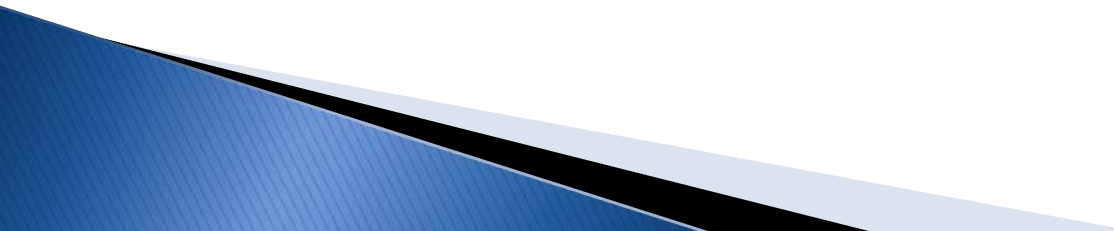


Missouri's Full Population Pilot Screening for Fabry Disease and the Implications for Families

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Fabry Disease

- ▶ X-linked lysosomal storage disorder
 - ▶ Deficient activity of the enzyme alpha-galactosidase A (GLA)
 - ▶ Progressive buildup of specific fat molecules, globotriaosylceramide (GL-3), in cells throughout the body
 - ▶ Most often affects the cells lining the blood vessels in the skin and cells in the kidneys, heart, and nervous system
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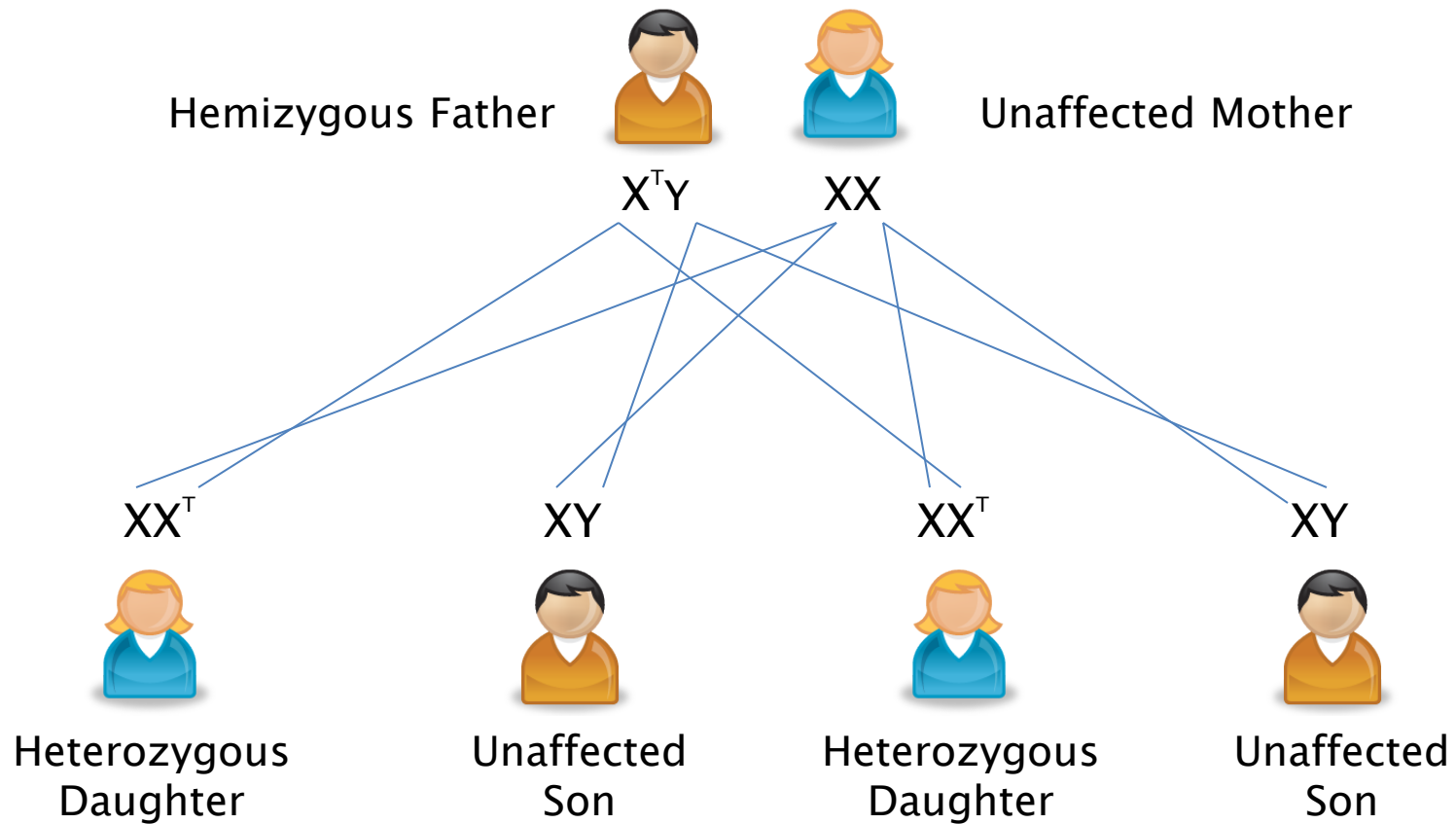
Symptoms

- ▶ Symptoms of Classical Fabry disease include:
 - Neuropathic pain
 - Acroparasthesias
 - Angiokeratomas
 - Altered temperature sensitivity
 - Hypohidrosis
 - Ophthalmological problems
 - Gastrointestinal problems
 - Auditory problems
- ▶ Fabry disease can lead to life threatening renal, cardiac, and neurological complications

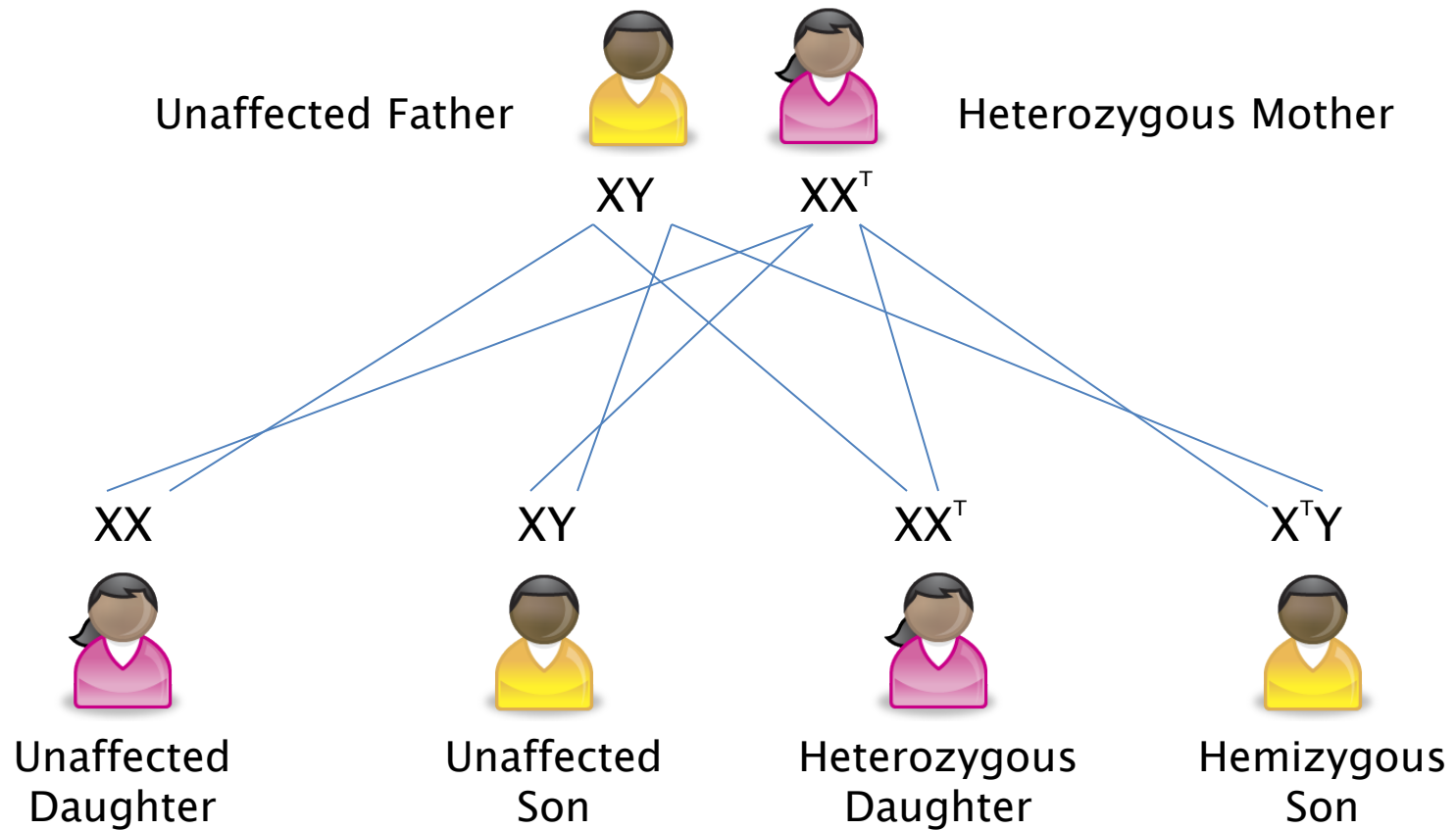
Incidence

- ▶ Approximately 1 in 40,000 to 60,000 males
- ▶ Found in all ethnic, racial, and demographic groups
- ▶ Transmitted by both males and females
- ▶ X-linked dominant disease with variable expressivity in males and females
- ▶ Hemizygous males typically more severe than heterozygous females
- ▶ Females may be as severely affected as males, have less severe symptoms with a later onset than males, or be completely asymptomatic

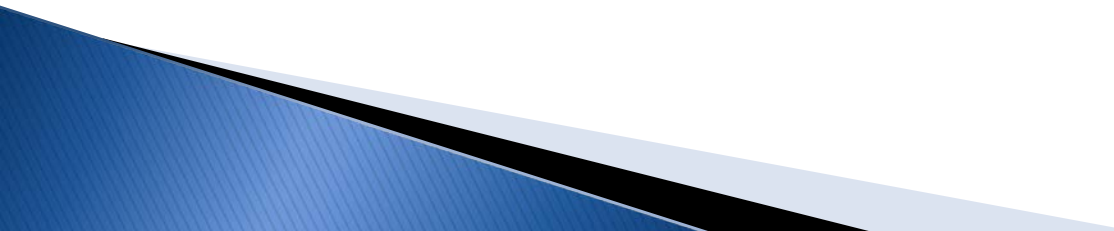
Inheritance



Inheritance



Treatment

- ▶ Individuals with Fabry disease may benefit from certain medications and treatments to help reduce signs and symptoms and to prevent future complications.
 - ▶ In males with classic Fabry disease, it is recommended that enzyme replacement therapy (ERT) be initiated in early childhood (age 4–6) in order to improve signs and symptoms and stabilize organ function.
 - ▶ Heterozygous females who are symptomatic may benefit from starting treatment early as well but typically recommended to start between 16–18 years.
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NBS for Fabry Disease

- ▶ On January 11, 2013 Missouri began an IRB approved full population pilot/implementation phase to screen newborns for Fabry disease.
- ▶ The Missouri State Public Health Laboratory utilized the digital microfluidics multiplex enzymatic assay technology provided by Advanced Liquid Logic, Inc., which is now Baebies, Inc.
- ▶ All positive Fabry screens were referred to one of four contracted genetic tertiary centers for further evaluation and confirmatory testing via enzyme analysis and mutation studies.
- ▶ The results of the evaluations and confirmatory testing along with the confirmatory diagnoses were then reported back to the Missouri Department of Health and Senior Services.

Results

- ▶ 90,682 newborn screening samples were screened at the Missouri State Public Health Laboratory.
- ▶ 30 newborns were identified with reduced enzyme activity and a mutation in the GLA gene.
 - 20 were identified with the A143T mutation.
 - 3 were identified with variants of unknown significance.
 - 2 were females.

Results

- ▶ Based on the first full year of screening incidence is:
 - 1 in 2,500 live births
 - 1 in 1,300 male live births
 - 1 in 19,000 female live births
- ▶ Incidence of A143T mutation:
 - 1 in 3,800 live births
- ▶ Incidence excluding A143T and variants of unknown significance:
 - 1 in 11,000 live births
 - 1 in 5,300 male live births

*Data is based on only one year of screening.
Incidence will need to be reevaluated in the future.

Results

Number of Cases	Mutation	Classification
20	A143T	Pathogenic ¹
3	I198T	Likely Pathogenic ¹
2	R118C	Likely Pathogenic ¹
1	L120P/L121T	Pathogenic (mother is a known Fabry patient) ²
1	c.369+5G>T	Variant of Unknown Significance ¹
1	W245L	Variant of Unknown Significance ¹
1	Y207H	Variant of Unknown Significance ¹
1	R122H	Renal Variant ²

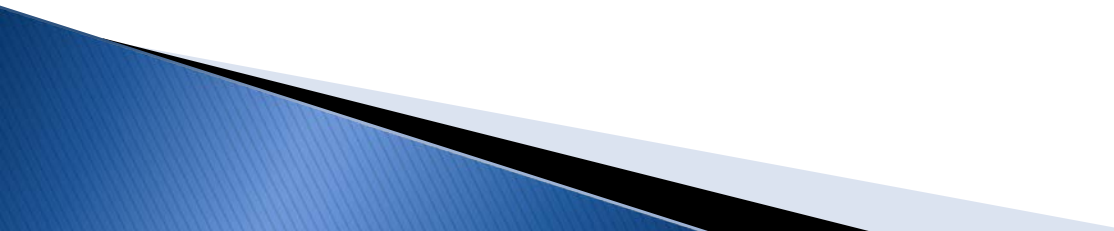
¹EmVClass, Emory Genetics Laboratory's Variant Classification Catalog, <http://genetics.emory.edu/egl/emvclass/emvclass.php>

²As reported by contracted genetic tertiary center.

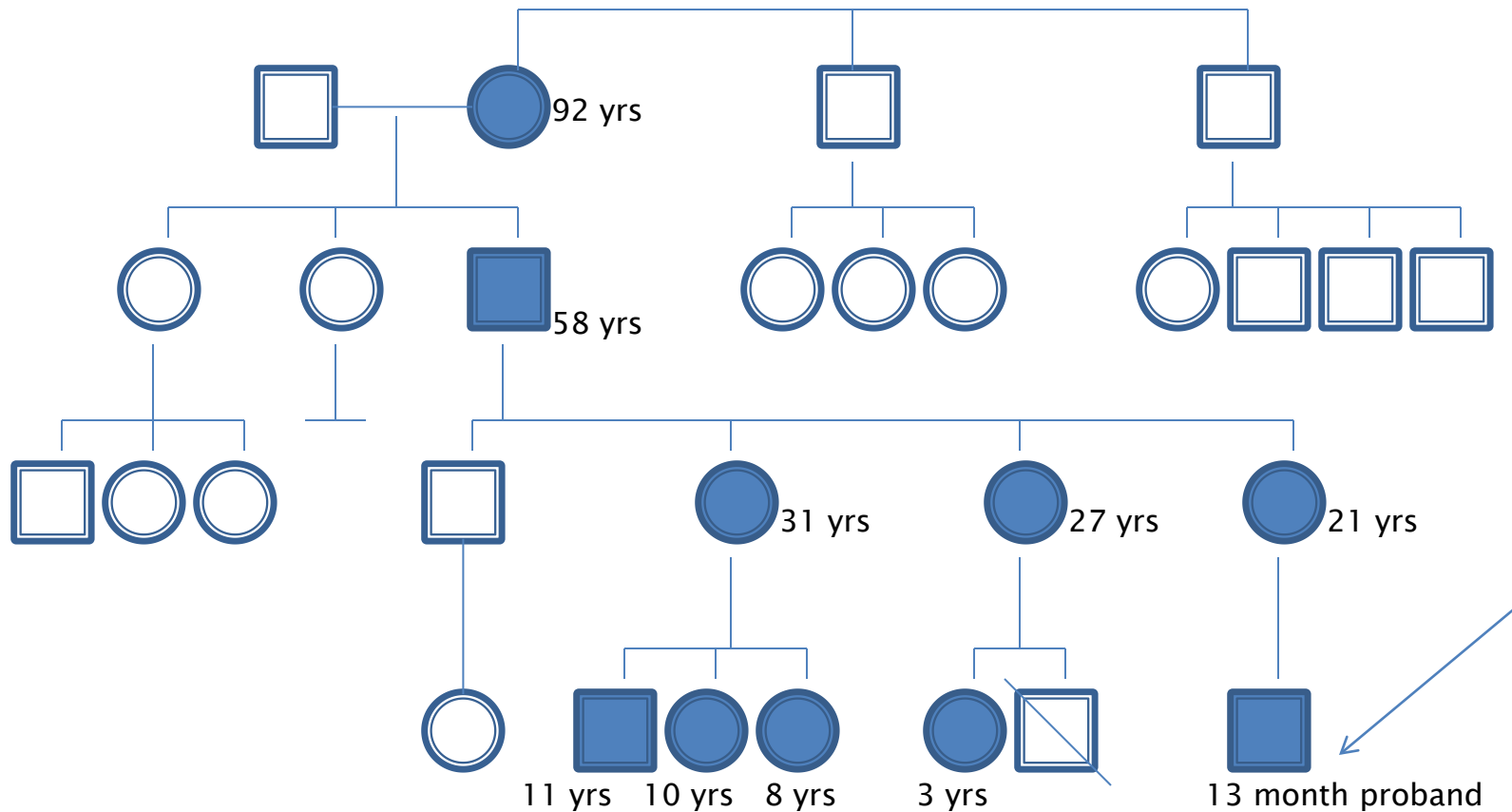
Follow-Up

- ▶ Each newborn was referred to one of four contracted genetic tertiary centers:
 - Children's Mercy Hospital, Kansas City, MO
 - University of Missouri Healthcare, Columbia, MO
 - Cardinal Glennon Children's Medical Center, St. Louis, MO
 - St. Louis Children's Hospital, St. Louis, MO

Follow-Up

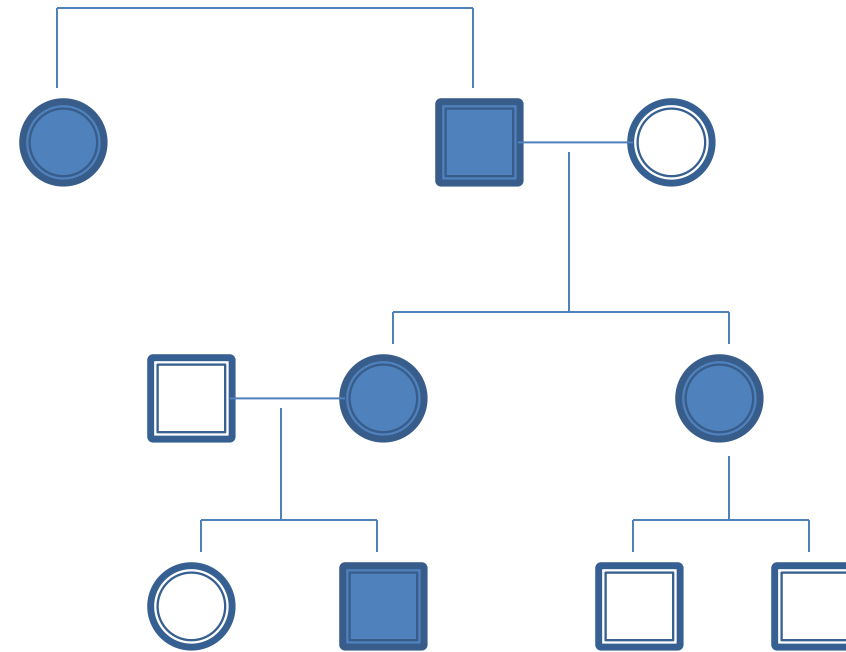
- ▶ 55 relatives were found to carry the same mutation as seen in the affected proband within their family.
 - ▶ Several were found to be symptomatic and a few have since begun treatment for Fabry disease.
 - ▶ Reported symptoms have ranged anywhere from renal or heart disease to asymptomatic males and females.
 - ▶ Complete formal evaluations of many of the affected relatives are still pending.
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Family Pedigrees

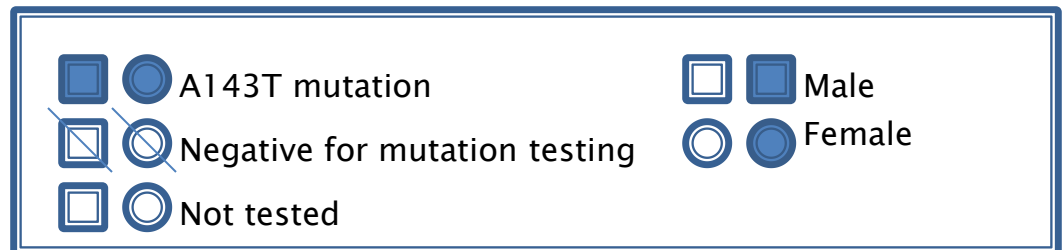


		c.352C>T mutation			Male
		Negative for mutation testing			Female
		Not tested			

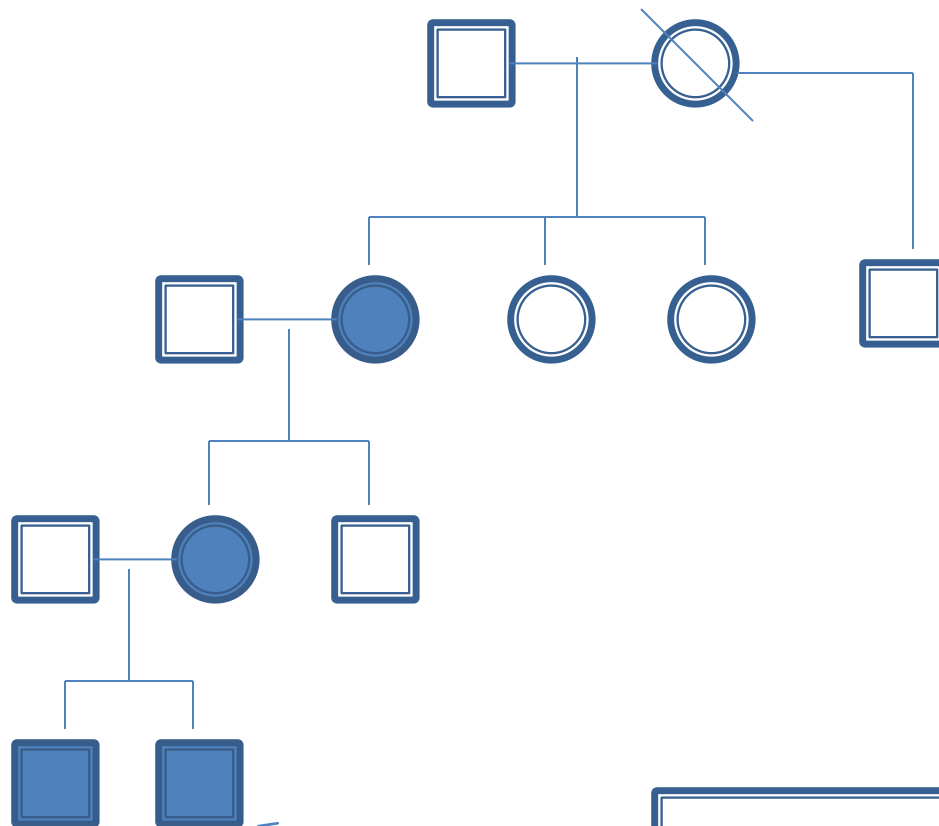
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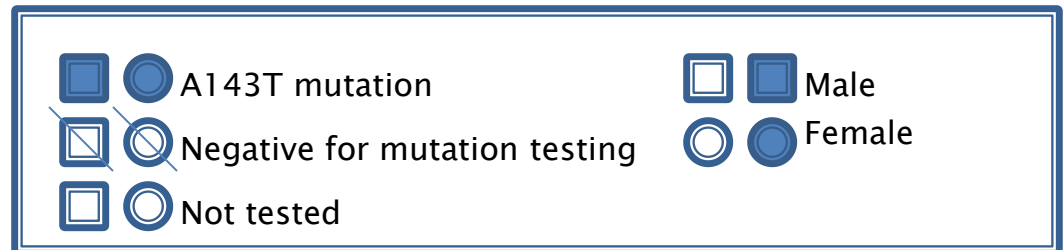
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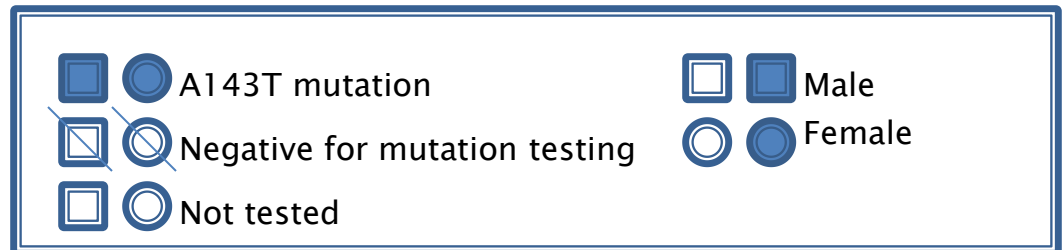
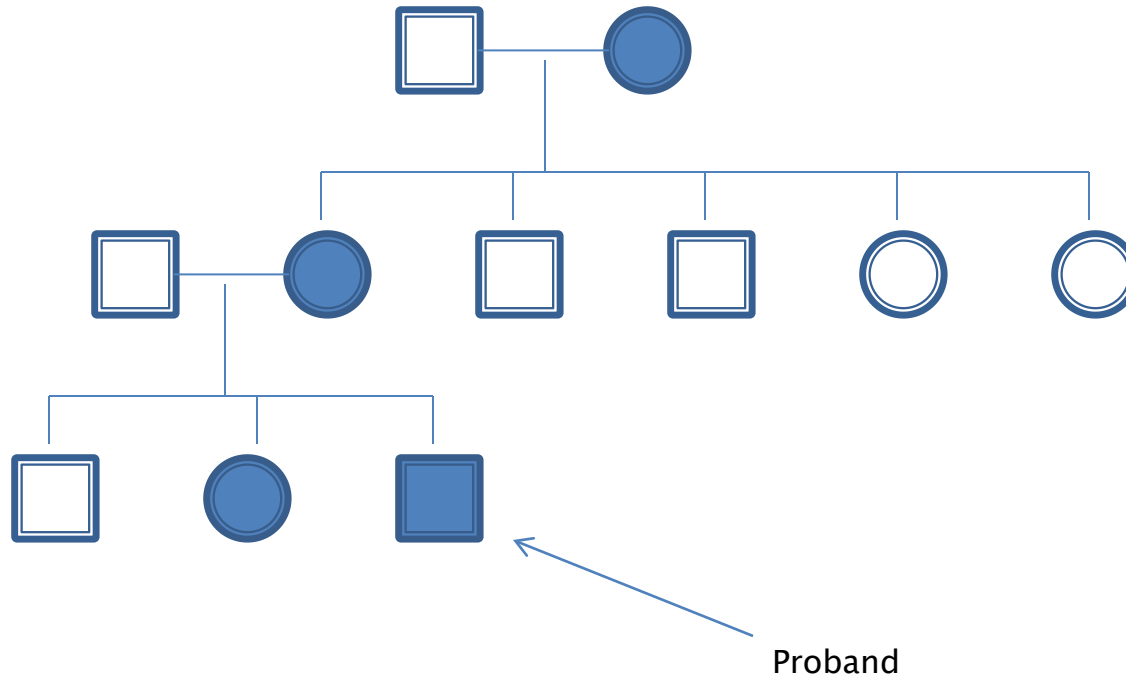
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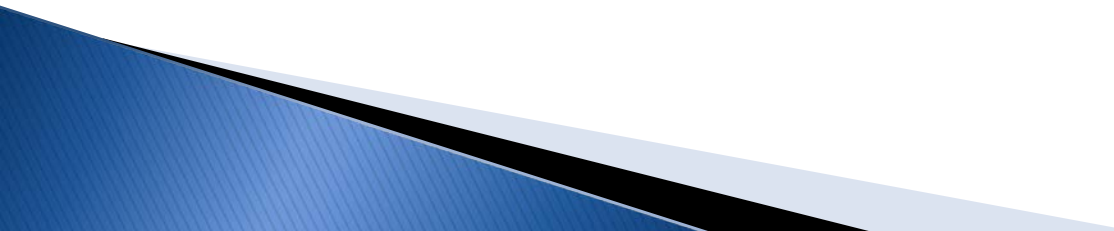
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Family Pedigrees



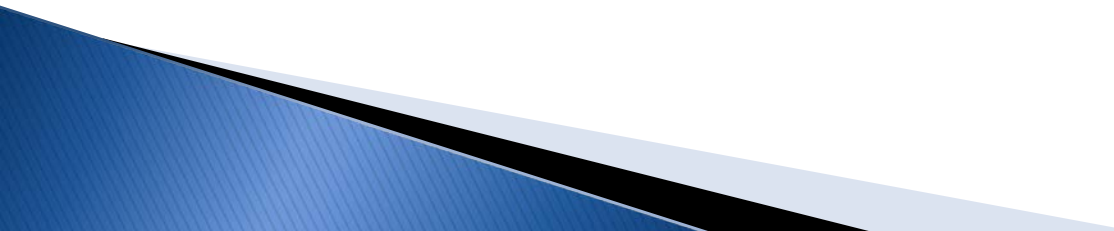
Overview of Findings

- ▶ There is a much higher incidence of Fabry in Missouri than was originally expected.
 - ▶ The A143T mutation is especially and surprisingly prevalent in the Missouri population.
 - ▶ Onset and type of symptoms vary greatly from family to family.
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Challenges

- ▶ Parents often express frustration due to the fact that there are no established surveillance and/or treatment protocols for newborns.
- ▶ The lack of available information on some mutations can be frustrating to both families and the genetic counselors that are providing support and guidance.
- ▶ For the A143T mutation and late-onset mutations, there is little evidence to indicate if or when symptoms will occur or when treatment should be initiated.

Implications for Families

- ▶ Early detection will allow for careful monitoring and the initiation of treatment as soon as clinically appropriate.
 - ▶ Treatment will help prevent or lessen the complications typically associated with Fabry disease.
 - ▶ As a result of newborn screening and genetic counseling, at-risk family members can be identified and evaluated for Fabry disease.
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Genetic Counseling

- ▶ The number of newborns and subsequent family members identified with Fabry disease emphasizes the great importance of genetic counseling in the short-term follow-up for Fabry disease.
- ▶ Genetic Counseling
 - Helps families cope with an unexpected diagnosis
 - Provides families with appropriate educational materials
 - Helps identify other affected relatives
 - Provides information regarding recurrence risks and family planning

Acknowledgments

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