metabolic syndrome (MIM 605552). For several others, AD and/or MF inheritance is described (abdominal aortic aneurysm, MIM 100070; atherosclerosis susceptibility (i.e., atherogenic lipoprotein phenotype), MIM 108725; familial combined hyperlipidemia, MIM 144250; and Schmidt syndrome, MIM 269200). Atypical modes of inheritance were described for the remaining disorders, including four disorders having mitochondrial inheritance (although Kearns-Sayre syndrome, MIM 530000, is usually a sporadic condition), imprinting (transient neonatal diabetes, MIM 601410), and AR inheritance with a mutation in a second locus (Bardet-Biedl syndrome, MIM 209901).

Of the selected Mendelian disorders, 45.8% featured more than one of the common chronic diseases under study (30.9% featured two diseases, 13.3% featured three diseases, and 1.6% featured four diseases). Examples of recurring combinations of common chronic diseases are reviewed in Table II. The cardiovascular diseases and diabetes disorders had more combinations of common chronic diseases than did the cancer syndromes. Of the 35 Mendelian cancer syndromes, 71.4%

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TABLE II. Recurring Combinations of Common Chronic Diseases of Adulthood Among the Selected Mendelian Disorders★

Combinations of diseases	Number of Mendelian disorders
Coronary artery disease and stroke	9
Coronary artery disease and diabetes	3
Diabetes and cardiomyopathy	6
Stroke and thrombosis	8
Stroke and aneurysm/arteriovenous malformation	13
Sudden death and arrhythmia	25
Sudden death and cardiomyopathy	9
Sudden death and aneurysm/arteriovenous malformation	6
Arrhythmia and cardiomyopathy	16
Breast and ovarian cancer	4
Breast and endometrial cancer	2
Breast and colon cancer	3
Colon and ovarian cancer	4
Colon and thyroid cancer	3
Thyroid and kidney cancer	2

★The Online Mendelian Inheritance in Man database was searched in 12/02.

featured only one cancer type, 11.4% featured two, 8.6% featured three, and 8.6% featured four. Among the 156 cardiovascular diseases and diabetes syndromes, 52.5% featured only one chronic disease, 34% featured two, and 13.5% featured three. The identified combinations of diseases featured by the selected Mendelian disorders probably is underestimated because many disorders probably feature other common diseases that are not mentioned in the OMIM reviews. For example, coronary artery disease (CAD) is a major complication of diabetes; however, only three syndromic forms of diabetes specifically mention CAD and/or myocardial infarction (MI) in the OMIM database.

Mendelian disorders also were identified that are associated with risk factors that predispose to several of these common chronic diseases. Examples included monogenic lipid disorders associated with increased risk for CAD and stroke; inherited forms of thrombophilia associated with CAD, MI, and stroke; disorders of iron overload associated with diabetes and cardiomyopathy; and disorders featuring obesity predisposing to diabetes.

For 68.8% of the selected Mendelian disorders, a gene or genes are known. At least one gene is known for 24 of the 35 hereditary cancer syndromes, and for 107 of the 156 cardiovascular disease and diabetes disorders. In several instances, more than one gene has been identified for any given disorder. Additionally, for many of the selected disorders linkage has been established, but the genes are not yet known.

According to the GeneTests database, genetic testing is available for most of the selected Mendelian disorders (Table III). For the 35 Mendelian cancer syndromes, clinical DNA-

For the 35 Mendelian cancer syndromes, clinical DNA-based testing is available for 21 and research testing is available for 21.

TABLE III. Availability of Genetic Testing for Selected Mendelian Syndromes That Feature Common Chronic Diseases of Adulthood

Chronic disease	No. of selected Mendelian syndromes[a]	No. of syndromes with known gene(s)[a]	Clinical DNA-based testing (no. of syndromes)[b]	Clinical biochemical testing (no. of syndromes)[b]	Research testing (no. of syndromes)[b]
Coronary artery disease/ Myocardial Infarction	27	20	9	15	11
Stroke	35	26	16	13	20
Thrombosis	17	14	6	11	5
Sudden death	36	25	15	2	20
Arrhythmia	35	27	17	0	22
Aneurysm/ Arterio-venous malformation	22	11	6	2	14
Cardiomyopathy	42	30	19	7	22
Diabetes	37	29	11	9[d]	20
Breast cancer	8	7	7	n/a	6
Ovarian cancer	7	6	6	n/a	5
Endometrial cancer	3	3	3	n/a	3
Prostate cancer	5	2	2	n/a	5
Colon cancer	11	8	8	n/a	8
Thyroid cancer	13	7	8[c]	n/a	8
Kidney cancer	7	7	7[c]	n/a	3

[a]The Online Mendelian Inheritance in Man database was searched in December, 2002.

[b]The GeneTests database was reviewed in April, 2003.

[c]Translocation in renal cell carcinoma on chromosome 8 due to t(3;8)(p14.2;q24.1) features kidney and thyroid cancer. This syndrome was not identified in the GeneTests database; however, chromosome analysis can reveal genetic predisposition.

[d]Testing for biochemical abnormalities other than hyperglycemia (e.g., studies of insulin resistance, iron studies).

n/a, not available.

based testing is available for 21 and research testing is available for 21. For four of the cancer syndromes, research testing is the only available testing option, including three hereditary prostate cancer syndromes (MIM 601518, 603688, and 300147) and papillary thyroid cancer (MIM 188550). Among the 156 disorders that feature cardiovascular diseases and diabetes, clinical testing is available for 82. Biochemical testing is available for 36 of these disorders, and for most (24), this testing (e.g., measurement of lipids, lipoproteins, homocysteine, or thrombophilia) is routinely available, which could infer the diagnosis in some cases. Clinical DNA-based testing is available for 62 of the cardiovascular diseases and diabetes disorders, and research testing is available for 77; for 23 of these disorders, research testing is the only available testing. For the cardiovascular disorders of CAD/MI, stroke, and thrombosis, biochemical testing is more often available than DNA-based testing. Conversely, clinical DNA-based testing is available more often for the disorders featuring cardiomyopathy, arrhythmia, and sudden death. For about half (18) of the 37 diabetes disorders, clinical biochemical or DNA-based testing is available. Hyperglycemia could be considered a marker of genetic risk for all of the diabetes disorders; however, biochemical testing is more specific. It includes assessment of biochemical manifestations that could be used to infer a specific Mendelian condition, such as iron overload associated with hemochromatosis or severe insulin resistance associated with insulin receptor defects. Clinical testing is available for almost all of the 17 thrombosis disorders. Except for the thrombosis disorders, opportunity exists to participate in research testing for most of the selected cardiovascular, diabetes, and cancer disorders.

Several policy statements from national professional organizations exist regarding genetic testing for cancer susceptibility [American Society of Human Genetics, 1994; ASCO Subcommittee on Genetic Testing for Cancer Susceptibility, 1996; American College of Obstetricians and Gynecologists, 1997; American College of Medical Genetics, 1999; American College of Medical Genetics/American Society of Human Genetics, 2000; American Gastroenterological Association, 2001; ACOG Technology Assessment, 2002], and statements exist regarding factor V Leiden testing [Grody et al., 2001], testing for hyperhomocysteinemia [American Society of Human Genetics/American College of Medical Genetics, 1998], and genetic evaluation and testing for Fabry disease [Bennett et al., 2002].

Guidelines for management and prevention were identified in the Gene/Reviews database for 63 (33.5%) of the 188 selected Mendelian disorders, including 16 of the 35 cancer syndromes and 49 of the 156 cardiovascular and diabetes disorders.

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For several disorders, no specific treatment or surveillance is recommended, only evaluation of involved systems with suggestions for supportive care (e.g., Niemann-Pick disease, type C, Friedreich ataxia, MELAS, and nemaline myopathy). For several disorders, knowledge of the diagnosis could be useful to prevent morbidity from unnecessary or potentially dangerous medications or procedures (e.g., angiography and the use of anticoagulants with CADASIL (cerebral arteriopathy, AD, with subcortical infarcts and leukoencephalopathy) or pseudoxanthoma elasticum, placement of arterial catheters in Ehlers-Danlos syndrome, type IV, and radiotherapy in nevoid basal cell carcinoma syndrome). Specific guidelines for initial evaluation, management, and follow-up for affected persons and surveillance for at-risk relatives were provided for syndromes such as Marfan syndrome, thoracic aortic aneuysm and aortic dissection cerebral cavernous malformation, hereditary hemorrhagic telangiectasia, AD polycystic kidney disease, the long QT syndromes, hereditary hemochromatosis, factor V Leiden, tuberous sclerosis, Cowden syndrome, Peutz-Jeghers syndrome, von Hippel-Lindau syndrome, multiple endocrine neoplasia, type 2, familial adenomatous polyposis, HNPCC [Smith et al., 2002], and Li-Fraumeni syndrome. For a few syndromes, proven effective treatments are available, including use of penicillamine or zinc for Wilson disease, enzyme replacement with alpha-Gal A for Fabry disease, phlebotomy for hemochromatosis, and cystine depletion therapy with cysteamine bitartrate for nephropathic cystinosis. However, for most, evidence is not yet available that proves the efficacy of these management and prevention strategies for reducing morbidity and mortality. (All references are from the GeneReviews at GeneTests http://www.genetests.org)

DISCUSSION

Recognition of Mendelian disorders that feature common chronic diseases requires an appreciation of the heterogeneity and pleiotropy of these disorders. In considering only 17 common chronic diseases of adulthood, 188 Mendelian disorders were identified in the OMIM database meeting the study criteria. Thus, significant clinical heterogeneity exists among the possible genetic diagnoses that might present as strong family histories of common chronic diseases of adulthood. Recogni-

tion of the different combinations of diseases within a pedigree, including heritable risk factors for disease and mode of inheritance, facilitates development of an appropriate differential diagnosis among high-risk families. Genetic testing often is available that can sometimes clarify genetic risk within a pedigree, and once the risk is defined by pedigree analysis or genetic testing, risk-appropriate strategies for management and prevention can be offered for many of the selected Mendelian disorders. Management options can range from supportive care to avoidance of aggravating factors to specific treatments that can prevent the associated common chronic conditions presenting in adulthood. However, for most Mendelian disorders, evidence proving the efficacy of such interventions is lacking, and outcomes research is needed.

Recognition of the different combinations of diseases within a pedigree, including heritable risk factors for disease, facilitates development of and mode of inheritance an appropriate differential diagnosis among high-risk families.

Individually, the Mendelian disorders identified in this study are rare, and for most, the public health burden is largely unknown, which limits development of public health policy. Prevalence estimates are not available for many of the selected Mendelian disorders, and for most of the common chronic diseases associated with these disorders, population-based penetrance estimates and the influences of gene-gene and gene-environment interactions are not known. Without these data, the proportion of common chronic diseases in the population that result from Mendelian disorders (i.e., the attributable fraction) is unknown, but probably is smaller than other risk factors [Yoon et al., 2002]. However, the absolute disease risks associated with Mendelian disorders are typically much greater than the risks associated with environmental exposures, behaviors, or positive family history, which can have profound clinical implications. To better appreciate the public health burden and the clinical manifestations of common chronic diseases associated with Mendelian disorders, population-based studies are needed that assess disease incidence, environmental exposures, behaviors, and genetic risk through collection and interpretation of comprehensive family history and genetic testing. This could be accomplished by including genetic investigations, such as evaluation of family history and DNA markers, in ongoing population-based studies such as the National Health and Nutrition Examination Survey. Moreover, population-based studies can collectively assess the burden of Mendelian disorders that feature specific common chronic diseases, which might be more appropriate when considering public health needs for genetic services.

For most (68.8%) of the selected Mendelian disorders in this study, one or more genes are known and this often translates to the availability of genetic testing, including DNA-based tests and biochemical testing, which can further refine disease risk within a pedigree. Clinical testing is available for 55% of the selected Mendelian disorders in this study; however, this estimate may be conservative because the GeneTests database may not be comprehensive.

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Clinical testing is likely to become increasingly available as more genes are identified and the cost of analysis decreases, which will present a challenge to practitioners because the evidence regarding validity and utility of genetic testing is minimal. Opportunities to participate in genetic testing under research protocols were identified for 52% of the selected Mendelian disorders. Individuals may not directly benefit from participation in such research, but identifying these opportunities for families can increase better understanding of the etiology and natural history of these disorders, as well as the validity and utility of genetic testing. An informed consent process for clinical and research testing is essential and requires appropriate genetic counseling and education [ASCO Subcommittee on Genetic Testing for Cancer Susceptibility, 1996; American Society of Human Genetics, 1996; McKinnon et al., 1997], an important component of the genetic evaluation for common chronic diseases [Scheuner and Gordon, 2002].

Because common chronic diseases have a preclinical phase or subclinical phenotypes, the opportunity for early detection and disease prevention exists. Guidelines for management and prevention were identified for 33.9% of the selected Mendelian disorders in this study. This probably underestimates the actual percentage because the GeneTests/Reviews database and websites that were reviewed might not be comprehensive. For example, hypertrophic cardiomyopathy has not been reviewed, but a comprehensive review has been published regarding management and molecular genetics [Fananapazir, 1999]. In other cases, the GeneReview might not include information regarding associated common chronic diseases, although evidence in the literature might exist. For example, management recommendations for the cardiovascular complications of neurofibromatosis type 1 have been published [Friedman et al., 2002]. For a few Mendelian disorders, specific treatments are known that can prevent the associated chronic conditions of adulthood. For many disorders, specific

guidelines for diagnostic evaluations, follow-up surveillance, and preventive strategies for affected and at-risk persons are available. However, recommendations for screening and prevention based on evidence derived from clinical studies exist for a minority of the selected Mendelian disorders, including hereditary breast cancer [Rebbeck et al., 1999; Brekelmans et al., 2001; King et al., 2001; Meijers-Heijboer et al., 2001], ovarian cancer [Kauff et al., 2002; Rebbeck et al., 2002], and colon cancer [Järvinen et al., 2000].

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In the absence of guidelines for Mendelian disorders, clinicians can suggest management and prevention strategies that have been proven effective for the general population. Such guidelines exist for CAD [Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001], stroke [Straus et al., 2002], diabetes [Diabetes Prevention Program Research Group, 2002], and cancer [Smith et al., 2002; Walsh and Terdiman, 2003]. However, clinicians must proceed with caution because interventions that are effective for the general population might not be effective for individuals at risk because of a Mendelian disorder. For example, evidence exists that women with hereditary risk for breast and ovarian cancer due to *BRCA1* gene mutations might, unlike other women, not benefit from use of oral contraceptives in reducing their ovarian cancer risk [Modan et al., 2001] or from Tamoxifen in reducing their breast cancer risk [King et al., 2001].

Designing prospective clinical trials investigating the clinical utility of interventions for Mendelian disorders is difficult because of their rarity. Therefore, clinical trials investigating early detection and prevention strategies for chronic diseases must consider the influence of genetic susceptibilities on health outcomes. Additional investigative approaches that can provide insight about Mendelian disorders include cost-effectiveness analyses and evaluation of risk-specific interventions based on familial risk stratification. The latter type of study is a component of an initiative at the Centers for Disease Control and Prevention that will evaluate the use of family history for assessing disease risk and influencing early detection and prevention strategies. More information about this initiative is available at the CDC website (http://www.cdc.gov/genomics/activities/famhx.htm). Until results from these investigations are available, clinicians must inform their patients who have Mendelian disorders about the limitations of knowledge about interpretation of genetic tests and strategies for management and prevention.

Family history collection with pedigree analysis is crucial for identifying persons at risk for chronic adult onset diseases resulting from Mendelian disorders. Unfortunately, review of the literature suggests physicians perform poorly with respect to collection and interpretation of family history for risk stratification and recommendation of risk-specific interventions [Hayflick et al., 1998; Acheson et al., 2000; Koscica et al., 2001; Sweet et al., 2002; Frezzo et al., 2003]. These studies demonstrate the need to develop self-administered instruments for family history collection with accompanying algorithms for risk interpretation and guidelines for clinical interventions and referral to geneticists and other specialists. Several national organizations have endorsed the development of such tools, including the National Coalition for Health Professionals Education in Genetics, the American Medical Association, the Health Resources and Services Administration, and the Centers for Disease Control and Prevention.

Family history collection with pedigree analysis iscrucial for identifying persons at risk for chronic adult onset diseases resulting from Mendelian disorders.

SUMMARY

We have described a process using existing databases that should aid in the assessment and management of persons with strong family histories for many common chronic diseases. This will have increasing significance as more and more professional societies and national organizations develop policies, guidelines, and curricula that incorporate genetic information and technology. We also have identified gaps in knowledge regarding the public health burden and clinical manifestations of common chronic diseases due to Mendelian disorders. Population-based studies are needed to assess the prevalence, penetrance, and attributable fraction of Mendelian disorders. Clinical studies are also needed to assess the validity and utility of genetic testing and the utility of interventions specific to Mendelian disorders for development of evidence-based guidelines.

ELECTRONIC DATABASE INFORMATION

URLs for data in this article are as follows:

Agency for Healthcare Research and Quality, available at http://ahcpr.gov.

American College of Medical Genetics, available at http://www.acmg.net.

American Medical Association, available at http://www.ama-assn.org.

American Society of Human Genetics, available at http://www.society@ashg. org.

Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention, available at http://www.cdc.gov/ogdp.

GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright 1997–2003, University of Washington, Seattle. Available at http://www.genetests.org. Accessed 3 April 2003 for Amos CI, Frazier ML, McGarrity TJ. (Updated 30 December 2002). Peutz-Jeghers syndrome; Astrin KH, Desnick RJ. (Updated 5 August 2002). Fabry disease; Bidichandani SI, Ashizawa T. (Updated 9 December 2002). Friedreich ataxia; Cox DW, Roberts E. (Updated 22 October 1999). Wilson disease; Dietz HC. (Updated 18 April 2001). Marfan syndrome; DiMauro S. (Updated 27 February 2001). MELAS; Evans DG, Fardnon PA. (Updated 20 June 2002). Nevoid basal cell carcinoma syndrome; Gahl WA. (Updated 22 March 2001). Cystinosis; Guttmacher AE, McDonald J. (Updated 26 June 2000). Hereditary hemorrhagic telangiectasia; Harris PC, Torres VE. (Updated 10 January 2002). Autosomal dominant polycystic kidney disease; Johnson EW. (Updated 24 February 2002). Familial cerebral cavernous malformation; Kowdley KV, Tait JF, Bennett RL, Motulsky AG. (Updated 3 April 2000). Hereditary hemochromatosis; Kujovich JL, Goodnight SH. (Updated 18 June 2002). Factor V Leiden thrombophilia; Lesnik Oberstein SAJ, Breuning MH, Haan J. (Updated 23 August 2002). CADASIL; Milewicz DM, Tran VT. (Updated 13 February 2003). Thoracic aortic aneurysms and aortic dissections; North KN. (Updated 25 November 2002). Nemaline myopathy; Northrup H, Au K-S. (Updated 3 December 2002). Tuberous sclerosis complex; Patterson M. (Updated 10 September 2001). Niemann-Pick disease, type C; Pepin MG, Byers PH. (Updated 15 April 2002). Ehlers-Danlos syndrome, vascular type; Pilarski R, Hampel H, Eng C. (Updated 30 December 2002). PTEN Hamartoma tumor syndrome (PHTS); Schimke RN, Collins DL, Stolle CA. (Updated 14 November 2002). Von Hippel-Lindau syndrome; Schneider KA, Li F. (Updated 30 December 2002). Li-Fraumeni syndrome; Solomon C, Burt RW. (Updated 18 January 2002). Familial adenomatous polyposis; Terry SF, Bercovitch L, Boyd CD. (Updated 14 March 2002). Pseudoxanthoma elasticum; Vincent GM. (Updated 20 February 2003). Romano-Ward syndrome; Weisner GL, Snow-Bailey K (Updated 21 January 2003). Multiple endocrine neoplasia, type 2.

GeneTests: Medical Genetics Information Resource (database online). Copyright 1993–2003, University of Washington and Children's Health System, Seattle. Updated weekly. Available at http://www.genetests.org. Accessed 3 April 2003.

Genetics in Primary Care: A Faculty Development Initiative, available at http://genes-r-us.uthscsa.edu/resources/genetics/primary_care.htm.

National Coalition for Health Professionals Education in Genetics, available at http://www.nchpeg.org.

National Guidelines Clearinghouse, available at www.guideline.gov.

National Society of Genetic Counselors, available at http://www.nsgc.org.

Online Mendelian inheritance in Man (OMIM), available at http:// www.ncbi.nlm.nih.gov/Omim.Accessed 1 December 2003 to 19 December 2003.

Appendix IA. The 156 Mendelian Disorders That Feature Coronary Artery Disease, Myocardial Infarction, Stroke, Thrombosis, Sudden Death, Arrhythmia, Aneurysm, Arteriovenous Malformation, Cardiomyopathy, and Diabetes in Adulthood

Mendelian disorder	OMIM entry	Known gene(s)	Mode of inheritance	Featured chronic diseases	GeneReview available
Abdominal aortic aneurysm	100070	Unknown (2% have COL3A1 mutations)	AD, MF	SUD, AN/AVM	No
Abdominal obesity-metabolic syndrome	605552	Unknown	MF	CAD/MI, DM	No
Aceruloplasminemia	604290	CP	AR	DM	No
Adult polycystic kidney disease	173900	PKD1, PKD2	AD	CVA, AN/AVM	Yes
Alstrom syndrome	203800	ALMS1	AR	DM	Yes

(*Continued*)

Appendix IA. (*Continued*)

Mendelian disorder	OMIM entry	Known gene(s)	Mode of inheritance	Featured chronic diseases	GeneReview available
Amyloidosis V	105120	GSN	AD	CM	No
Amyloidosis VI	105150	CST3, ABCA1, ITM2B	AD	CVA	No
Amyloidosis VII	105210	Unknown	AD	CVA	No
Antithrombin III deficiency	107300	AT3	AD	CVA, THR	No
Apolipoprotein(a)	152200	LPA	AD	CAD/MI, CVA, THR	No
Apolipoprotein A-I	107680	APOA1	AD	CAD/MI, CVA	No
Arteriovenous malformation of the brain	108010	Unknown	AD	AN/AVM	No
Arthrogryposis and ectodermal dysplasia	601701	Unknown	AR	DM	No
Atherosclerosis susceptibility	108725	Unknown	AD, MF	CAD/MI	No
Atrial cardiomyopathy with heart block	198770	Unknown	AD	ART, CM	No
Autoimmune polyendocrinopathy syndrome, type I	240300	AIRE	AD	DM	No
AD Emery-Dreifuss muscular dystrophy	181350	LMNA	AD	SUD, ART, CM	No
AD hemochromatosis	606069	SLC11A3	AD	CM, DM	Yes
Autosomal dominant nemaline myopathy	161800	TPM3, ACTA1	AD	CM	Yes
AD pseudoxanthoma elasticum	177850	ABCC6	AD	CAD/MI, CVA, AN/AVM	Yes
AR dilated cardiomyopathy	212110	Unknown	AR	ART, CM	No
AR hypercholesterolemia	603813	ARH	AR	CAD/MI	No
AR nemaline myopathy 2	256030	NEB, ACTA1	AR	CM	Yes
AR Noonan syndrome	605275	Unknown	AR	CM	Yes
Bardet-Biedl syndrome	209901	BBS1, BBS2, BBS4, BBS6	AR and a mutation in a second locus	DM	No
Barth syndrome	302060	TAZ	XL	CM	No
Becker type muscular dystrophy	300376	DMD	XL	CM	Yes
Berardinelli-Seip congenital lipodystrophy	269700	AGPAT2	AR	DM	No
Bicuspid aortic valve	109730	Unknown	AD	AN/AVM	No
Bloom syndrome	210900	RECQ2	AR	DM	No
Brugada syndrome	601144	SCN5A	AD	SUD, ART	No
CADISIL	125310	NOTCH3	AD	CVA	Yes
Cardiac conduction defect	115080	Unknown	AD	SUD, ART	No
Cardiomyopathy-hypogonadism-collagenoma syndrome	115250	Unknown	AD	ART, CM	No
Cataract and cardiomyopathy	212350	Unknown	AR	CM	No
Cerebral cavernous malformations	116860	KRIT1	AD	CVA, SUD, AN/AVM	Yes

Cerebrotendinous xanthomas	213700	CYP27A1	AR	CAD/MI	No
Cerebrovascular disease with thin skin, alopecia and disk disease	600142	Unknown	AR	CVA	No
Cortisol 11-beta-ketoreductase deficiency	218030	HSD11B2	AR	CVA	No
Costello syndrome	218040	Unknown	AR	CM	No
Dilated cardiomyopathy	115200	LMNA, TNNT2, TTN, SGCD, DES	AD	ART, CM	No
Dilated cardiomyopathy with wooly hair and keratoderma	605676	DSP	AR	ART, CM	No
Duchenne type muscular dystrophy	310200	DMD	XL	CM	Yes
Dysfibrinogenemia	134820	FGA, FGB, FGG	AD	CVA, THR	No
Ehlers-Danlos syndrome, type IV	130050	COL3A1	AD	CVA, SUD, AN/AVM	Yes
Ehlers-Danlos syndrome, type VI	225400	PLOD	AR	CVA, SUD, AN/AVM	Yes
Ehlers-Danlos syndrome, type unspecified	130090	Unknown	AD	AN/AVM	No
Emery-Dreifuss muscular dystrophy	310300	EMD	XL	SUD, ART, CM	No
Endocardial fibroelastosis	226000	Unknown	AR	CM	No
Fabry disease	301500	GLA	XL	CAD/MI, CVA, CM	Yes
Familial antiphospholipid syndrome	107320	Unknown	AD	THR	No
Familial arrhythmogenic right ventricular dysplasia	107970	Unknown	AD	SUD, ART, CM	No
Familial combined hyperlipidemia	144250	HYPLIP1, LPL	AD, MF	CAD/MI	No
Familial defective apo B	144010	APOB	AD	CAD/MI	No
Familial defective release of tissue plasminogen activator	173370	PLAT	AD	THR	No
Familial hyperaldosteronism, type 1	103900	Unequal crossing over between CYP11B1 and CYP11B2	AD	CVA	No
Familial hypercholesterolemia	143890	LDLR	AD	CAD/MI	No
Familial hypertrophic cardiomyopathy	192600, 115197	TNNT2, TPM1, MYBPC3	AD	SUD, ART, CM	No
Familial hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome	600858	PRKAG2, TNNI3	AD	SUD, ART, CM	No
Familial idiopathic prepubertal edema	129840	Unknown	AD	DM	No
Familial lipoprotein lipase deficiency	238600	LPL	AR	DM	Yes
Familial mitral valve prolapse	157700	Unknown	AD	CVA, SUD	No
Familial partial lipodystrophy	151660	LMNA	AD	CAD/MI, DM	No
Familial pseudohyperkalemia due to red cell leak	177720	Unknown	AD	CAD/MI, CM	No
Familial restrictive cardiomyopathy	115210	Unknown	AD	ART, CM	No
Familial thoracic aortic aneurysm	132900	Unknown	AD	SUD, AN/AVM	Yes
Familial ventricular tachycardia	192605	Unknown	AD	SUD, ART	No
Fibromuscular dysplasia of arteries	135580	Unknown	AD	CAD/MI, CVA, AN/AVM	No
Friedreich ataxia	229300	FRDA	AR	CM, DM	Yes

(*Continued*)

Appendix IA. (*Continued*)

Mendelian disorder	OMIM entry	Known gene(s)	Mode of inheritance	Featured chronic diseases	GeneReview available
Generalized juvenile polyposis with pulmonary AVM*	175050	Unknown	AD	CVA, AN/AVM, CC	No*
Hemochromatosis (classical and type 3)	235200, 604250	HFE, TFR2	AR	CM, DM	Yes
Heparin cofactor II deficiency	142360	HCF2	AD	CAD/MI, THR	No
Hereditary hemorrhagic telangiectasia, type 1	187300	ENG	AD	CVA, AN/AVM	Yes
Hereditary hemorrhagic telangiectasia, type 2	600376	ALK1	AD	CVA, AN/AVM	Yes
Hereditary neurocutaneous angioma	106070	Unknown	AD	AN/AVM	No
Hereditary pancreatitis	167800	PRSS1, CFTR, SPINK1	AD	DM	No
Hermansky-Pudlak syndrome	203300	HPS1, AP3B1, HPS3, HPS4	AR	CM	Yes
Histidine-rich glycoprotein	142640	Unknown	AD	THR	No
Homocystinuria	236200	CBS	AR	CAD/MI, CVA, THR	No
Homocysteinemia/homocystinuria due to N(5,10)-methylenetetrahydrofolate reductase deficiency	236250	MTHFR	AR	CAD/MI, CVA, THR	No
Hyperkalemic periodic paralysis	170500	SCN4A	AD	SUD, ART	No
Hyperlipoproteinemia, type III	107741	APOE	AR with pseudodominance	CAD/MI	No
Hyperostosis frontalis interna	144800	Unknown	AD	DM	No
Insulin receptor defect	147670	INSR	AD	DM	No
Insulin-resistant diabetes mellitus with acanthosis nigricans and hypertension	604367	PPARG	AD	DM	No
Intracranial berry aneurysm	105800	Unknown	AD	CVA, AN/AVM	No
Juvenile hemochromatosis	602390	HAMP	AR	CM, DM	Yes
Kearns-Sayre syndrome	530000	Mitochondrial deletions	MT, but usually sporadic	CM	No
Leber optic atrophy	535000	Multiple mitochondrial loci	MT	SUD, ART	Yes
LEOPARD syndrome	151100	PTPN11	AD	CM	No
Limb-girdle muscular dystrophy, type 1B	159001	LMNA	AD	ART, CM	Yes
Long QT1 (Romano Ward syndrome)	192500	KCNE1	AD	SUD, ART	Yes
Long QT2	152427	HERG	AD	SUD, ART	Yes
Long QT3	603830	SCN5A	AD	SUD, ART	Yes
Long QT4	600919	Unknown	AD	SUD, ART	Yes
Long QT5 (Lange-Nielsen syndrome)	220400	KCNE1	AR	SUD, ART	Yes

Long QT6	603796	KCNE2	AD	SUD, ART	Yes
Long QT7 (Andersen cardiodysrhythmic periodic paralysis)	170390	KCNJ2	AD	SUD, ART	No
Mal de Meleda	248300	SLURP1	AR	SUD, ART, CM	No
Malignant hyperthermia susceptibility 1	145600	RYR1	AD	SUD, ART	No
Marfan syndrome	154700	FBN1	AD	SUD, AN/AVM	Yes
Maternally transmitted diabetes-deafness syndrome	520000	Mitochondrial tRNA for leucine (UUR)	MT	DM	No
Maturity onset diabetes of the young	606391	HNF4A, GCK, HNF1A/TCF1, IPF1, CF2	AD	DM	No
MELAS	540000	MTTL1, MTND6, MTTQ	MT	CVA	Yes
Moyamoya	252350	Unknown	AR	CVA	No
Multiple epiphyseal dysplasia with early-onset diabetes mellitus	226980	EIF2AK3	AR	DM	No
Myotonic dystrophy	160900	DMPK	AD	ART, DM	Yes
Naxos disease	6021214	JUP	AR	SUD, ART, CM	No
Nephropathic cystinosis	219800	CTNS	AR	DM	Yes
Neurofibromatosis, type 1	162200	NF1	AD	AN/AVM	Yes
Niemann-Pick disease (types C and E)	257200	SMPD1	AR	CAD/MI	Yes
Nodal rhythm	163800	Unknown	AD	SUD, ART	No
Noonan syndrome	163950	PTPN11	AD	CM	Yes
Obesity and endocrinopathy due to impaired processing of prohormones	600955	PCSK1	AR?	DM	No
Obstructive sleep apnea	107650	Unknown	AD	SUD	No
Pancreatic beta cell agenesis with neonatal diabetes mellitus	600089	Unknown	AR	DM	No
Parkinsonism with alveolar hypoventilation and mental depression	168605	Unknown	AD	SUD	No
Paroxysmal familial ventricular fibrillation	603829	SCN5A (some cases)	AD	SUD, ART	No
PHACE association	606519	Unknown	XL?	AN/AVM	No
Pineal hyperplasia, insulin-resistant diabetes mellitus, and somatic abnormalities	262190	INSR	AR	DM	No
Plasminogen activator inhibitor 1	173360	PAI1	AD	THR	No
Plasminogen defects	173350	PLG	AD	CVA, THR	No
Polycystic ovary syndrome 1	184700	CYP11A, INSR	AD	DM	No
Progeria	176670	Unknown	AD	CAD/MI	No
Progressive familial heart block, 1 and 2	113900	SCN5A	AD	SUD, ART	No
Protein C deficiency	176860	PROC	AD (AR lethal)	CVA, THR	No
Protein S deficiency	176880	PSA	AD	THR	No

(*Continued*)

Appendix IA. (*Continued*)

Mendelian disorder	OMIM entry	Known gene(s)	Mode of inheritance	Featured chronic diseases	GeneReview available
Pseudoxanthoma elasticum	264800	ABCC6	AR	CAD/MI, CVA, AN/AVM	Yes
Schmidt syndrome	269200	Unknown	AD vs. MF, AR?	DM	No
Sitosterolemia	210250	ABCG8, ABCG5	AR	CAD/MI	No
Sneddon syndrome	182410	Unknown	AD	CVA	No
Spontaneous coronary dissection	122455	Unknown	AD	CAD/MI, SUD	No
Stress-induced polymorphic ventricular tachycardia	604772	RYR2, CASQ2	AD	SUD, ART	No
Tangier disease	205400	ABC1	AR	CAD/MI	No
Tardive tibial muscular dystrophy	600334	TTN	AD	CM	No
Thiamine-responsive megaloblastic anemia syndrome	249270	SLC19A2	AR	DM	No
Three M syndrome	273750	Unknown	AR	AN/AVM	Yes
Thrombophilia due to deficiency of activated protein C	188055	F5 (factor V Leiden)	AD	THR	Yes
Thrombophilia due to thrombomodulin defect	188040	THBD	AD	CAD/MI, THR	No
Tissue factor pathway inhibitor	152310	TFPI	AD	THR	No
Transient neonatal diabetes	601410	Unknown	AD (imprinted, paternally expressed)	DM	No
Transthyretin	176300	TTR	AD	CVA, SUD, CM	Yes
Tuberous sclerosis	191100	TSC1, TSC2	AD	ART	Yes
Type I hyperlipoproteinemia due to apolipoprotein C-II deficiency	207750	APOC2	AR	DM	Yes
Type IV hyperlipidemia	238500	Unknown	AR	DM	No
Von Hippel-Lindau syndrome	193300	VHL	AD	CVA, AN/AVM, KC	Yes
Welander distal myopathy (SMAIII)	604454	Unknown	AD	CM	Yes
Werner syndrome	277700	RECQL2	AR	CAD/MI, DM	Yes
Williams syndrome	194050	Hemizygous deletion (ELN+LIMK1 +/−RFC2)	AD	CAD/MI, CVA	Yes
Wilson disease	277900	ATP7B	AR	CM	Yes
Wolff-Parkinson-White	194200	PRKAG2	AD	SUD, ART, CM	No
Wolfram syndrome	222300	WFS1	AR	CVA, CM, DM	No
XL dilated cardiomyopathy	302045	DMD	XL	ART, CM	Yes
XL immunodysregulation, polyendocrinopathy, and enteropathy	304790	FOXP3	XL	DM	No
XL sideroblastic anemia	301300	Unknown	XL	CM, DM	No

AD, autosomal dominant; AR, autosomal recessive; MF, multifactorial; MT, mitochondrial; XL, X-linked; CAD/MI, coronary artery disease and/or myocardial infarction; CVA, cerebrovascular accident (stroke); THR, thrombosis; SUD, sudden death; AN/AVM, aneurysm and/or arteriovenous malformation; ART, arrhythmia; CM, cardiomyopathy; DM, diabetes mellitus; CC, colon cancer; KC, kidney cancer.

Appendix IB. The 35 Mendelian Disorders That Feature Breast, Ovarian, Endometrial, Prostate, Colon, Kidney and Thyroid Cancer in Adulthood

Syndrome	OMIM entry	Known gene(s)	Mode of inheritance	Featured cancers	GeneReview available
Alagille syndrome	118450	JAG1	AD	TC	Yes
Ataxia telangiectasia	208900	ATM	AR (heterozygotes have BC risk)	BC	Yes
Nevoid basal cell carcinoma syndrome	109400	PTCH	AD	OC	Yes
Birt-Hogg-Dube syndrome	135150	FLCL	AD	KC	No
Breast cancer, type 1	113705	BRCA1	AD	BC, OC, CC, PC	Yes
Breast cancer, type 2	600185	BRCA2	AD	BC, OC	Yes
Breast cancer, type 3	605365	Unknown	AD	BC	Yes
Cowden syndrome	158350	PTEN	AD	BC, EC, KC, TC	Yes
Diamond-Blackfan anemia	205900	S19	AD	CC	No
Familial adenomatous polyposis	175100	APC	AD	CC, TC	Yes
Familial thyroglossal duct cyst	188455	Unknown	AD	TC	No
Follicular thyroid carcinoma	188470	Unknown	AD	TC	No
Generalized juvenile polyposis with pulmonary AVM	175050	Unknown	AD	AN/AVM, CC	No*
Hereditary desmoid disease	135290	APC	AD	CC	No*
Hereditary leiomyomatosis and renal cell cancer	605839	FH	AD	KC	No
Hereditary medullary thyroid carcinoma	155240	RET	AD	TC	Yes
Hereditary nonpolyposis colon cancer	114500	MSH2, MLH1, MSH6, PMS1, PMS2	AD	CC, EC, OC	No
Hereditary prostate cancer	601518	RNASEL	AD	PC	No
Juvenile intestinal polyposis	174900	SMAD4/DPC4, BMPR1A, MPSH	AD	CC	No
Li-Fraumeni syndrome	151623	TP53, CHK2	AD	BC	Yes
Muir-Torre syndrome	158320	MSH2, MLH1	AD	BC, OC, EC, CC	No
Multinodular goiter 1	138800	Unknown	AD	TC	No
Multiple endocrine neoplasia, type 2	171400	RET	AD	TC	Yes
Multiple endocrine neoplasia, type 2b	162300	RET	AD	TC	Yes
Nonmedullary thyroid carcinoma with cell oxyphilia	603386	Unknown	AD	TC	No
Ovarian germ cell cancer	603737	Unknown	AD	OC	No
Papillary renal cell carcinoma	605074	MET	AD	KC	
Papillary thyroid cancer	188550	Unknown	AD	CC, TC	No
Peutz-Jeghers syndrome	175200	STK11	AD	BC, OC, CC	Yes
Prostate cancer/brain cancer susceptibility	603688	Unknown	AD	PC	No
Translocation in renal cell carcinoma on chromosome 8	603046	Unknown	AD	TC, KC	No
Tuberous sclerosis	191100	TSC1,TSC2	AD	KC	Yes
Turcot syndrome	276300	APC	AD	CC, TC	Yes

(*Continued*)

Appendix IB. (*Continued*)

Syndrome	OMIM entry	Known gene(s)	Mode of inheritance	Featured cancers	GeneReview available
Von Hippel-Lindau syndrome	193300	VHL	AD	KC	Yes
XL hereditary prostate cancer	300147	Unknown	XL	PC	No

AD, autosomal dominant; AR, autosomal recessive; MF, multifactorial; MT, mitochondrial; XL, X-linked; AN/AVM, aneurysm and/or arteriovenous malformation; CVA, cerebrovascular accident (stroke); BC, breast cancer; OC, ovarian cancer; EC, endometrial cancer; PC, prostate cancer; CC, colon cancer; KC, kidney cancer; TC, thyroid cancer.

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