

# Fabry Disease in Females

## A Guide for Physicians

Silently Progressive.  
Increasingly Debilitating.  
Often Life-Threatening.

**Understanding the  
Spectrum of Severity**

**genzyme**  
A SANOFI COMPANY

Females  
and  
Fabry  
Disease



**Fabry disease** is an inherited disorder that affects men, women, and children of all ethnicities. Females can have significant disease manifestations, even though they were once thought only to be carriers. Because the theoretical prevalence of Fabry disease is only 1 in 117,000<sup>1</sup> live births, clinical data about this ultra-orphan disease have been slow to accumulate. Recent research shows that most females who carry the gene for Fabry disease develop symptoms.<sup>2-5</sup> In a cohort of symptomatic heterozygous females, the incidence of cardiac, renal, or cerebrovascular abnormalities was 91%.<sup>6</sup> Fabry disease symptoms are more variable in females than they are in males, and can affect fewer organ systems. However, potentially life-threatening complications can develop in specific organs, even in females whose presentation may suggest a more moderate disease course.



**About the cover:**  
The renal capillary endothelium is heavily laden with glycosphingolipid inclusions in a Fabry disease patient.

# About Fabry Disease

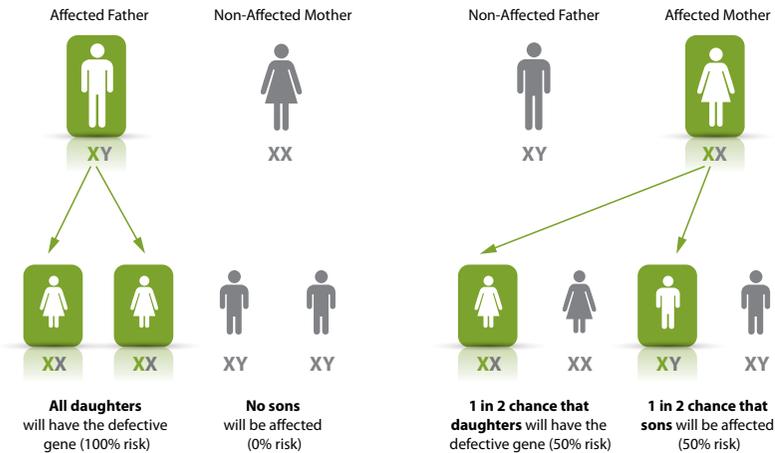
Silently Progressive.  
Increasingly Debilitating.  
Often Life-Threatening.

Fabry disease is a multisystemic genetic disorder that ultimately results in irreversible, potentially life-threatening disease of the kidney, heart, and brain.

The disease is characterized by the progressive and unrelenting cellular accumulation of a lipid substrate called globotriaosylceramide (or GL-3). Ongoing build-up of this substance is caused by deficiency of the lysosomal enzyme alpha-galactosidase A (or  $\alpha$ -GAL), which usually metabolizes GL-3 and keeps it from accumulating. Without enough of this essential enzyme, GL-3 accumulates in the lysosomes of most cell types over the course of a lifetime, often causing debilitating symptoms in childhood and adolescence and potentially irreversible tissue damage by adulthood.

## Inheritance

Fabry disease is an X-linked disorder. Males with the defective gene are always affected. Females with the defective gene are affected to varying degrees due to random X inactivation (lyonization), which will be discussed in more detail, since it is critical to understanding Fabry disease in women.



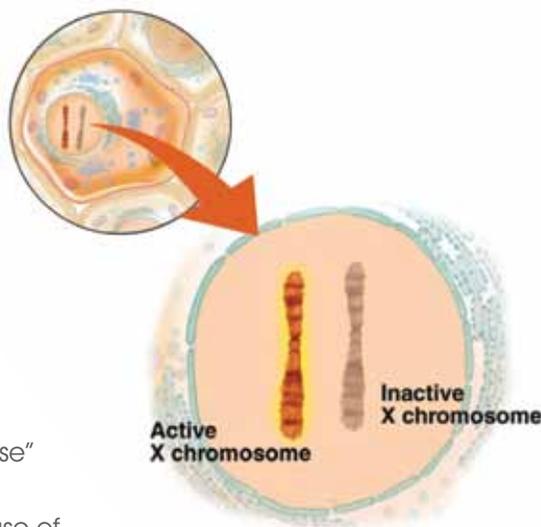
- Males who inherit a mutated  $\alpha$ -GAL gene on their X chromosome will be affected by Fabry disease (because they only have one X chromosome).
- Females who inherit a mutated  $\alpha$ -GAL gene on one of their two X chromosomes may have disease manifestations to varying degrees.
- Females with Fabry disease are heterozygotes because they have two X chromosomes, only one of which in each cell has the mutated  $\alpha$ -GAL gene.

# X-Inactivation (Lyonization): the Key to Variable Disease Expression in Females

Fabry disease severity varies widely in females, from virtually symptom-free to the more classical male profile of clinical manifestations.<sup>7</sup> Older literature characterized Fabry disease as X-linked recessive, but more recently it has been recognized as X-linked dominant.<sup>4</sup> Therefore, female heterozygotes should not be called “carriers.”

Unlike men, women have two X chromosomes, of which, only one has the mutated gene. That mutated gene will only be active in some cells due to a process called lyonization. Only cells that have the mutated gene will be affected by Fabry disease.

Early in female embryonic development, this phenomenon occurs when one of the two X chromosomes is inactivated in each cell. Genes on the inactivated X chromosome are not expressed. This is a random event and occurs independently in each cell. This process assures that males and females have the same “dose” of genes that are found on the X chromosome. In females, because of lyonization, some cells and tissues produce “normal”  $\alpha$ -GAL enzyme and others produce “mutant”  $\alpha$ -GAL enzyme.



Since lyonization is completely random, the organ systems affected will vary from female to female. Some females may have the  $\alpha$ -GAL enzyme deficiency in heart and skin cells, while others may have it in kidney and brain cells, for example. This explains why females with Fabry may experience disease manifestations limited to a few organ systems, and why each female’s disease presentation and clinical course is different.

# Disease Manifestations in Females

Clinical manifestations in women with the defective  $\alpha$ -GAL gene are increasingly being reported. Data suggest that females with the defective  $\alpha$ -GAL gene are often severely affected.<sup>2-5</sup> A cross-sectional study of 57 symptomatic heterozygous women found that, although all had normal plasma GL-3 levels, 91% (n = 52) had cardiac, renal, or cerebrovascular abnormalities.<sup>6</sup>

Studies of specific disease manifestations in females are summarized below.

## Heart

- Data from the Fabry Registry reported that 10% of females (n = 106) and 12.8% of males (n = 145) presented with cardiac manifestations at median ages of 33.4 and 21.6, respectively.<sup>2</sup> Cardiac manifestations included myocardial infarction, significant cardiac procedures, arrhythmia, angina pectoris, congestive heart failure, and left ventricular hypertrophy.
- A prospective study of cardiac manifestations in 55 females diagnosed with Fabry disease found a strong correlation between left ventricular hypertrophy (LVH) and age ( $r=0.905$ ;  $p<0.0001$ ). The mean patient age was 39.6 (range 6.1 to 70.8 years). All 25 of the women over age 45 had LVH.<sup>8</sup>
- In a study of 34 consecutive women diagnosed with late-onset hypertrophic cardiomyopathy, four (12%) carried the defective  $\alpha$ -GAL gene. In each of these women, the heart was the only clinically affected organ.<sup>9</sup>
- In a study of 129 Fabry disease patients (80 females and 49 males) 39% of females (n = 31) and 30% of males (n = 15) were affected by right ventricular hypertrophy.<sup>10</sup>
- In a European outcomes database known as the Fabry Outcome Survey that included 366 Fabry disease patients (201 males and 165 females), cardiac symptoms including angina, arrhythmias, and dyspnea, were reported in 69% of males and 65% of females. LVH was observed in 46% of males and 28% of females, with an average age of onset of 38.0 and 55.4 years, respectively.<sup>11</sup>



## Cerebrovascular

- Data from the Fabry Registry reported that 4.2% of females (n = 44) and 4.8% of males (n = 54) reported experiencing a stroke at median ages of 43.8 and 39.5, respectively.<sup>2</sup> In addition, 3.9% of females (n = 4) and 1.7% of males (n = 19) reported experiencing transient ischemic attack.
- Cerebrovascular events were reported to be more likely in females than males, with 27% of 165 females and 12% of 201 males in the European outcomes database experiencing stroke, transient ischemic attack, or prolonged reversible ischemic neurologic deficit.<sup>11</sup>
- A study of white matter lesion severity in 13 males and 14 females with Fabry disease found a comparable incidence (36% of females and 31% of males) and level of severity in both groups.<sup>12</sup>

## Neurological

- Neurological symptoms have been the most frequently reported symptoms in both males and females.<sup>2</sup>
- In an analysis of Fabry Registry data, 457 females (43.3%) and 716 males (63.3%) reported experiencing pain beginning at ages 14.2 and 10.4, respectively.<sup>2</sup>

## Gastrointestinal

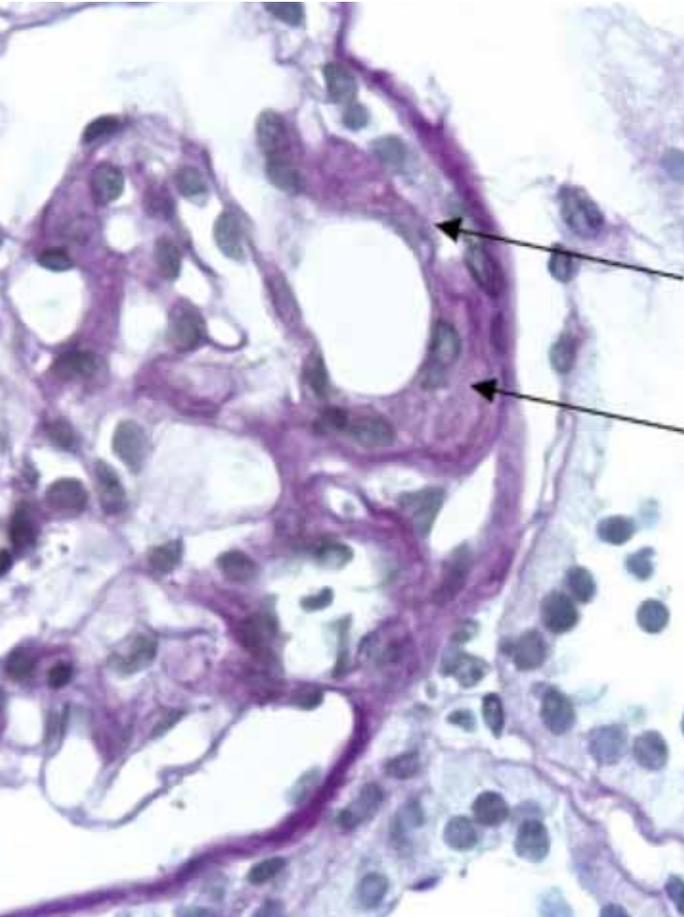
- Initial symptoms that were gastrointestinal in nature were reported by 209 males (18.5%) and 126 females (11.9%) in the Fabry Registry, with an average age of onset of  $10.8 \pm 9.6$  years in males and  $18.7 \pm 13.4$  years in females.
- However, when data from clinical follow-up assessments were combined with enrollment medical history data, a higher percentage of female patients reported abdominal pain and diarrhea, as compared to males.
- Among females, 226 (21.4%) reported abdominal pain and 199 (18.9%) reported diarrhea; whereas abdominal pain and diarrhea were reported by 152 (13.4%) and 135 (11.9%) male patients.<sup>2</sup>

## Dermatologic

- In the European outcomes database, dermatologic symptoms were reported in 78% of males and 50% of females, and angiokeratomas were reported present from a mean age of 17.9 in males and 29.1 years in females.<sup>11</sup>
- In the Fabry Registry, skin symptoms were reported in 118 females (11.2%) and 359 males (31.7%).<sup>2</sup>

## Kidney

- According to Fabry Registry data, many female patients were reported to exhibit significant kidney involvement as manifested by proteinuria and reduced eGFR. Among the 1,055 females, 23 (2.2%) had reached end-stage renal disease (ESRD), requiring dialysis or transplantation at a mean age of 39.2 years (range 17–77 years). Among males, 156 (13.8%) had reached ESRD at a similar mean age, 38.2 years (range 14–79 years). Compared to males, a lower percentage of female patients exhibited renal manifestations across all categories. However, among females who did exhibit renal manifestations, the mean age at which these were reported was similar or only slightly higher than what was reported for male patients.<sup>2</sup>
- In the European outcomes database, proteinuria was observed in 33% of females (vs. 44% of males) and end-stage renal failure was present in 1% of females aged greater than 18 years (vs. 17% of males).<sup>11</sup>
- A study of two females with Fabry disease found that diffuse GL-3 storage occurred in all types of glomerular cells and in interstitial endothelial cells. In addition, platelets were frequently observed in glomerular vessels.<sup>13</sup>



### Changes in the kidney can occur very early in girls with Fabry disease.<sup>14</sup>

In this renal biopsy from a 14 year-old female with Fabry disease, the arrow points to glomerulus with early signs of focal segmental glomerulosclerosis.

## Ophthalmologic

- Corneal verticillata, visible through slit lamp ophthalmoscopy, have been reported in 70% of females.<sup>4</sup>
- In the Fabry Registry, ophthalmologic findings were reported in 12.5% (n = 132) of females and 10.1% (n = 114) of males.<sup>2</sup>

## Quality of Life

- According to Fabry Registry data, quality of life, as measured by the SF-36 survey, was impaired at a later age in females than in males, but both genders experienced significantly impaired quality of life from the third decade of life onward.<sup>2</sup>
- An analysis of data on 44 heterozygous females followed at Cedars-Sinai Medical Center found that quality of life, measured by the SF-36 survey, was globally reduced, and that pain affected mood and enjoyment of life.<sup>3</sup>



18% of women with Fabry disease have had at least one serious renal, cardiovascular, or stroke event (N= 1,748).<sup>15</sup>

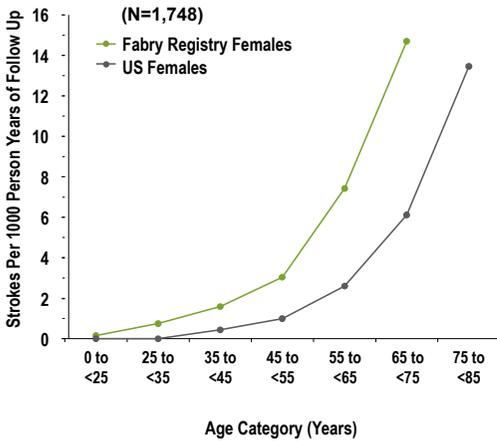
### About the Fabry Registry

The Fabry Registry is a global, observational, voluntary program, sponsored and administered by Genzyme, that has been established to collect data related to the onset and progression of Fabry disease, as well as the different ways in which Fabry disease affects men and women.

## Incidence of Stroke is Elevated in Women with Fabry Disease<sup>15</sup>

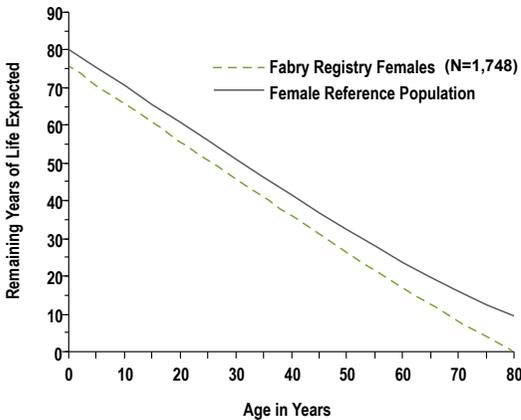
Stroke incidence rates in the general US population are from the Framingham Study and from the American Heart Association Statistics Committee and the Stroke Statistics Subcommittee

(Wolfe et al. In: Stroke: Pathophysiology, Diagnosis, and Management, 3rd ed. New York, NY: Churchill Livingstone; 2004:3-13; Rosamond et al. Circulation 2007; 115:e69-e171).



## Life Expectancy is Diminished in Women with Fabry Disease<sup>16</sup>

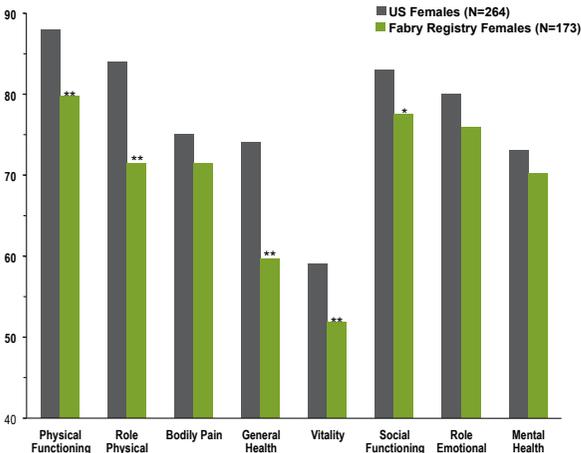
The dashed line shows life expectancy of Fabry Registry females at birth, based on data available as of August 2, 2008. The solid line shows the life expectancy of females in the general US population.



## Quality of Life is Diminished in Women with Fabry Disease<sup>15</sup>

Data are expressed as average SF-36 scores in women age 35 to <45 years in the general US population (N=264, grey bars) and in the Fabry Registry (N=173, green bars).

All data were obtained from untreated patients or from before any enzyme replacement therapy was initiated. SF-36 scores are based on a 100-point scale, with a higher score indicating better HRQL.



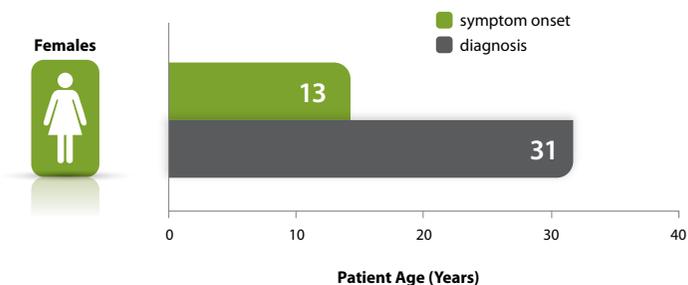
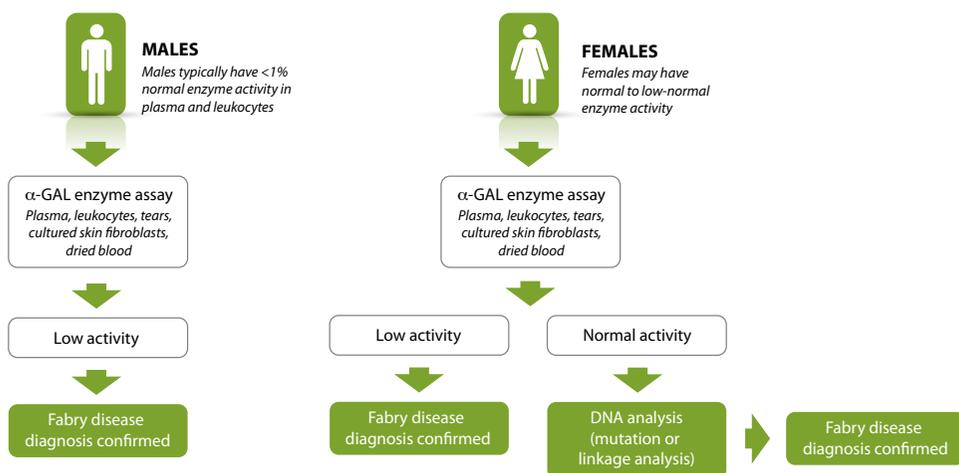
\*\*p<0.005 05 by t-test; \*p<0.05 by t-test. US norm data are from Ware et al, SF-36 Health Survey Manual and Interpretation Guide, New England Medical Center, The Health Institute, Boston, MA, 1993.

# Diagnosis

Unlike in males – where confirming a diagnosis of Fabry disease is straightforward and can be accomplished by enzyme assay in plasma, leukocytes, tears, cultured skin fibroblasts, or dried blood – confirming the diagnosis in females can be more complicated.

As noted earlier, females with Fabry disease may have enzyme activity in the normal to low-normal range. Therefore, if a female is suspected to have Fabry, and enzyme assay reveals normal activity, Fabry disease cannot be ruled out. She should also receive DNA analysis (either mutation analysis or linkage analysis, depending on whether the family mutation is known).

A number of laboratories across the United States and worldwide perform diagnostic testing for Fabry disease.



## Gap between symptom onset and diagnosis<sup>2</sup>

Misdiagnoses and diagnostic delays are common, which can result in progressive, irreversible tissue damage. In this analysis of patients in the Fabry Registry, females on average reported symptom onset at age 13, with a diagnosis not until age 31.

# The Importance of Family Screening

Although Fabry disease is rare in the general population, diagnosis of one patient may lead to others within that family. Once a female has been diagnosed with Fabry disease, there is the opportunity to identify other family members, and family screening should be conducted.

Since Fabry disease is progressive and can result in irreversible organ damage, early diagnosis of affected family members has the potential to change the course of the disease in those people.

A medical genetic counselor can work with patients to develop a medical pedigree and establish who within the family is at risk.

## Potential Challenges in Managing Females with Fabry Disease

Many females with Fabry disease are also caregivers who may place the needs of others before their own, or may have been told that they were just a carrier. It is very important that female patients be evaluated carefully and at regular intervals. They can experience significant organ damage in the absence of overt symptomatology.

Fabry disease is progressive and any complications should be managed as they occur, in order to halt worsening or possibly prevent irreversible damage.

# Genzyme Support Services

Genzyme is committed to helping medical professionals get the information and resources they need to provide comprehensive care for their patients with Fabry disease.

## **Please contact Genzyme for:**

- Patient resources and advocacy groups to help connect patients and their families to others living with Fabry disease
- Information about diagnostic testing
- Fabry disease information and educational resources
- Information on the Fabry Registry, a resource to help increase the understanding of Fabry disease

## **For more information**

Contact Genzyme Medical Information at 800-745-4447 (option 2)

[www.fabrycommunity.com](http://www.fabrycommunity.com)

## **Patient Resources**

### **Genzyme Case Managers**

<http://support.genzyme.com>

1-800-745-4447, option 3

### **Fabry Support and Information Group (FSIG)**

[www.fabry.org](http://www.fabry.org)

### **National Fabry Disease Foundation (NFDF)**

[www.thenfdf.org](http://www.thenfdf.org)



## References

1. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA* 1999;281:249-254.
2. Wilcox WR, Oliveira JP, Hopkin RJ, et al. Females with Fabry disease frequently have major organ involvement: Lessons from the Fabry Registry. *Mol Genet Metab* 2008;93:112-28.
3. Wang RY, Lelis A, Mirocha J, Wilcox WR. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. *Genet Med* 2007;9:34-45.
4. Whybra C, Kampmann I, Willers J, et al. Anderson-Fabry disease: Clinical manifestations of disease in female heterozygotes. *J Inherit Metab Dis* 2001;24:715-724.
5. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: Clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet* 2001;38:769-775.
6. Gupta S, Ries M, Kotsopoulos S, Schiffmann R. The relationship of vascular glycolipid storage to clinical manifestations of Fabry disease: A cross-sectional study of a large cohort of clinically affected heterozygous women. *Medicine* 2005;84:261-268.
7. Dobrovolny R, Dvorakova L, Levinova J, et al. Relationship between X-inactivation and clinical involvement in Fabry heterozygotes. Eleven novel mutations in the  $\alpha$ -galactosidase A gene in the Czech and Slovak population. *J Mol Med* 2005; 83:647-654.
8. Kampmann C, Baehner F, Whybra C, et al. Cardiac manifestations of Anderson-Fabry disease in heterozygous females. *J Am Coll Cardiol* 2002;40:1668-1674.
9. Chimenti C, Pieroni M, Morgante E, et al. Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. *Circulation* 2004;110:1047-1053.
10. Kampmann C, Baehner FA, Whybra C, et al. The right ventricle in Fabry disease. *Act Paediatrica* 2005;94(Suppl 447):15-18.
11. Mehta A, Ricci R, Widmer U, et al. Fabry disease defined: Baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *Eur J Clin Invest* 2004;34:236-242.
12. Fellgiebel A, Muller MJ, Mazanek M, et al. White matter lesion severity in male and female patients with Fabry disease. *Neurology* 2005;65:600-602.
13. Tosconi A, Nebuloni M, Zerbi P, Vago L. Ultrastructural study of renal involvement in two females with Anderson-Fabry disease. *Ultrastructural Pathology* 2005;29:203-207.
14. Tøndel C, Bostad L, Hirth A, Svarstad E. Renal biopsy findings in children and adolescents with Fabry disease and minimal albuminuria. *Am J Kidney Dis* 2008; 51:767-76.
15. Fabry Registry Annual Report 2010. Genzyme Corporation.
16. Waldek S, Patel M, Banikazemi M, Lemay R, Lee P. Life expectancy and cause of death in males and females with Fabry disease: Findings from the Fabry Registry. *Genet Med*. 2009; 11:790-796.





Contact Genzyme Medical Information at 800-745-4447, option 2 for more information on diagnostic testing or for additional information on Fabry disease.

**genzyme**  
A SANOFI COMPANY

[www.genzyme.com](http://www.genzyme.com)

500 Kendall Street  
Cambridge, MA 02142

©2012 Genzyme Corporation. All rights reserved. FABR-US-P305-06-12