Fabry Disease, an Under-Recognized Multisystemic Disorder: Expert Recommendations for Diagnosis, Management, and Enzyme Replacement Therapy

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Fabry disease (α-galactosidase A deficiency) is an X-linked recessive lysosomal storage disorder. Although the disease presents in childhood and culminates in cardiac, cerebrovascular, and end-stage renal disease, diagnosis is often delayed or missed. This paper reviews the key signs and symptoms of Fabry disease and provides expert recommendations for diagnosis, follow-up, medical management, and the use of enzyme replacement therapy. Recommendations are based on reviews of the literature on Fabry disease, results of recent clinical trials, and expertise of the authors, all of whom have extensive clinical experience with Fabry disease and lysosomal storage disorders and represent subspecialties involved in treatment.

All males and female carriers affected with Fabry disease should be followed closely, regardless of symptoms or treatment status. Clinical trials have shown that recombinant human α-galactosidase A replacement therapy—the only disease-specific therapy currently available for Fabry disease—is safe and can reverse substrate storage in the lysosome, the pathophysiologic basis of the disease. Enzyme replacement therapy in all males with Fabry disease (including those with end-stage renal disease) and female carriers with substantial disease manifestations should be initiated as early as possible. Additional experience is needed before more specific recommendations can be made on optimal dosing regimens for reversal; maintenance; and prevention of disease manifestations in affected males, symptomatic carrier females, children, and patients with compromised renal function.

RECOMMENDATIONS

Formation of Expert Panel and Basis of Recommendations

In June and July of 2001, two groups of investigators published randomized, placebo-controlled trials that demonstrated that enzyme replacement therapy in Fabry disease can reverse the major pathologic consequences and improve outcomes (12, 13). With a disease-specific therapy finally available, the need for prompt and accurate diagnosis of this devastating, progressive disease became paramount so that patients could be identified and treated before incurring irreversible organ damage. Recognizing the need for initial guidelines for diagnosis, management, and the use of enzyme replacement therapy, Dr. Robert Desnick and Dr. Roscoe Brady (senior authors of the enzyme replacement trials) assembled an international panel of ex-
experts with extensive clinical experience and diverse subspecialty expertise in Fabry disease and lysosomal storage disorders.

Panelists met face-to-face to identify and discuss salient issues. An independent coordinator conducted numerous global and specific searches of the MEDLINE database (1991–2001), including a global search of the recent literature on Fabry disease. The coordinator then interviewed each panelist in detail and, with the first author, prepared a draft statement. In a second face-to-face session, the draft was reviewed, revised, and finalized by the panel. A teleconference was convened to revise the manuscript after journal review. Support for the expert panel process was obtained from the Genzyme Corporation (Cambridge, Massachusetts), which had no formative role in the literature review, the formulation of recommendations, or the drafting and revising of the manuscript.

As would be expected for a rare, under-recognized disease, the literature on Fabry disease mostly consists of single or small case studies and reviews in addition to book chapters written by Fabry experts. The few larger studies focus on disease manifestations and mechanisms of disease rather than the effectiveness of interventions or disease management. The literature on enzyme replacement therapy is limited to the clinical trials published in the last 2 years. Thus, clinical experience and expertise played an important role in the formulation of these recommendations.

**DISEASE PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS**

The major debilitating manifestations of Fabry disease result from the progressive accumulation of globotriaosylceramide in the vascular endothelium (Figure 1), leading to ischemia and infarction, especially in the kidney, heart, and brain. The ischemia and infarction of small vessels are primarily due to vascular occlusion (5); however, evidence for a prothrombotic state has recently been published (14).

In addition, early and substantial deposition of globotriaosylceramide occurs in podocytes, leading to proteinuria and, with age, in cardiomyocytes, causing cardiac hypertrophy and conduction abnormalities (Figure 1). Patients are generally divided into two major groups on the basis of the absence or presence of residual α-Gal A activity: classic disease and milder, later-onset, atypical variants (5). Presentation and clinical course can vary within these phenotypes, and an intermediate phenotype has also been described (15–17).

A. Electron micrograph showing the vascular endothelium of a small vessel from a patient with Fabry disease. Note the electron-dense vesicles (lysosomes) in the endothelium containing undegraded glycosphingolipid. The progressive lysosomal accumulation in the vascular endothelium leads to ischemia and infarction of these vessels. B. Electrocardiogram of a 41-year-old man with classic Fabry disease showing sinus bradycardia with short PR interval (88 msec) and left ventricular hypertrophy with QRS widening and a repolarization abnormality.
The Classic Phenotype

Males with classic disease have no or very low α-Gal A activity, resulting in severe renal, cardiac, and cerebrovascular disease manifestations. Before treatment of uremia became available, the average lifespan of affected males was about 40 years (18). With the advent of renal dialysis or transplantation, the median survival was about 50 years (19). Clinical manifestations (Figures 1 and 2), which usually begin in childhood or adolescence, include intermittent pain in the extremities (acroparesthesias); episodic "Fabry crises" of acute pain lasting hours to days; characteristic skin lesions (angiokeratomas); a corneal opacity that does not affect vision; hypohidrosis; heat, cold, and exercise intolerance; mild proteinuria; and gastrointestinal problems. By adulthood, the renal involvement inevitably results in end-stage renal disease, which requires dialysis or transplantation (20, 21). Cardiac manifestations include left ventricular hypertrophy, valvular disease (especially mitral insufficiency), ascending aortic dilatation, coronary artery disease, and conduction abnormalities (Figure 1), leading to congestive heart failure, arrhythmias, and myocardial infarction (5, 22–24). Cerebrovascular manifestations include early stroke, transient ischemic attacks, white matter lesions, hemiparesis, vertigo or dizziness, and complications of vascular disease (such as diplopia, dysarthria, nystagmus, tinnitus, hemiataxia, memory loss, and hearing loss) (5, 25).

Clinical manifestations in carrier females range from asymptomatic to full-blown disease as severe as that in affected males (5, 26–28). Although many carriers will be relatively asymptomatic and have a normal lifespan, carriers may experience symptoms in childhood and adolescence (such as pain and proteinuria) and adulthood (such as cardiac or, more rarely, renal manifestations). In late adulthood, some carriers develop left ventricular hypertrophy and substantial cardiomyopathy. Data on carriers are limited. A recent study of obligate carrier females found significant disease manifestations in 20 of 60 women, including 17 of whom who had experienced transient ischemic attacks or cerebrovascular accidents (28).

Atypical Variants

Atypical male variants have a milder, later-onset phenotype (5–7, 17, 29). Because of low residual α-Gal A levels, these patients do not have the early major clinical manifestations of classic Fabry disease. For example, cardiac variants present with cardiomegaly and mild proteinuria usually after 40 years of age, when patients with classic Fabry disease would be severely affected or would have died (6, 7, 29). Two recent studies have suggested that the cardiac variant of Fabry disease may be an important cause of idiopathic left ventricular hypertrophy (7) or late-onset hypertrophic cardiomyopathy (30). Tissue biopsies or autopsy studies of cardiac variants reveal globotriaosylceramide accumulation in the myocardium and not in the vascular endothelium throughout the body (5, 6, 29). These findings suggest that even low levels of α-Gal A can prevent globotriaosylceramide accumulation in the microvasculature and that this lack of accumulation is associated with the absence or attenuation of disease manifestations. Thus, reversal of the underlying vascular endothelial pathology by enzyme replacement therapy will probably be clinically therapeutic in patients with classic Fabry disease.

Enzymatic and Molecular Diagnosis

In affected males with the classic or variant phenotype, the disease is readily diagnosed by determining the α-Gal A activity in plasma or peripheral leukocytes. In contrast, female carriers can have normal to very low α-Gal A activity; therefore, their specific family mutation in the α-Gal A gene must be demonstrated. Most kindreds have family-specific or private mutations; to date, more than 300 mutations have been identified, of which most are missense (amino acid substitutions) or nonsense (causing premature truncation of the amino acid sequence) mutations. Splicing
to the phase II study, patients in this study were not
randomized, double-blind, placebo-controlled. In contrast to the
clinical setting, patients who were not assigned to receive placebo
or treatment exhibited improvements in pain and quality-of-life
assessments, compared with baseline assessments, both treatment
groups maintained normal or near-normal renal capillary endothelium
(13). The primary efficacy end point was the percentage of patients
whose renal capillary endothelial globotriaosylceramide deposits cleared
to normal or near normal. The histologic clearance of microvascular
endothelial globotriaosylceramide deposits in the heart and skin
and changes in pain (Short-Form McGill Pain Questionnaire) and
in quality of life (Medical Outcomes Study Short Form-36 General
Health Survey) were also evaluated. In 20 of 29 patients (69%) treated
with r-hoGalA compared with 0 of 29 patients receiving placebo,
the accumulated globotriaosylceramide cleared from the renal
capillary endothelium (P < 0.001). Compared with the placebo
group, patients treated with r-hoGalA also had markedly decreased
microvascular endothelial globotriaosylceramide in the skin
(P < 0.001) and heart (P < 0.001). Patients receiving r-hoGalA cleared the
accumulated globotriaosylceramide in plasma to nondetectable levels.
Compared with baseline assessments, both treatment groups
had improvements in pain and quality-of-life assessments,
which were indistinguishable from a placebo effect. In contrast
to the phase II study, patients in this study were not
selected for pain and therapy with pain medications
was not discontinued during treatment.

All 58 patients who completed the phase III trial received
r-hoGalA in an extension study. After 6 months of
the open-label therapy, all 22 patients formerly in the placebo
group and 20 of 21 patients formerly receiving
r-hoGalA (42 of 43; 98%) who had biopsies achieved or
maintained normal or near-normal renal capillary endothelial
histology. Similar results were observed for skin capillary
endothelium; 96% of both former placebo recipients
(22 of 23) and of r-hoGalA recipients (23 of 24) who had
biopsies achieved normal or near-normal histology. In the
capillary endothelium of the heart, histology scores
improved with duration of treatment. Among patients
who had heart biopsies, 67% (10 of 15) attained normal or
near-normal histology after 6 months of r-hoGalA treat-

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ment and 82% (14 of 17) attained normal or near-normal histology after 12 months.

RECOMMENDATIONS FOR DIAGNOSIS AND TREATMENT
When Should the Diagnosis of Fabry Disease Be Considered?

In children, pediatricians and family practitioners should be alert to acute, unexplained episodes of pain often accompanied by fever and unresponsive to conventional analgesics; chronic pain or discomfort in the extremities; heat, cold, and exercise intolerance; unexplained gastrointestinal disturbances (diarrhea, vomiting, nausea, and abdominal pain); angiokeratomas (Figure 2); hypohidrosis; or mild proteinuria. In most patients, these symptoms persist or worsen with adulthood (19). In adults, other hallmarks of the disease include unexplained renal dysfunction progressing to end-stage renal disease; unexplained cardiomyopathy, especially left ventricular hypertrophy; arrhythmias; valvular abnormalities; stroke; unexplained fatigue or heat intolerance; hearing loss; obstructive pulmonary disease (39); and the characteristic corneal opacity (Figure 2). Even in classic Fabry disease, presentation can vary and the absence of certain signs or symptoms should not rule out the diagnosis. If Fabry disease is a possibility, an α-Gal A enzyme level should be obtained before invasive evaluations or treatments are initiated.

What Are the Optimal Methods for Diagnosing Fabry Disease in Affected Males and Carrier Females?

Fabry disease can be diagnosed reliably in males by markedly deficient or absent α-Gal A activity in plasma or peripheral leukocytes by using commercially available 4-methylumbelliferyl-α-D-galactoside as substrate (40). To inhibit cross-reactivity with α-galactosidase B, the α-Gal A assay mixture must include 500 mmol of N-acetylgalactosamine per L (41). Normal enzyme values differ depending on the enzyme source, substrate concentrations, and assay variables.

Carrier detection with the α-Gal A assay is not reliable because some obligate heterozygotes have normal α-Gal A activity. Thus, all women at risk for carrying the disease gene should have molecular studies to detect the family’s mutation.

When a diagnosis is made, genetic counseling should be provided to inform the patient of the natural history of the disease; its inheritance; and the options for treatment, including enzyme replacement therapy. Patients should be advised to inform other family members of the availability of diagnostic testing and genetic counseling.

Fabry disease can be diagnosed prenatally by demonstration of an XY karyotype and deficient α-Gal A activity in cultured amniocytes or chorionic villi (42). If the family’s α-Gal A mutation is known, molecular studies can replace or confirm the enzymatic diagnosis.

How Should Disease Progression Be Followed?

All patients with Fabry disease should be followed regularly, regardless of disease status or treatment protocols. The course of the disease varies, even among family members with the same mutation. Although signs and symptoms will dictate the frequency and extent of follow-up, lack of overt symptoms does not preclude the need for an annual comprehensive medical evaluation because kidney, cardiac, or cerebrovascular function can decline so insidiously.

Clinical evaluations should involve a multidisciplinary team of subspecialists, which should be coordinated by a physician experienced in the care of patients with Fabry disease. Annual evaluations ensure that patients receive optimal interventions and support and also provide data on the natural history of the disease and the effectiveness of various interventions.

All health professionals who treat patients with Fabry disease should be sensitive to the psychosocial burden of a chronic, rare, progressive disease. Clinical depression and denial among affected males can lead to suicidal tendencies or substance abuse. Guilt among carriers is associated with passing the abnormal gene on to their male offspring. Therefore, emotional support and family counseling should be an integral part of patient care. In addition, providing patients with the resources to learn about their disease and to contact other patients and families struggling with similar issues may help ameliorate feelings of isolation, loneliness, and despair (See Appendix, available at www.annals.org).

The recommendations for following patients with Fabry disease and carriers are based on the clinical experience of the authors and the current understanding of Fabry disease pathophysiology. Because the manifestations and disease progression can vary greatly, recommendations are necessarily general, with additional monitoring dictated by each patient’s individual clinical course.

Baseline Evaluation and Follow-up for Patients with Classic Fabry Disease

After a diagnosis of Fabry disease is confirmed, all affected persons should have a detailed medical and family history taken. ABO blood type (43) and secretor status (44) should also be determined because the B blood group antigen is a glycosphingolipid that accumulates in Fabry disease and may be associated with a more severe prognosis.

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creatinine-to-albumin ratio) and creatinine clearance tests to determine renal function; at least every 2 years, patients should also have echocardiography and electrocardiography to detect and monitor cardiac abnormalities. Abnormal findings should be monitored more frequently, as indicated. In early adulthood or before initiation of enzyme replacement therapy, baseline magnetic resonance imaging of kidney, heart, and brain is useful to document disease progression and assess effect of therapy.

**Follow-up for Carriers in Classic Fabry Families**

Even in the absence of symptoms, all female carriers should have a complete baseline examination (as described earlier) performed by a physician with expertise in Fabry disease. Asymptomatic females can be reevaluated every 3 to 5 years, with increasing frequency with age. Symptomatic carriers should be followed annually with tests focused on their disease manifestations.

**Follow-up for Atypical Patients with Fabry Disease**

Atypical males with Fabry disease usually receive a diagnosis when disease manifestations become evident. They should undergo complete baseline and annual evaluations similar to those described for patients with classic Fabry disease in order to monitor disease progression, especially cardiac and renal symptoms.

**What Therapies Are Available?**

Fabry disease traditionally has been managed with various supportive, palliative, and nonspecific measures, most of which are standard interventions for the presenting symptom—for example, valve replacement for valvular disease or dialysis and transplantation for renal failure. In the clinical experience of the authors, the following interventions have provided benefit.

Pain, the earliest and most debilitating symptom in childhood and adolescence, can be controlled prophylactically with diphenylhydantoin (45), carbamazepine (46), or gabapentin (47). Narcotic analgesics should be avoided, if possible, because patients may become vulnerable to drug abuse as a result of the depression and psychosocial aspects of Fabry disease. Nonsteroidal anti-inflammatory drugs are generally ineffective for pain relief and may have effects on renal function. Lifestyle modifications to avoid stimuli that precipitate pain can also be important.

Pancræolipase or metoclopramide can ameliorate gastrointestinal symptoms (48). Control of hypertension is essential to minimize renal, cardiovascular, and cerebrovascular disease. Prophylaxis with antiplatelet or anticoagulant medication can be important for patients who have had transient ischemic attacks or a stroke. For patients with proteinuria, use of angiotensin-converting enzyme inhibitors and decreasing dietary sodium and protein intake are recommended (47). Hearing loss can be treated with hearing aids, and noise trauma should be avoided to preserve hearing. Patients should be encouraged not to smoke.

For advanced renal disease, dialysis or transplantation can prolong life because renal failure is the most frequent cause of death in classic Fabry disease. Engrafted kidneys remain free of disease, but other organ system damage continues unabated, particularly the vascular disease of the heart and brain (49, 50).

**Who Should Be Treated with Replacement Therapy?**

Fabry disease is an inborn error of metabolism with profound clinical consequences and a pathology that begins at birth. Enzyme replacement therapy supplies the patient with the biologically deficient protein and reverses metabolic and various pathologic abnormalities. Therefore, we recommend that enzyme replacement therapy be initiated in all patients with Fabry disease even though important questions regarding dosing and long-term benefits still must be addressed with additional research. Treatment should ideally begin as soon as clinical signs and symptoms, such as pain or isosthenuria, are observed. Although enzyme replacement therapy has not yet been evaluated in affected children, experience in type 1 Gaucher disease indicates that enzyme replacement infusions are well tolerated by young children. Carriers with substantial disease manifestations should also be treated with enzyme replacement therapy. This is an active area of research. There are no published studies of enzyme replacement therapy in patients with Fabry disease who are undergoing dialysis or have received a kidney transplant. However, because these patients are at high risk for cardiac and cerebrovascular complications, including transient ischemic attacks and stroke, enzyme replacement therapy is recommended for these patients.

**What Are the Risks and Safety Concerns of α-Gal A Replacement Therapy?**

Because of a theoretical risk for inhibited intracellular α-Gal A activity, human α-Gal A should not be co-administered with chloroquine, amiodarone, benoquin, or gentamicin. To date, no patient has experienced an anaphylactic reaction to either α-Gal A product. Use during pregnancy and lactation is cautioned because clinical data are not available.

Treatment with both α-Gal A products has been well tolerated, except for mild to moderate infusion-associated reactions, which have been managed conservatively. Although both products are administered at different doses, the initial rates of infusion-associated reactions in the clinical trials were essentially the same: 57% for ga-hoGalA (dose, 0.2 mg/kg) and 59% for r-hoGalA (dose, 1 mg/kg). However, when the infusion time was increased from 20 to 40 minutes for ga-hoGalA, the rate of infusion reactions decreased to about 10%. These reactions were associated with the formation of non-neutralizing IgG antibodies. Renal biopsies did not show evidence of immune complex deposition. The reactions can be managed conservatively with preadministration of ibuprofen and nonselecting antihistamines and by decreasing the infusion rate. More se-
vere reactions can be managed with prednisone. After tolerance is established, the reactions cease and the infusion rate can be increased accordingly. For at least the first 6 months of therapy, all infusions should be performed at a medical facility or under close physician supervision. If infusions are well tolerated thereafter, patients can move to a home-care setting.

Serocconversion rates in the placebo-controlled trials were 64% for ga-hoGalA and 88% for r-hoGalA (88%). These differences presumably reflect the fivefold difference in dose and sensitivity of the immunoprecipitation assay. Because patients with the classic phenotype have little, if any, enzyme protein, the antibody response elicited by infusion of human α-Gal A in the clinical trials was expected. However, in contrast to the clinical experience with protein replacement therapy in hemophilia (51, 52), there is no evidence that antibody formation alters efficacy (12, 13).

What Does Therapy Cost?

As with other recombinant protein therapies, human α-Gal A treatment, including the cost for infusions, is expensive. In Europe, 1 year of treatment for a 70-kg patient costs approximately $160,000 for either Replagal (0.2 mg/kg biweekly) or Fabrazyme (1 mg/kg biweekly). Costs in the United States are currently unknown.

What Are the Goals of Enzyme Replacement Therapy, and How Can Therapeutic Effectiveness Be Assessed?

In young patients, the goal of enzyme replacement therapy is to prevent disease. For older patients with more advanced disease, the goal is to both halt disease progression and reverse the underlying pathologic abnormalities and the resultant organ dysfunction. Clinical experience with Gaucher disease supports these goals (53–56).

Patients receiving enzyme replacement therapy should be followed at least once annually, as we have described earlier. If plasma globotriaosylceramide levels prove to be a useful marker of disease burden and treatment efficacy (13, 31, 33), a goal of therapy may be to normalize plasma levels. For children, monitoring the frequency and severity of peripheral pain and gastrointestinal symptoms also will indicate clinical effectiveness.

What Dose Should Be Used?

The optimal doses for the reversal, maintenance, and prevention of globotriaosylceramide accumulation in the kidney, heart, and vasculature are unknown. Doses of 0.2 mg/kg (12) and 1 mg/kg (13) have been studied in separate randomized clinical trials but trial end points differed. Experience with 1 mg/kg showed clearance of globotriaosylceramide in the vascular endothelium of the kidney, heart, and skin. In addition, renal interstitial and mesangial cells were cleared after 6 to 12 months of treatment (57). However, a higher dose or longer treatment may be required to clear the massive, lifelong accumulation of globotriaosylceramide in podocytes and cardiomyocytes. Thus, long-term experience is required to determine optimal dosing protocols, including frequency of infusions, especially for children, symptomatic carriers, and males treated for end-stage renal disease. Experience with Gaucher disease shows that enzyme delivery and substrate clearance in certain tissues may require higher doses. Preclinical studies in mice with Fabry disease and clinical trials of enzyme replacement therapy support this concept (13, 31, 33).

CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

With the availability of enzyme replacement therapy, prompt diagnosis and treatment of Fabry disease have assumed new importance. There is no comparable alternative to enzyme replacement therapy for this devastating, progressive disease. Future research should address the development of protocols for early diagnosis as well as optimal enzyme protocols for reversal, maintenance, and prevention of the underlying pathology of Fabry disease, especially for children, patients with compromised renal function, and those with cardiac disease. Enrollment of all patients in a Fabry disease registry is encouraged (See Appendix, available at www.annals.org) to increase knowledge of the natural history and complications of the disease and the efficacy of treatment regimens.

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References
APPENDIX. ORGANIZATIONS AND WEB SITES FOR PATIENTS WITH FABRY DISEASE AND THEIR FAMILIES

Organizations that Provide Information and Support for Patients with Fabry disease and Their Families

- **Fabry Community**
  - e-mail: fabry@genzyme.com
  - Web site: www.fabrycommunity.com
  - Phone: 617-768-9000, 800-745-4447
  - Fax: 617-591-7178, 800-737-3642

- **Fabry Support and Information Group**
  - e-mail: JJohnson@fabry.org
  - Web site: www.fabry.org
  - Phone: 660-463-1355
  - Fax: 660-463-1356

- **Genetic Leadership Collaborative**
  - Web site: www.geneticleadership.com

- **The International Center for Fabry Disease**
  - Department of Human Genetics
  - Mount Sinai School of Medicine
  - Fifth Avenue and 100th Street
  - New York, NY 10029
  - e-mail: fabry.disease@mssm.edu
  - Web site: www.mssm.edu/genetics/fabry/fabry.html
  - Phone: 866-MD-FABRY (322-7963)
  - Fax: 212-360-1809

- **Lysosomal Storage Disease Network**
  - Web site: www.lsdn.com

- **National Institute of Neurological Disorders and Stroke**
  - National Institutes of Health
  - Bethesda, MD 20892
  - Web site: www.ninds.nih.gov

- **National Organization for Rare Disorders (NORD)**
  - PO Box 8923
  - 100 Route 37
  - Fairfield, CT 06812-8923
  - e-mail: orphan@rarediseases.org
  - Web site: www.rarediseases.org
  - Phone: 203-746-6518, 800-999-NORD (6673)
  - Fax: 203-746-6481

Web sites with Medical, Technical, and Bibliographic Information about Fabry Disease and Its Mutations

- [www.uwcm.ac.uk/uwcm/mg/search/119272.html](http://www.uwcm.ac.uk/uwcm/mg/search/119272.html)
  - Web site of The Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff, from the University of Wales College of Medicine

  - OMIM Web site (Online Mendelian Inheritance in Man).
  - A catalog of human genes and genetic disorders. The data base contains textual information, pictures, reference information, and copious links to NCBI’s Entrez database of MEDLINE articles and sequence information.

- [http://bioinfo.weizmann.ac.il/cards](http://bioinfo.weizmann.ac.il/cards)
  - Weizmann Institute of Science GeneCards Web site. A data base of human genes, their products, and their involvement in disease

**Fabry Disease Registries**

- **Fabry International Research Exchange (FIRE)**
  - Web site: http://spitfire.emmes.com/study/fire

  **Fabry Registry**
  - Web site: www.fabryregistry.com

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