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Rationale and Design of the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) Registry

The GenTAC Consortium

Abstract

Background—Although the management of thoracic aortic aneurysms (TAAs) has improved significantly, patients presenting with aortic dissections, rupture or other acute complications of TAAs continue to suffer high rates of morbidity and mortality. Accumulating data have indicated that many TAAs are due to underlying gene mutations. A comprehensive approach to the study of TAAs resulting from genetic mutations is needed to translate this information into advances in treatment.

Objective—The National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) was established to provide a biospecimen inventory and bioinformatics infrastructure to enable research to advance the clinical management of genetically-triggered TAAs and related complications.

Methods—The GenTAC Registry is a longitudinal observational cohort study enrolling patients with conditions related to genetically-induced TAAs from five regional clinical centers in the United States.

Results—Over 700 subjects with associated clinical histories, physical examinations, imaging data, and biospecimens have been enrolled in the Registry to date. Enrollment is expected to continue until September 2010. Total enrollment of nearly 3,000 subjects is expected. No interim analysis has yet been undertaken.

Conclusions—GenTAC has been established to facilitate studies by GenTAC investigators and others that will advance multiple scientific frontiers in thoracic aortic disease. Genotypic, proteomic, clinical, and imaging data will be integrated systematically with outcomes data to determine the optimal clinical management of patients suffering from genetically-induced TAAs.

Introduction

Thoracic aortic aneurysms (TAAs) predispose patients to life threatening aortic complications, including aortic dissection and rupture. Aortic dissection has been estimated to cause more than 2,000 deaths per year in the United States (1). In addition, when TAAs involve the aortic root, they cause aortic regurgitation and heart failure. TAAs are the etiology of up to 30% of cases of isolated severe aortic regurgitation in adults (2). The treatment of complications arising from TAAs is complex, with high rates of morbidity, mortality, and surgical procedures (3–5). The disease is a significant burden on the health care system.

TAAs are associated with degeneration of elastic fibers in the aortic wall. This degeneration may be caused by atherosclerosis, hypertension, and inflammation, particularly in elderly

patients, but genetic mutations are the cause of TAAs in many young or middle-aged patients (6–8). TAAs may form as part of syndromes such as Marfan syndrome (6) but familial TAA occurs in the absence of syndromic features (9). While diagnostic and treatment advances have dramatically improved care for patients with genetically triggered TAAs, many questions remain about how best to identify and treat these disorders.

Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and vascular Ehlers-Danlos syndrome (also termed EDS type IV) are well described genetic disorders associated with high risk for TAA (10–12,16–18). Examples of genetically determined aortic disorders that are less well characterized include TAAs associated with bicuspid aortic valve and Turner syndrome (13–15,19–22). In addition, up to 20% of patients with TAAs or dissection have a family history of TAAs without being affected by a known syndrome. The genes that predispose to non-syndromic inherited forms of TAAs have only recently begun to be identified (23–26). Numerous questions remain unanswered regarding gene-specific clinical manifestations, diagnosis, genotype-phenotype correlations, natural history, and syndrome-specific optimal treatment approaches.

In order to facilitate ongoing and future investigations, we have developed a longitudinal Registry for individuals affected by genetically transmitted thoracic aortic conditions (GenTAC) that will collect clinical and biological data. The Registry has established a biospecimen inventory and bioinformatics infrastructure that will enable research to determine best practices to advance the optimal clinical management of genetically-triggered TAAs and related complications. The Registry will also record the characteristics and clinical outcomes of patients undergoing open and endovascular repair of aneurysms, process tissue and blood samples, analyze collected data, and provide access of these resources to investigators who are advancing our fundamental understanding of genetically-mediated TAAs and their causes, diagnosis, and optimal treatment.

Registry Design

GenTAC is a longitudinal observational cohort study consisting of patients with conditions related to genetically-induced TAAs. There is no disease free or control group. The study will compare cross-sectional and longitudinal data on risk factors related to diagnosis, treatment, and outcome among groups of enrolled patients. Data on treatment and outcome will be recorded as they become available. No interventions are planned; all decisions regarding approaches to treatment will be made by the patients and their care teams.

Sponsor

GenTAC is co-sponsored by the National Heart Lung and Blood Institute (NHLBI) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). NHLBI manages the Registry contract, has technical oversight, and monitors expenditures and deliverables. The NHLBI and the investigators share responsibility for the scientific direction and performance of the Registry.

Data Coordinating Center

Research Triangle Institute International (RTI) serves as the data coordinating center (DCC). RTI is responsible for data management; coordination of training, logistics and communications; the study website; and statistical design and analysis. In collaboration with the GenTAC Steering Committee, the DCC is responsible for developing the protocol, data collection forms, and manual of operations, and for preparing manuscripts and presentations (Figure 1).

Study Chair

The GenTAC Study Chair is responsible for conducting Steering Committee and Operations Committee meetings. The Chair ensures that consensus is built and that decisions are made in a timely manner. In collaboration with the DCC Principal Investigator (PI), the Chair provides scientific and administrative oversight of the Registry and contributes to decisions regarding data elements, and data analyses. The Study Chair helps to organize and authorize policies, procedures, conference calls, and face to face meetings along with the DCC PI, co-sponsors, and Study Steering Committee (Figure 1).

Regional Clinical Centers

The GenTAC population is being derived from five Regional Clinical Centers (RCCs) that provide care to patients from a wide geographic catchment area, drawing patients from more than 15 states in the Northeast, Mid Atlantic, South, and the West (Figure 2).

The targeted enrollment of patients for GenTAC includes adults and children of all races and ethnicities in one or more of 13 clinical categories. Inclusion criteria are listed in Table I. It is expected that approximately 3,000 subjects will be enrolled in the Registry, or 60% of the estimated total of over 5,000 eligible patients at the participating RCCs. The majority of the pediatric patients enrolled will come from the Johns Hopkins University School of Medicine. Minority enrollment will be encouraged at all sites but it is expected that the patients enrolled in the study will represent the population receiving care at each institution.

Biospecimen Repository

Blood or saliva samples will be obtained from every consenting GenTAC participant to provide a source of DNA. Plasma from the samples will be used for biomarker studies. Excess tissue will be obtained on those undergoing corrective aortic surgical procedures. These biospecimens will be stored and made available to approved investigators with permission from NHLBI and the GenTAC Steering Committee.

Committees

The GenTAC Steering Committee (SC) is comprised of up to three investigators from each RCC, Project Officers from NHLBI, the PI and co-investigator from the DCC, and the Study Chair. The SC is the governing body for GenTAC and establishes the scientific direction of the Registry. Members of the SC also serve on subcommittees that oversee various GenTAC activities, including ancillary studies, publications and presentations.

The Operations Committee (OC) includes the Study Chair, the NHLBI Project Officers, and the DCC PI. The OC has oversight and authority for day to day operations of the study.

The Observational Study Monitoring Board (OSMB) oversees conduct of the GenTAC. Comprised of a multidisciplinary group of experts, the OSMB reviews and approves the study protocol, monitors study progress, and assures quality research. The OSMB reviews, assesses, and makes recommendations regarding:

- Performance of individual centers
- Participant safety and informed consent
- Adequacy of progress such as enrollment, quality control, data analysis, and publications
- Participant burden
- Impact of proposed ancillary studies on participant burden and overall study goals

Scientific direction of the study

Data Collection

To assure patient confidentiality, each patient is assigned a unique identifier at enrollment which will be used for the life of the Registry. The DCC maintains the data under the unique ID and does not have access to identifiers such as patient names and social security numbers. The link between the patient name and the ID is retained by each RCC. Data are further protected by a Certificate of Confidentiality.

Enrollment data are abstracted from medical records or obtained through patient interviews. The data collected include clinical evaluations and historically diagnosed conditions and outcomes; patient reported quality of life, drug treatment, co-morbidities, family history, smoking, alcohol use, and pregnancy history; most recent imaging evaluations, genetic testing, blood chemistry, and surgical interventions.

Follow-up data will be collected at regular intervals for each patient enrolled. The follow-up interval varies according to the inclusion diagnosis (Table II). Follow-up data include clinical and imaging evaluations and treatment and lifestyle changes since the enrollment visit.

Biological Specimens

Blood, buccal cell samples, and excess tissue gathered at the time of surgery are processed, inventoried, and stored according to established protocols. Each specimen receives a preprinted subject ID label as well as readable text. After proper preparation and subject identification, samples are shipped to the storage facility in prelabeled standardized shipping containers. The storage lab maintains and prepares samples for analysis as dictated by protocol and the SC. DNA will be extracted from the buffy coat to allow sequencing of candidate genes. Available plasma will be tested for biomarkers that may be related to diagnosis, outcome, or response to treatment. Tissue will be used for RNA analysis, histology, and immunohistochemistry.

Statistical Analysis

It is anticipated that the GenTAC will include nearly 3,000 patients receiving treatment for genetically-induced thoracic aortic aneurysms and dissections. In general, the analysis of data will be descriptive and exploratory in nature, and thus will generate hypotheses more often than testing or validating hypotheses.

Regression methods will be used to examine the relationship between specific factors and an outcome of interest while controlling for potential confounding factors. Subgroups will be compared using the chi-square test or Fisher's exact test for categorical variables, a t-test for continuous variables and Pearson correlations to measure association between groups. For repeated measures we will employ rates or slopes to compare groups as well as generalized estimating equations (GEE) methodology. Also different diagnostic methods may be compared using the area under the curve (AUC) or the Receiver Operating Characteristic (ROC) curve.

The sample size will provide considerable statistical power for identifying associations between various categories of TAA and their diagnostic criteria, morbidity and natural history, predictors of treatment selection, drug treatment, disease progression, and genetic/molecular/proteomic markers related to phenotype variation and prognosis. For example, with a two sided test at $\alpha=0.05$ and at least 90% power we can detect a small effect size (difference of means or proportions or slopes/standard deviation) of 0.25 with a sample size of 338 per group. With a total sample of under 900 and with an event: no event proportion of 1:5 we can estimate the AUC within a margin of error of 0.05. Lastly, with a sample size of 500 per group and event

proportion in one group larger than 20% we are able to detect an odds ratio of at least 1.6 with more than 87% power.

Results

Patient enrollment began in November 2007. Characteristics of the first 500 patients enrolled are presented in Table III. Enrollment is expected to be completed in September 2010.

Discussion

Over the past 30 years, advances in imaging, medical and surgical practice, and critical care have improved the safety and efficacy of the management of TAAs and their complications. Until a life threatening event like aortic dissection or rupture takes place, however, a TAA patient is often unaware of his or her aortic disease. Our understanding of the genetic basis of predisposition to thoracic aortic disease has expanded but there is considerable room for improvement. Recognizing individuals with these genetic mutations will help to prevent premature deaths due to thoracic aortic disease. A comprehensive approach that links genetic and clinical information in the study of TAAs is needed but to date, the clinical and genetic aspects have remained largely distinct. The GenTAC will provide a resource that combines clinical and biological data from a large and diverse population of patients with inherited TAA disorders.

The GenTAC investigators envision a series of research studies over the next five years. Potential topics to be addressed are organized into five categories: Diagnostic Criteria, Natural History Outcomes, Phenotypic and Anatomic Indications for Interventional Therapies and Outcomes, Drug Treatment, and Genetic/Molecular/Proteomic Markers for Phenotypic Variation (Table IV). Because of the large number of patients with TAAs that will be enrolled in the Registry, GenTAC offers a unique opportunity to advance multiple scientific frontiers in thoracic aortic disease through a systematic approach to studies correlating genotypic, protein, clinical, imaging, and response to treatment data. It is expected that the investment in GenTAC will foster substantial progress in diagnosis and treatment of patients with genetically triggered TAAs.

The Registry will be available as a resource to investigators who are not part of the GenTAC consortium provided they propose studies that are consistent with GenTAC aims but do not significantly overlap with research being conducted by GenTAC investigators. Ancillary studies will fall into two distinct categories. Category I encompasses studies that utilize existing GenTAC resources, including biospecimens and clinical data. In category II studies, investigators will request additional samples and/or data not included in on-going GenTAC activities. In all cases ancillary studies will be fully funded by the ancillary study PI. In addition to funding the study, PIs of category II ancillary studies will be required to fund any GenTAC activities that are outside the currently funded GenTAC mission. Additional activities may include collecting supplementary data and/or biological samples from current GenTAC registrants at one or more of the RCCs. Services such as assistance with biostatistical analyses and data management may also be requested from the DCC. All ancillary studies must be approved by the GenTAC Ancillary Studies subcommittee, which will review ancillary study proposals for the basic required elements shown in Table V. This will ensure that the GenTAC meets its maximum potential as a national resource for the study of TAA disorders.

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Project Organization

Figure I.
GenTAC Project Organization chart.

Figure II.
GenTAC Regional Centers and a number of the states they will serve as the registry enrolls patients.

Table I

Inclusion criteria for GenTAC*

	Conditions Diagnosed	Age Range	Minimum Thoracic Aortic Enlargement Required	Family History Required
1	Marfan Syndrome	All ages	No	No
2	Turner Syndrome	All ages	No	No
3	Ehlers-Danlos Syndrome	All ages	No for vascular EDS Other types: Yes ¹	No
4	Loeys-Dietz Syndrome	All ages	No	No
5	<i>FBNI</i> , <i>TGFBR1</i> , <i>TGFBR2</i> , <i>ACTA2</i> or <i>MYH11</i> genetic mutation ²	All ages	No	No
6	Bicuspid aortic valve without known family history of TAA	All ages	Yes ¹	No
7	Bicuspid aortic valve with family history of TAA	All ages	No	Yes ³
8	Bicuspid aortic valve with coarctation	All ages	No	No
9	Familial Thoracic Aortic Aneurysms and Dissections	All Ages	Yes ¹	Yes ⁴
10	Shprintzen-Goldberg Syndrome	All Ages	No	No
11	Other aneurysms and dissections of the thoracic aorta not due to trauma	≤50 years of age	Yes ¹	No
12	Other congenital heart disease (e.g. Tetralogy of Fallot, coarctation)	All ages	Yes ¹	No
13	1 st degree family members of probands already enrolled in the GenTAC registry ⁵	All ages	No	Yes

¹Two standard deviations above normal based on nomograms (from Roman MJ et al. Am J Cardiol 1989;64:507–12) OR prior dissection OR significant enlargement compared to adjacent area.

²*ACTA2* and *MYH11* mutations causing thoracic aortic disease should be confirmed by a GenTAC principal investigator.

³Family history for BAV = First degree relative with thoracic aortic enlargement 2 SD above normal based on nomograms, prior thoracic aortic aneurysm repair or dissection, significant enlargement compared to adjacent area, BAV, or aortic coarctation.

⁴Family history for FTAAD = 1) First or second degree relative of any age with thoracic aortic enlargement 2 SD above normal or prior thoracic aortic aneurysm repair or aortic dissection OR 2) Nonsmoking (for > 15 years) first degree relative less than or equal to 50 years of age with aneurysms or dissection of the abdominal aorta or any artery.

⁵Subjects are not yet being recruited under this inclusion criterion.

FBNI – fibrillin-1

TGFBR – transforming growth factor beta receptor

ACTA2 – smooth muscle alpha-actin

MYH11 – smooth muscle beta-myosin heavy chain

Table II

Targeted Disease Categories and Follow-up Interval*

Condition	Follow-up Interval
Marfan Syndrome	2 years
Turner Syndrome	2 years
Ehlers-Danlos Syndrome	2 years
Loeys-Dietz Syndrome	6 months, 1 year, and 2 years
<i>TGFBR1</i> and <i>TGFBR2</i> mutations	6 months, 1 year, and 2 years
ACTA2 and MYH11 mutations	2 years
Fibrillin 1 mutation	2 years
Bicuspid aortic valve	2 years
Familial Thoracic Aortic Aneurysm and Dissections	2 years
Shprintzen-Goldberg Syndrome	2 years
Other aneurysms and dissections of the thoracic aorta not due to trauma.	2 years

* TGFBR – transforming growth factor beta receptor.

Table III

Characteristics of the First 500 Patients Enrolled into GenTAC

Characteristics	N	%	Age at Diagnosis (years)
Primary Eligibility Diagnosis			
Marfan syndrome	214	42.8	17.3
Turner syndrome	12	2.4	3.4
Ehlers-Danlos	14	2.7	25.3
Loeys Dietz	11	2.2	15.4
BAV with aortic enlargement	126	25.2	30.7
BAV with family history	5	1.1	26.3
BAV with coarctation	0	-	-
Shprintzen-Goldberg syndrome	0	-	-
Familial TAA with aortic enlargement	70	14.1	39.0
Other aneurysm/dissection in person under 50 years of age	41	8.1	20.1
Other congenital heart disease	4	0.8	31.7
<i>FBNI, TGFBRI, TGFBRI2, ACTA2, MYH11</i> mutations and none of the above conditions	3	0.5	16.3
Gender			
Male	302	60.4%	
Female	198	39.6%	
Age at Enrollment			
< 5	16	3.2%	
5–17	82	16.4%	
18–39	156	31.2%	
40–69	228	45.6%	
>69	18	3.6%	
Race/Ethnicity			
White, non-Hispanic	447	89.4%	
Black-non-Hispanic	17	3.4%	
Hispanic	21	4.2%	
Asian	9	1.8%	
American Indian/Alaskan Native	0	0.0%	
Pacific Islander	1	0.2%	
Unknown	5	1.0%	
Thoracic Aorta			
History of TAA	434	86.7%	
History of TAA dissection	67	13.4%	
History of surgical intervention	288	57.6%	

Table IV

Research Questions To Be Addressed by the GenTAC *

Diagnostic Criteria	Natural History Outcomes Related to Diagnosis and Severity of Disease
<ul style="list-style-type: none"> How do the new and old Ghent criteria categorize this population? What is the full spectrum of Loeys-Dietz syndrome? Test proposed diagnostic criteria for Loeys-Dietz syndrome Do all patients with <i>TGFBR1</i> or <i>TGFBR2</i> mutations present with features of Loeys-Dietz syndrome? 	<ul style="list-style-type: none"> Which outcomes appear to be uniquely influenced by aging? What are the outcomes by inclusion diagnosis and organ system involvement? What gene mutations are present in children presenting with TAAs? Do the rare childhood MFS patients actually represent Loeys-Dietz patients who were misdiagnosed? Is absolute size or rate of change in ST diameter a better predictor of aortic valve insufficiency? Are there anatomic or clinical predictors of impending dissection? What is optimal frequency of follow-up? Does the natural history of aortic disease differ based on the underlying genetic mutation? Do clinical features or underlying genetic mutations predict long-term outcomes?
Phenotypic and Anatomic Indications for Interventional Therapies and Outcomes	Drug Treatment and Relation to Disease Progression
<ul style="list-style-type: none"> What are the current phenotype-specific indications for open and percutaneous aortic procedures? What procedures provide the best clinical outcomes? How do procedural indications and outcomes differ between patients with MFS and other genetically triggered disorders? Should all patients with <i>TGFBR2</i> and <i>TGFBR1</i> mutations be referred for surgical repair prior to an aortic diameter of 5.0 cm, and if so what anatomical features should trigger recommendations for aortic repair? 	<ul style="list-style-type: none"> Is there evidence that ARBs retard disease progression? Is there synergy between β-blockers and ARBs? Which medications beyond ARB and β-blockers affect disease progression? Which medication classes are associated with the best quality of life?
Genetic/ Molecular/ Proteomic Markers for Phenotypic Variation and Prognosis	
<ul style="list-style-type: none"> Does C-reactive protein or other markers of inflammation have prognostic significance for aortic dissection? Does monitoring fibrillin-1 or elastin degradation products aid in monitoring progression of arterial wall damage? What proportion of non-MFS familial TAA can be characterized by existing known mutations? Does the amount of circulation biomarker like TGF-β, C-reactive protein, D-Dimer, Calponin, etc. correlate with disease severity? Does TGF-β signaling correlate with increased expression/activation of matrix degrading enzymes like MMP 2 or 9 in aneurysms other than MFS or Loeys-Dietz? Are there genetic modifiers of vascular disease that influence phenotypic-genotypic correlations among families and unrelated individuals? What is the phenotypic variation among individuals that harbor the same mutation? 	

Diagnostic Criteria	Natural History Outcomes Related to Diagnosis and Severity of Disease
<ul style="list-style-type: none">What are the pathogenetic mechanisms that contribute to aortic aneurysm in conditions such as BAV with TAA and non-MFS familial TAA?	

* ST – sinotubular; MFS - Marfan Syndrome; ARB – angiotensin II receptor blocker; TGF – transforming growth factor; MMP - matrix metalloproteinase; BAV – bicuspid aortic valve; TAA – thoracic aortic aneurysm.

Table V**Required Elements for Ancillary Studies***

1	The goals of the study must generally conform to the goals of GenTAC.
2	The study must meet the Ancillary Studies subcommittee's standard of scientific excellence in terms of significance, approach, and the overall likelihood of success.
3	The available study population (including non-GenTAC samples) must constitute a statistically significant sample size.
4	The study may not interfere with other parts of the GenTAC protocol.
5	Availability of the proposed study population and requested samples must be confirmed by GenTAC.
6	The study must not have significant overlap with proposed or on-going studies by GenTAC investigators, including depleting resources needed by GenTAC studies (<i>i.e.</i> DNA, tissues).
7	Confirmation that the study will not hamper continued participation of study subjects in the Registry.
8	The study does not place an undue burden on the DCC and the RCCs.
9	Requested or available funds must be adequate to support the proposed study (particularly in case of unfunded studies). Category I studies must have sufficient funds to support the proposed study, exclusive of resources provided by GenTAC. Category II studies must provide sufficient funds to support the expanded GenTAC activities as well as the proposed study.
10	Individual RCCs may refuse to participate in a Category II study.

DCC – data coordinating center; RCC – regional clinical center.