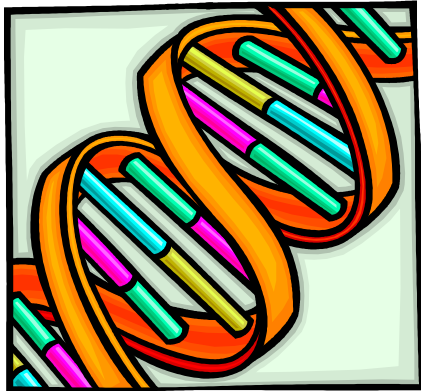


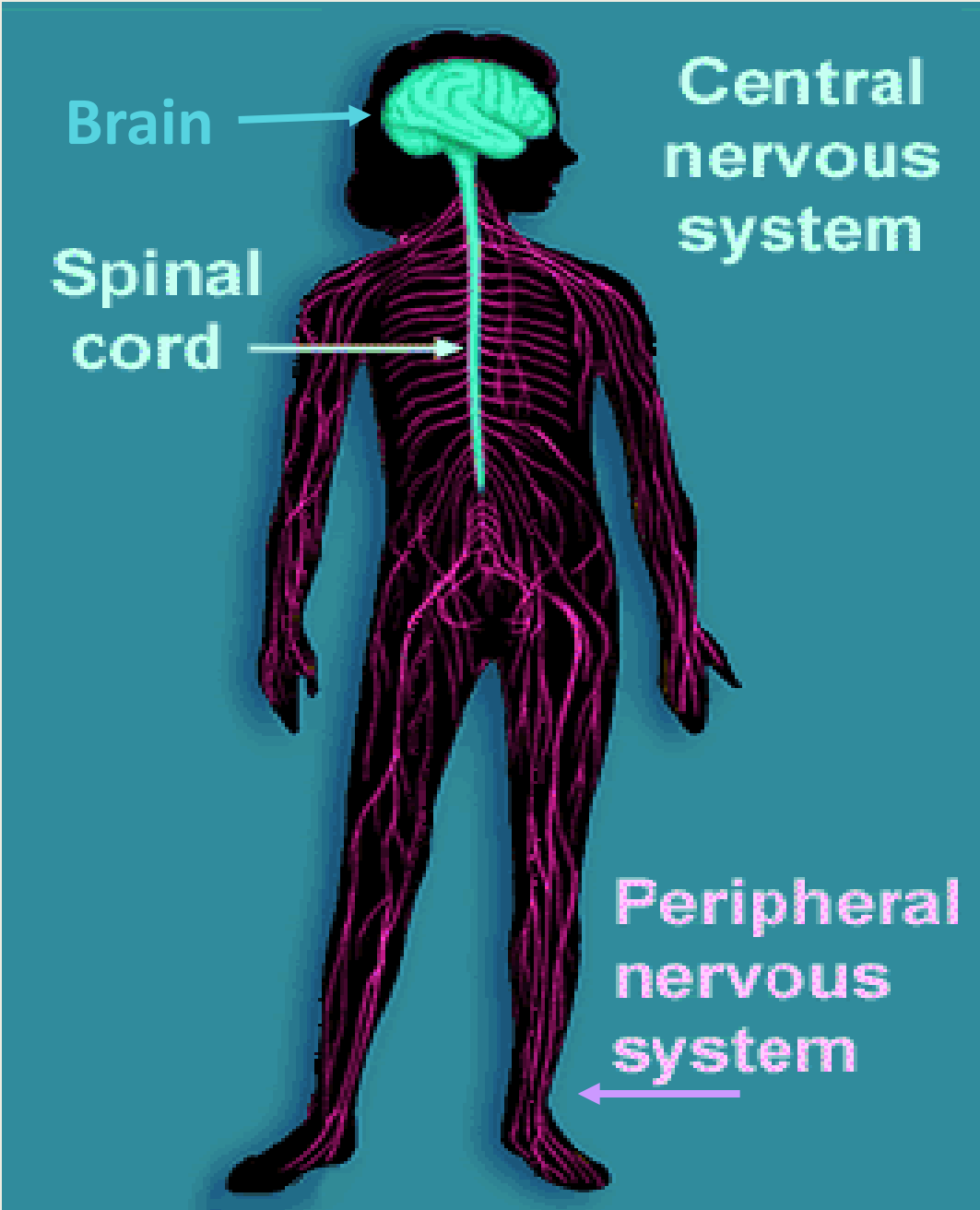
Genetics of CMT

Shawna Feely, MS, CGC
Certified Genetic Counselor
University of Iowa Healthcare



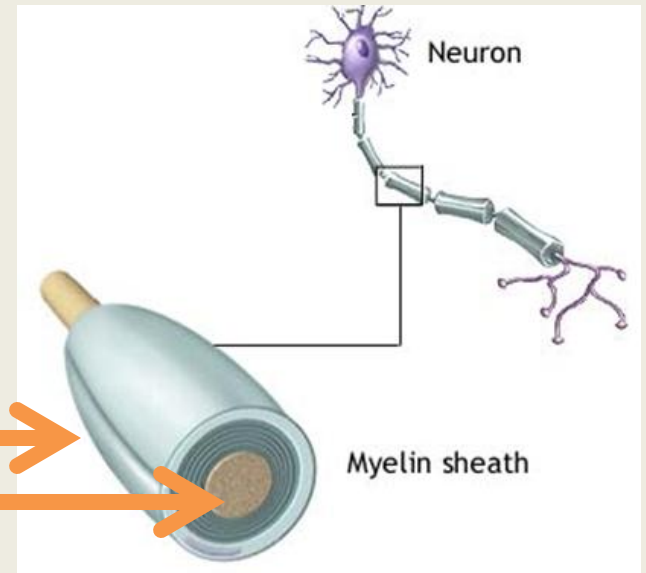
Agenda

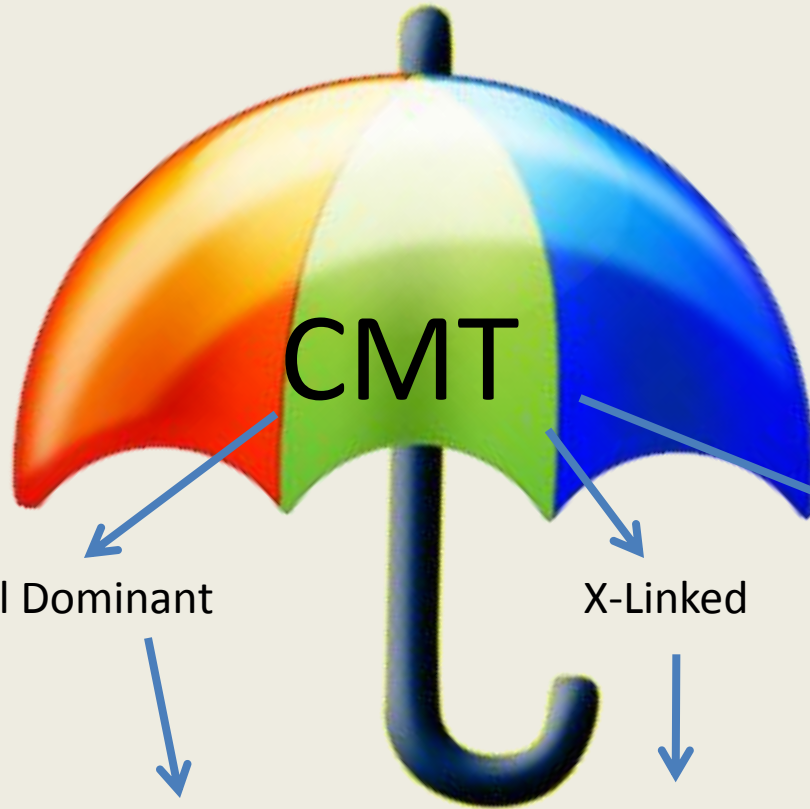
- **Background of CMT**
- **Background of Genetics**
- **Genetics of CMT**
- **Genetic testing**
- **Reproduction Options**
- **Family history – taking a pedigree**



What is CMT?

- Neuropathies: Primary diseases of nerve
- Peripheral Nerves
 - Demyelinating Neuropathy
 - Axonal Neuropathy
- Clinical Hallmarks
 - Distal muscle weakness and atrophy
 - Loss of proprioception and sensation
 - Classical steppage gait, pes plannus or pes cavus
 - Fatigue and depression can often accompany disease
- Genetic heterogeneity
 - Over 50 known genetic causes





CMT

Autosomal Dominant

X-Linked

Autosomal Recessive

Demyelinating
(Type 1)

Axonal
(Type 2)

Intermediate
(Type X)

Demyelinating OR Axonal
(Type 4)

Subtypes of CMT

CMT subtype	Gene
HNPP	<i>PMP22</i> (deletion)
CMT1A	<i>PMP22</i> (duplication)
CMT1B	<i>MPZ</i>
CMT1C	<i>LITAF/SIMPLE</i>
CMT1D	<i>EGR2</i>
CMT1E	<i>PMP22</i> (point mutation)
CMT1X	<i>GJB1 (Cx32)</i>
CMT2A	<i>MFN2</i>
CMT2B	<i>RAB7</i>
CMT2D	<i>GARS</i>
CMT2E	<i>NFL</i>
CMT2F	<i>HSP27/HSPB1</i>
CMT2L	<i>HSPB8</i>
CMT4A	<i>GDAP1</i>
CMT4B1	<i>MTMR2</i>
CMT4B2	<i>SBF2</i>
CMT4C	<i>SH3TC2</i>
CMT4D	<i>NDRG1</i>
CMT4E	<i>EGR2</i>
CMT4F	<i>PRX</i>
CMT4J	<i>FIG4</i>
dHMN V	<i>GARS</i> and <i>BSCL2</i>
HSN	<i>SPTLC1</i>

Subtypes of CMT

CMT subtype	Gene
HNPP	<i>PMP22</i> (deletion)
CMT1A	<i>PMP22</i> (duplication)
	<i>EGR2</i>
	<i>PRX</i>
	<i>FIG4</i>
	<i>GARS</i> and <i>BSCL2</i>
	<i>SPTLC1</i>

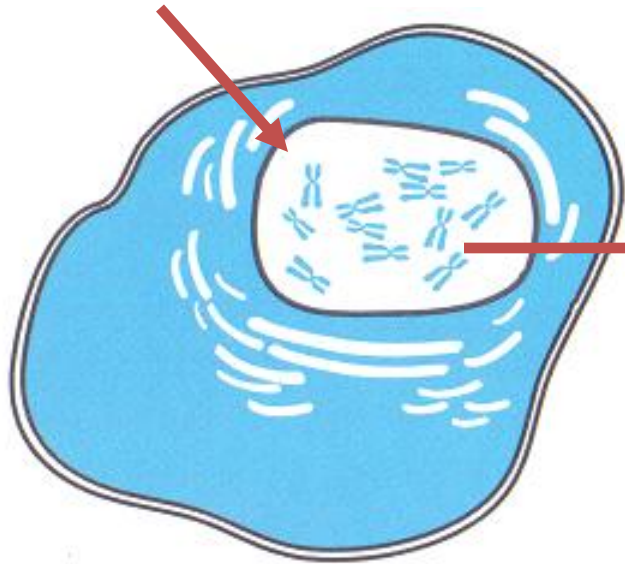
Total Cost for Complete CMT Panel:
\$17,910

Points to Consider

- Family history
- Clinical exam
- Nerve conduction studies

Chromosomes Are Found In Each Cell

Nucleus

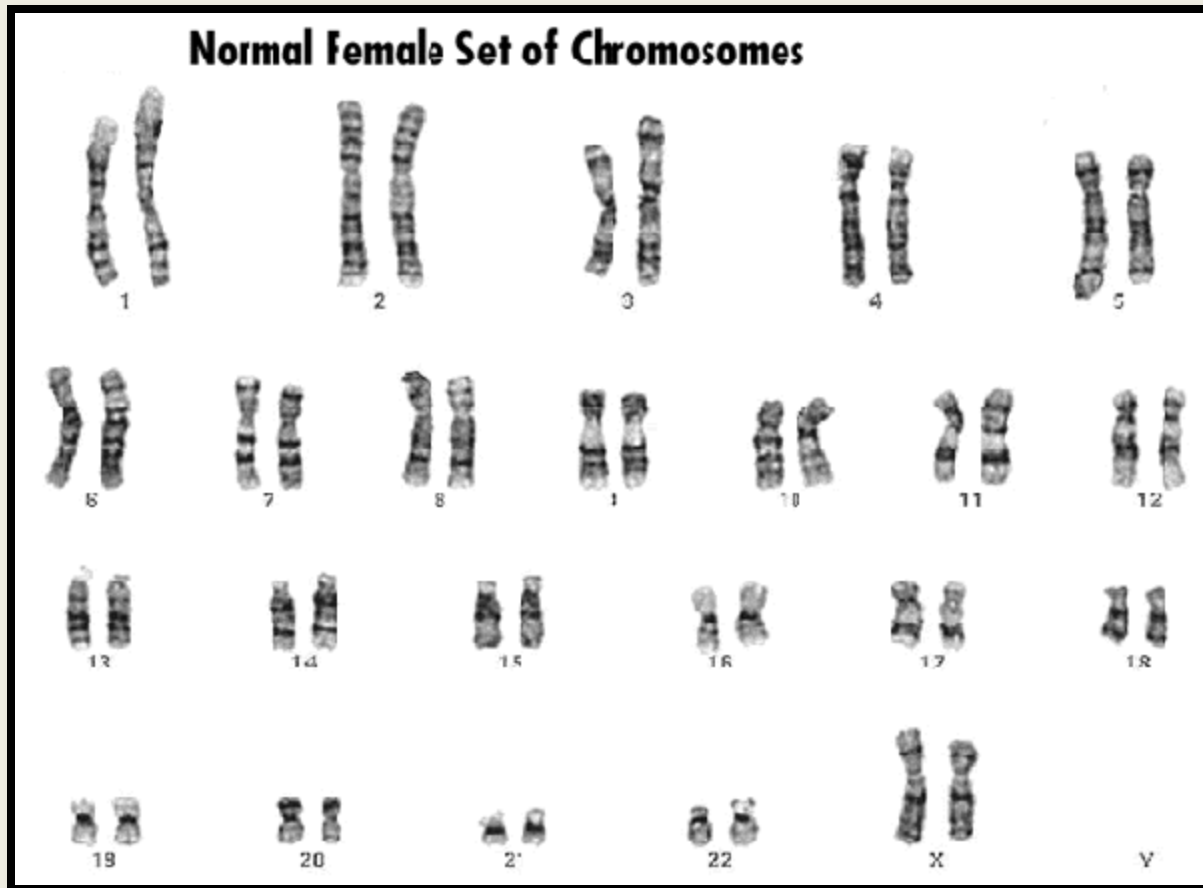


Cell

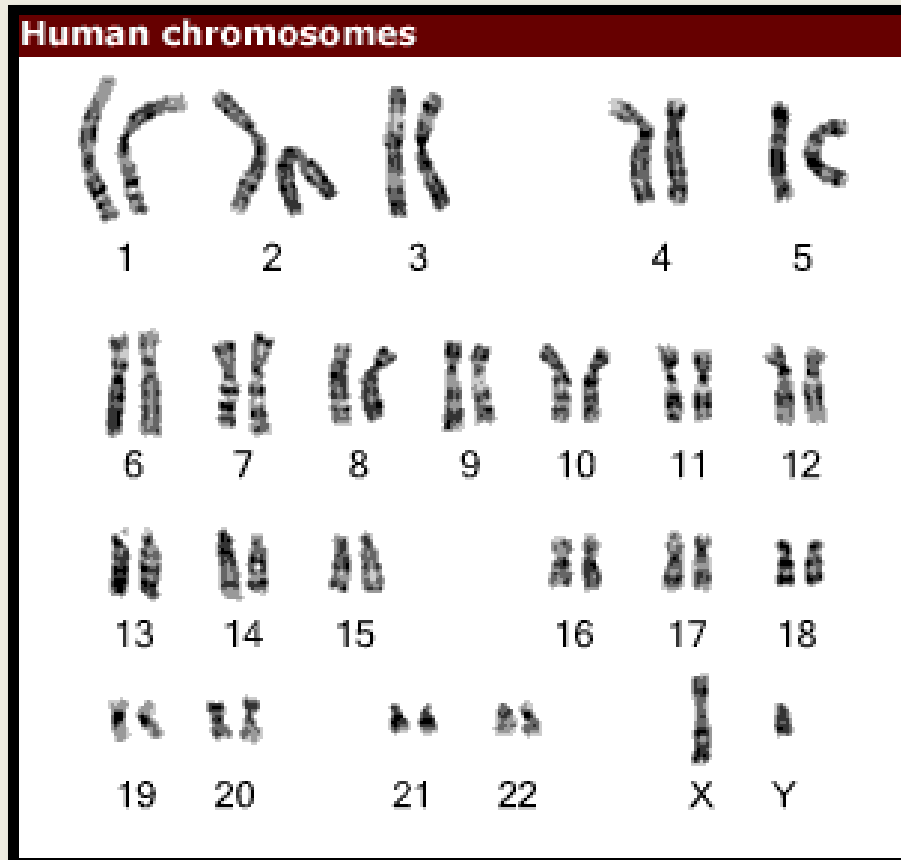


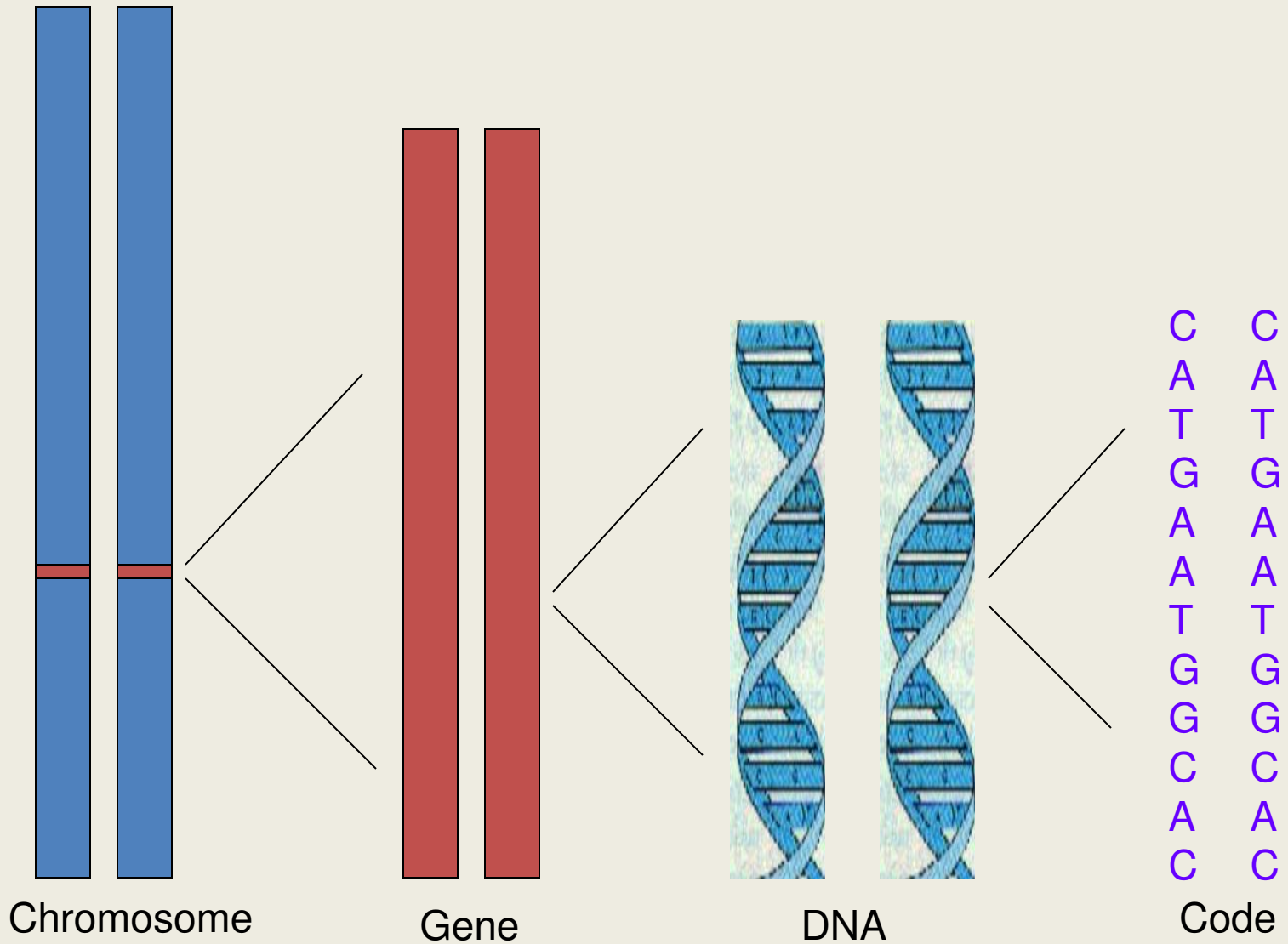
Chromosomes

Chromosomes - Female



Chromosomes - Male



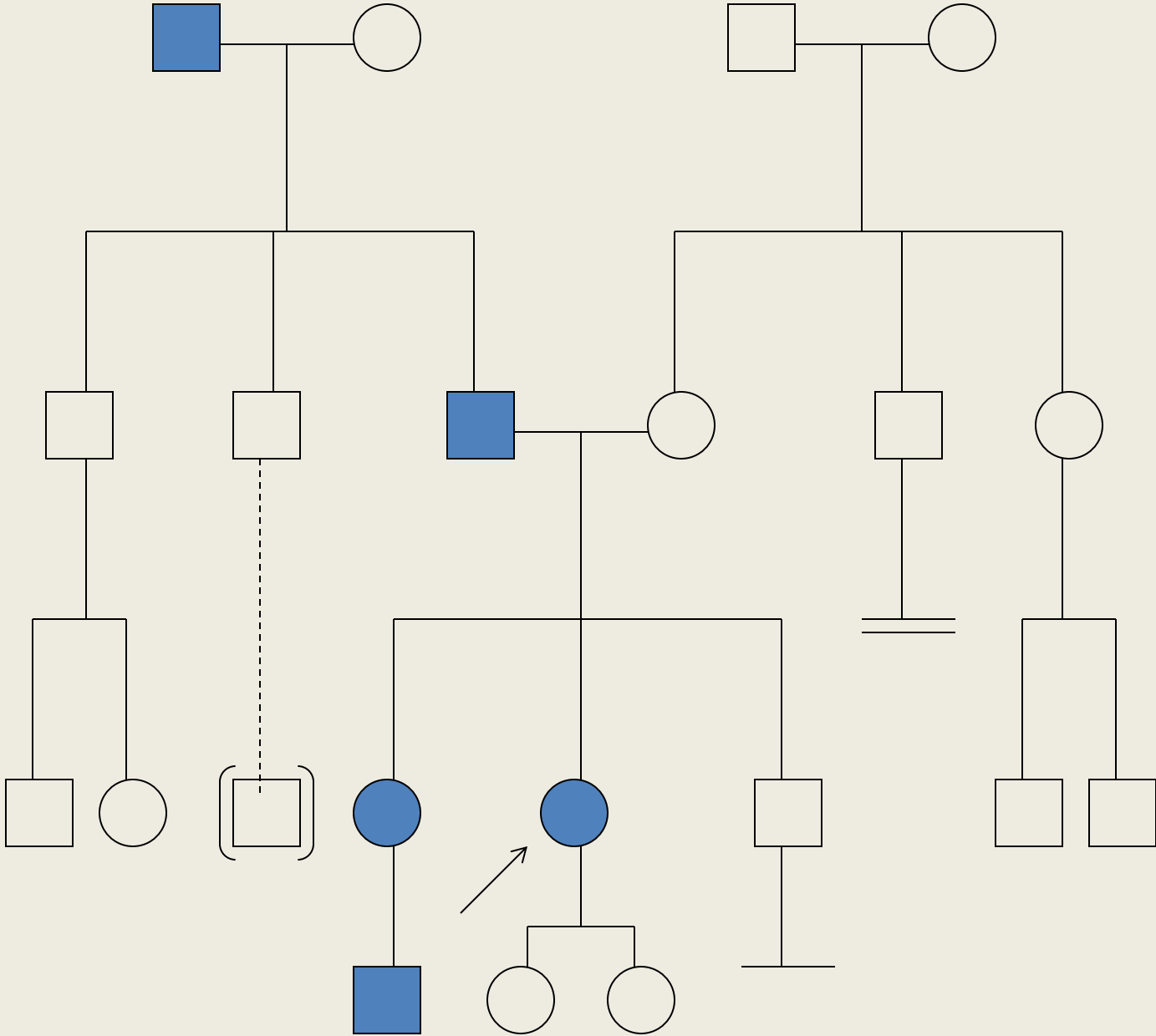


Family History: Modes of Inheritance

- Three main methods of inheritance:
 - Autosomal Dominant
 - Autosomal Recessive
 - X-linked
- The method of inheritance does not change within a family



Autosomal Dominant Inheritance



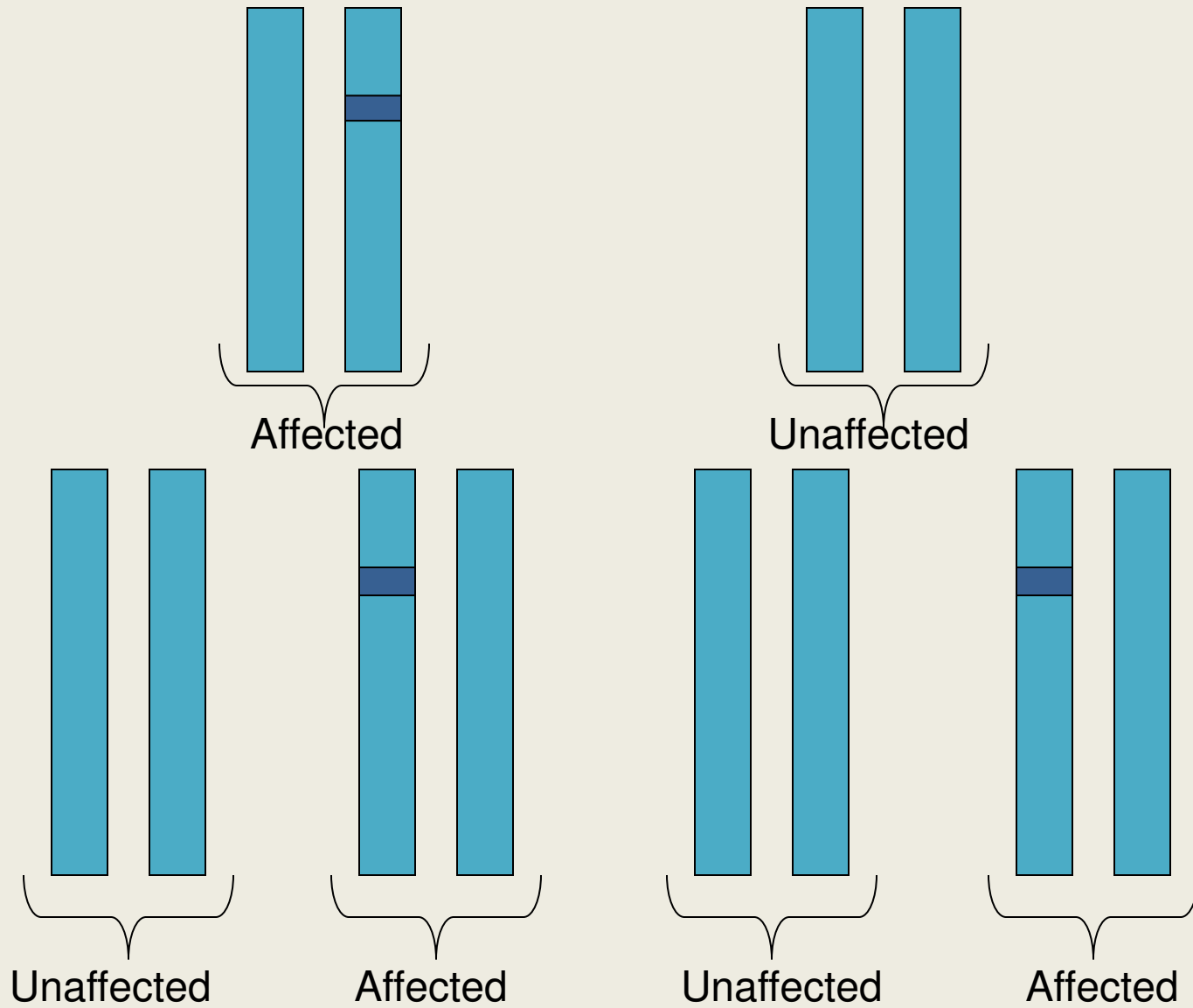
Genetics in CMT

- Type 1
 - Myelin is affected
 - Slowing of signal during nerve conduction studies
 - Autosomal dominant inheritance
 - May see multiple generations affected or may be first affected person in family
 - Examples: CMT1A, CMT1B, CMT1C, CMT1E

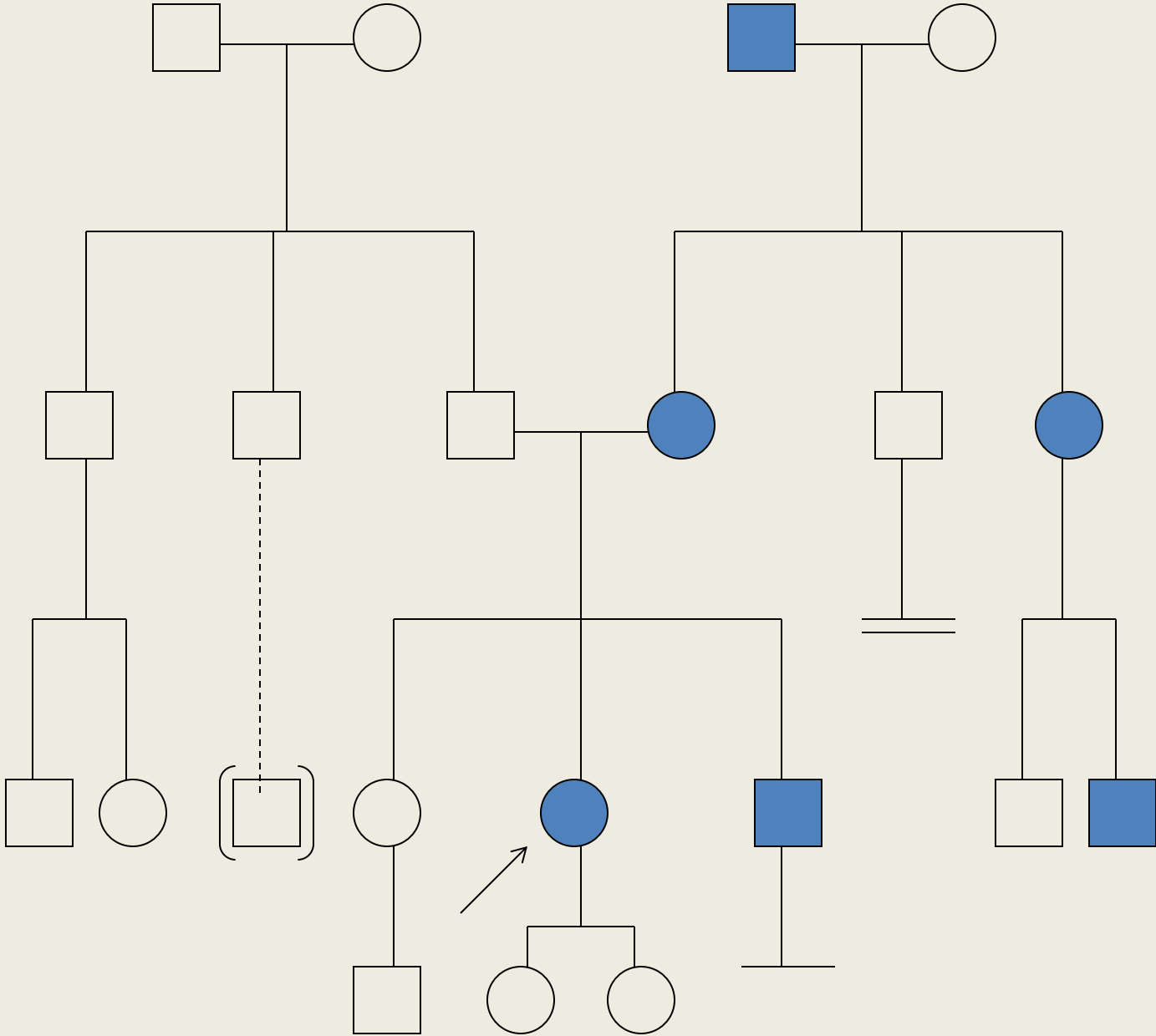
Genetics in CMT

- Type 2
 - Axon is affected
 - Reduced amplitude (strength of signal) during nerve conduction studies
 - Autosomal dominant inheritance
 - May see multiple generations affected or may be first affected person in family
 - Examples: CMT2A, CMT2E, CMT2K

Dominant Inheritance



X-Linked Inheritance



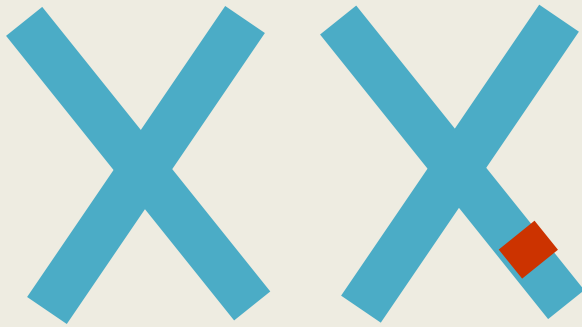
Genetics of CMT

- Type X
 - The mutation is carried on the X chromosome
 - Females are typically less affected than males
 - Females can pass on to sons and daughters
 - Males will only pass on to their daughters
 - Absence of male-to-male transmission
 - Examples: CMT1X, CMTX3, CMTX5

X-Linked

Mom

Dad



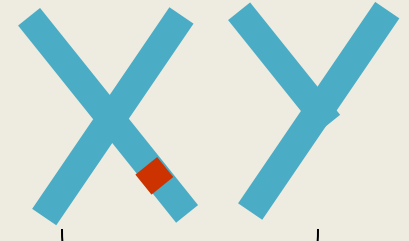
Unaffected Female



Unaffected Male



Affected Female

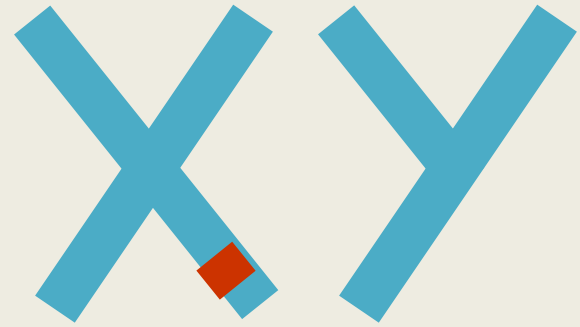
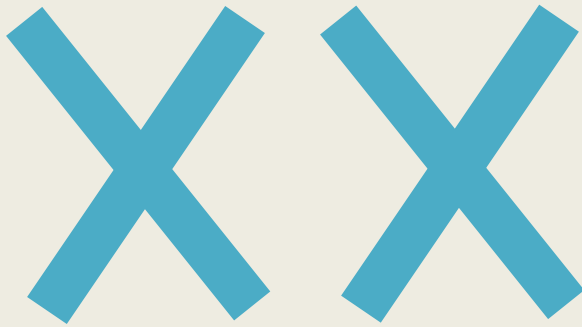


Affected Male

X-Linked

Mom

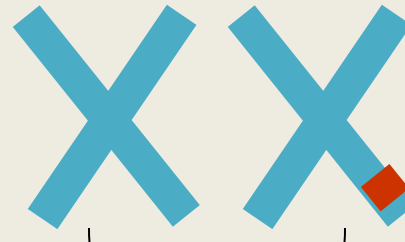
Dad



Affected Female



Unaffected Male

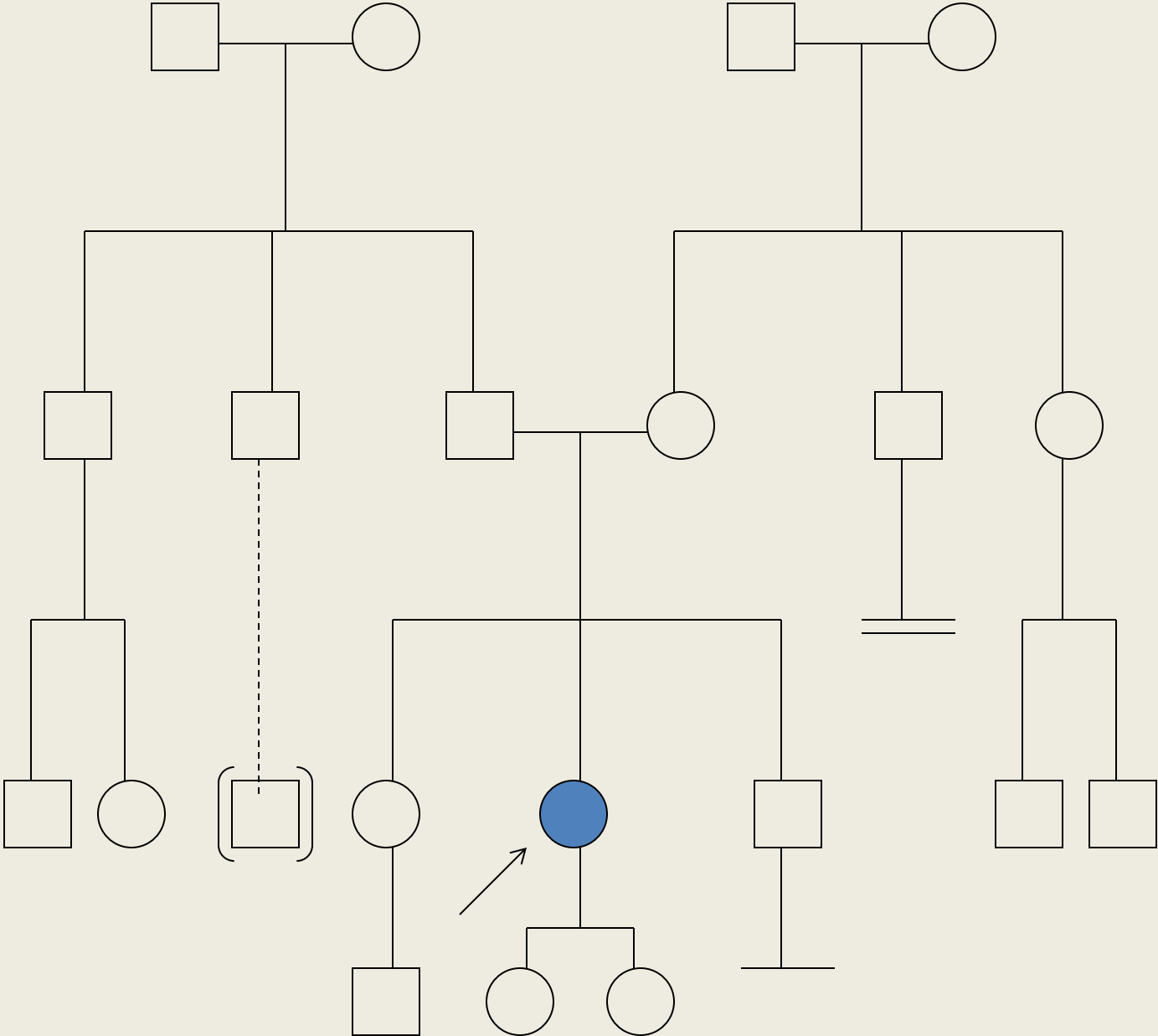


Affected Female



Unaffected Male

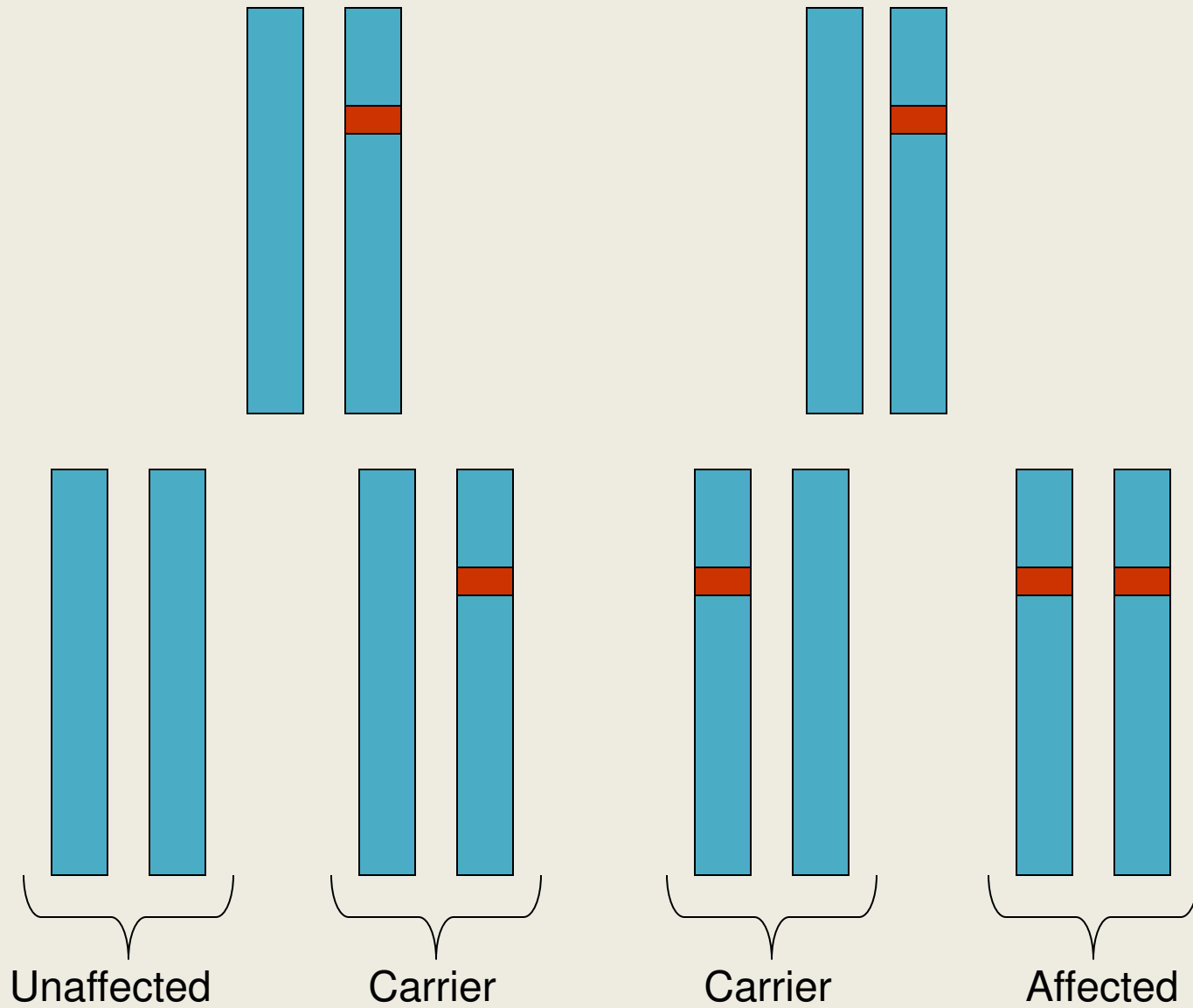
Autosomal Recessive Inheritance



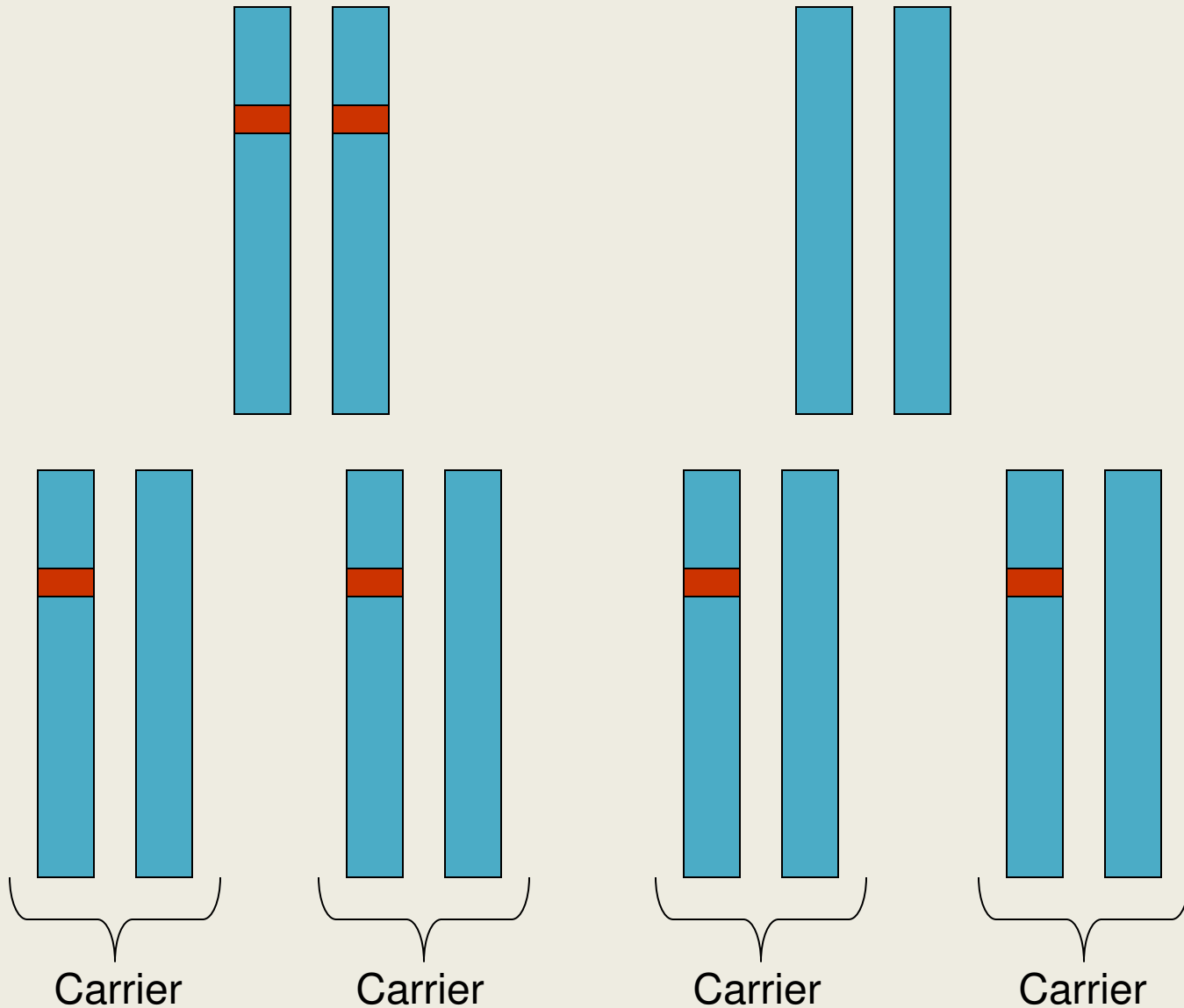
Genetics of CMT

- Type 4
 - Autosomal recessive
 - May be axonal or demyelinating
 - Possibly consanguineous parents
 - May be only person affected in the family
 - Low risk of passing on CMT unless partner is a family member
 - Examples: CMT4C, CMT4A, CMT4J

Recessive Inheritance



Recessive Inheritance



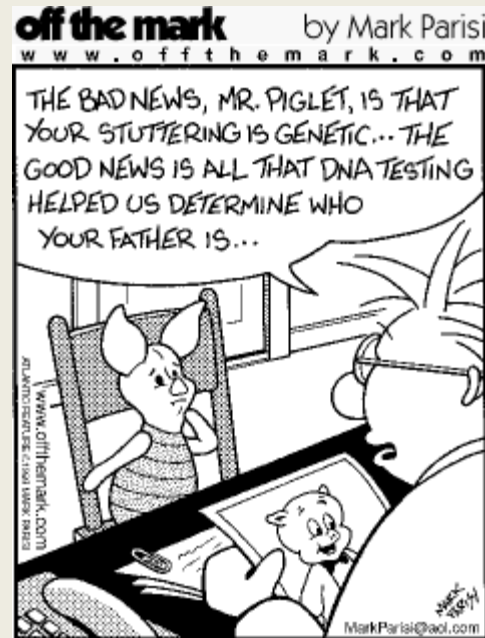
Genetic Testing

- What is it?
- Should genetic testing be performed?

Genetic Testing

Pros

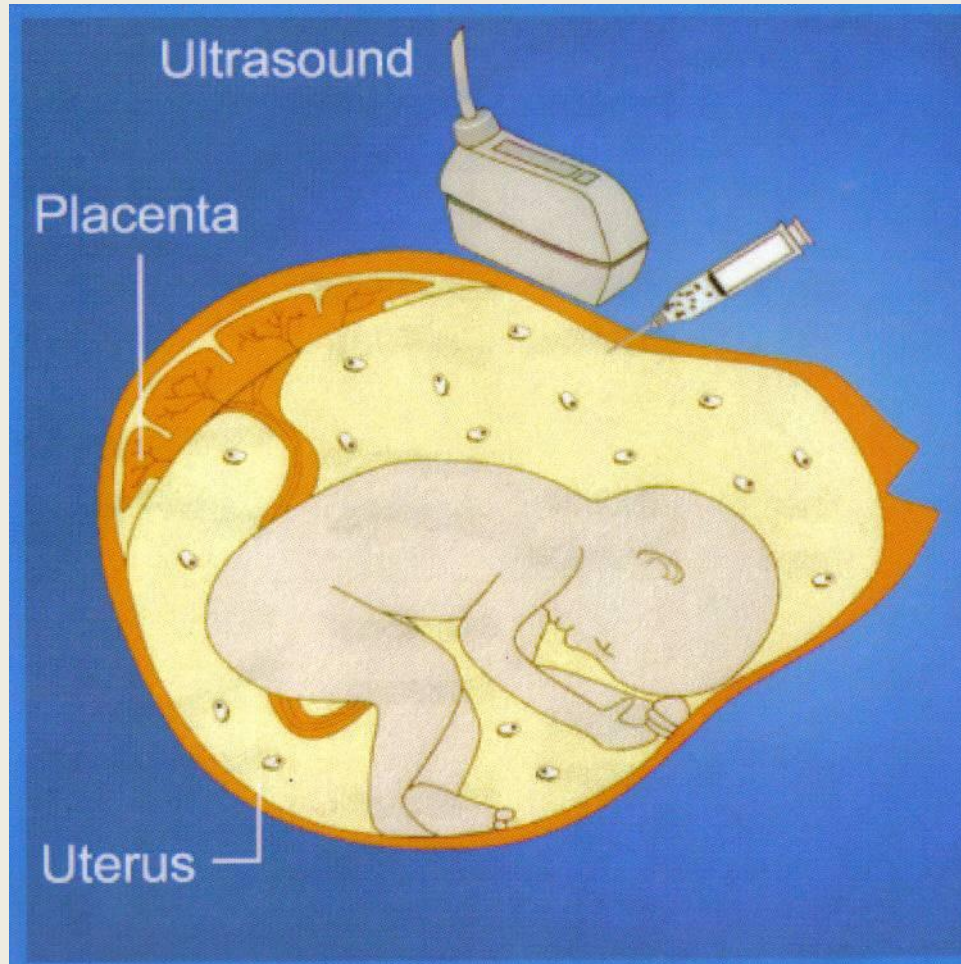
- To determine if other family members are at risk
- Family planning
- Possible access to treatment trials to further research
- Having a definitive diagnosis



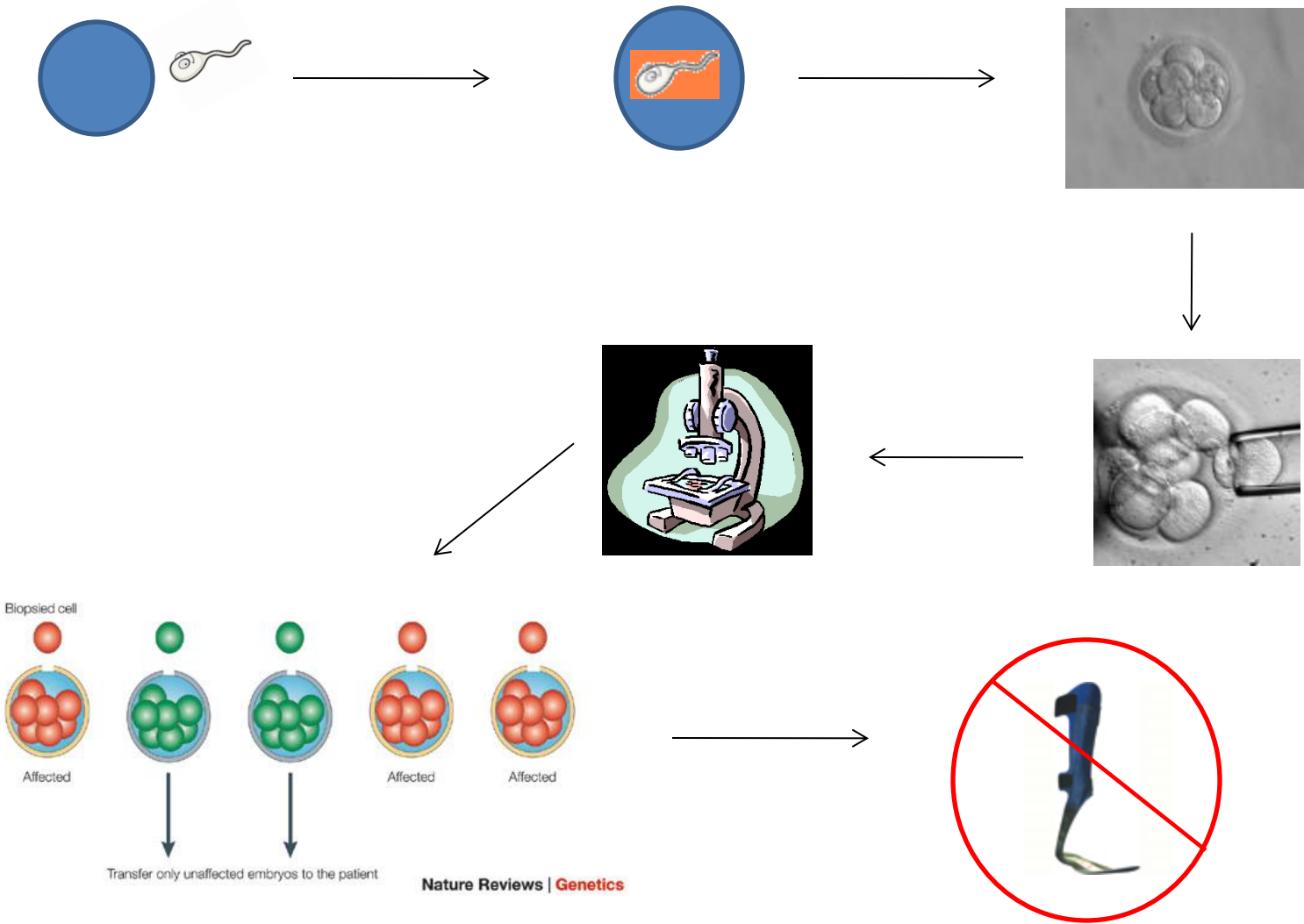
Family Planning Options

- During Pregnancy:
 - Chorionic Villus Sampling (CVS)
 - Amniocentesis
 - Maternal fetal cell analysis
- Before Pregnancy:
 - Preimplantation Genetic Diagnosis (PGD)

Prenatal Diagnosis



Preimplantation Genetic Diagnosis



Genetic Testing

Cons

- May have inconclusive results – what then?
- Emotional impact of positive *or* negative results
- May not have a genetic test available
- Genetic Discrimination



Genetic Testing

- Other issues:
 - Should we test a child?
 - Cost
 - Impact on the family system
 - Research based testing

Genetic Testing Results

- Positive result
 - Affected
 - Carrier (for a recessive condition)
- Negative result
- Variant of uncertain significance
- Inconclusive result

Diagnosis Service Report

Patient		
Date of Birth	Sex	Social Security Number
Specimen Type		
Whole Blood		
Test Category		
Not Available		
Test Requested		
Connexin32 DNA Sequencing Test		

Requesting Physician
Michael Shy, MD
Report to
Michael Shy, MD
Address
421 E. Canfield, RM 3217
Detroit, MI 48201
Additional Reports to:

Accession Number
Family Number/Kindred Number
Patient Number
Specimen Collection Date
NO Date
Accession Date
Report Date

Interpretation

This individual possesses a DNA sequence alteration in the coding region of the Cx32 gene that is a known disease-associated mutation. Therefore this individual is likely to be affected with, or predisposed to developing, X-linked CMT (CMTX1).¹⁻⁴

Technical Results

Connexin32 allele 1: Transition: A > G
 Nucleotide position: 307
 Codon position: 103
 Amino acid change: Lysine > Glutamic Acid
 Connexin32 allele 2: No sequence alteration detected

Methods

Direct testing for Cx32 gene sequence alterations was performed by PCR amplification and automated sequencing of both genomic DNA strands which code for the entire mature protein. The technical analysis, as performed here, is greater than 99% accurate.

Abbreviation: CMT1 - Charcot-Marie-Tooth disease Type 1; CMT1A - Charcot-Marie-Tooth disease Type 1A; HNPP - Hereditary Neuropathy with liability to Pressure Palsies; CMTX1 - X-linked Charcot-Marie-Tooth disease Type 1; CMT1B - Charcot-Marie-Tooth disease Type 1B; DSS - Dejerine-Sottas Syndrome; CHN - Congenital Hypomyelination; Cx32 - Connexin 32; PMP-22 - Peripheral Myelin Protein; MPZ - Myelin Protein Zero; EGR2 - Early Growth Response 2.

This testing service is performed pursuant to a PCR license agreement with Roche Molecular Systems, Inc. The Cx32 DNA sequencing test is protected by U.S. Patent No 5,691,144.

Comments

Sequencing of this individual's Cx32 gene demonstrated a DNA sequence alteration which contains one of the previously-reported disease-associated mutations. This individual's other Cx32 allele is either normal or possesses a benign polymorphism (known or predicted). Current literature indicates that DNA sequence alterations in the Cx32 gene are usually associated with CMTX1.¹⁻⁴

Males with two sequence alterations are shown as having two Cx32 alleles solely to provide details of both alterations. The number of X-linked alleles is not determined in this analysis but is assumed to be two for females and one for males.

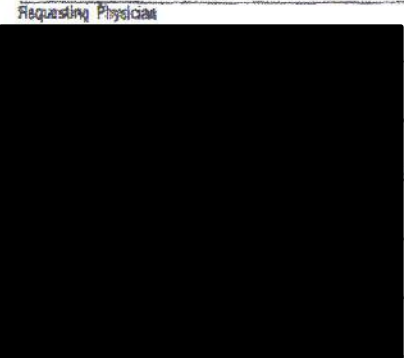
CMTX1 is inherited as an X-linked dominant disorder in which both males and females manifest symptoms of the disease.^{1,2} Affected females have a 50% risk of transmitting the mutation to their male and female offspring, while affected males would normally transmit the mutation to all female offspring but no male offspring.^{1,2}

Athena recommends genetic counseling for this individual and his/her family members as they are at risk for possessing or inheriting this



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Worcester, Massachusetts 01605
(800) 394-4493 - (508) 756-2886

Patient _____
 Date of Birth _____ Sex _____ Social Security Number _____
 Specimen Type
Whole Blood
 Test Category
Diagnostic (Symptomatic)
 Test Requested
Complete CMT Evaluation



Accession Number _____
 Family Number/Kinship Number _____
 Patient Number _____
 Specimen Collection Date _____
 Accession Date _____
 Report Date _____

Interpretation

This individual possesses a novel DNA sequence alteration in the PRX gene (one allele only) as specified in the table in the Technical Results section of this report. Although this DNA sequence alteration has not been previously described in the published literature, this individual is likely to be a carrier of or affected with a CMT4F or DSS type peripheral neuropathy.^{16,17} All other tests performed as a part of this profile exhibited either 1) no sequence alterations, 2) benign polymorphisms or 3) inconclusive test results. Please refer to the Comments section of this report for further details.

PRX allele 2: No sequence alteration detected
Additional Polymorphisms detected:
Thr102Thr, Ala882Val, Pro885Pro
Ile921Met, Pro1083Arg

Comments

This profile analyzes patient's DNA for PMP22 gene dosage (duplication/deletion) and sequence alterations in genes indicated in the table in the Technical Results section of this report. The PRX sequencing assay within this profile demonstrated a novel DNA sequence alteration (one allele only) that is predicted to result in significant alteration of the PRX protein structure and disrupt its normal function.^{16,17} The PRX gene on this individual's other allele is either normal or possesses a benign polymorphism. This novel DNA sequence alteration has not been previously described in the published literature and it is unknown whether the mutation is dominant or recessive. If the mutation is dominant, this individual is likely to be affected with or predisposed to developing peripheral neuropathy types CMT4F or DSS. Conversely, if the mutation is recessive, this individual is likely to be a carrier of peripheral neuropathy types CMT4F or DSS.

Mutations of this type in PRX usually autosomal recessive.^{16,17} Athena recommends genetic counseling for this individual and his/her family members as they are at risk for possessing or inheriting this dominant or recessive mutation. Please contact Athena Client Services at 800-394-4493 for information on genetic counselors in your area and family.

William K. Seitzer

William K. Seitzer, PhD, FACMG, Laboratory Director

Technical Results

Test	Result	Alert
PMP-22 dup/del	No duplication/deletion	
Cx32 Sequencing	No Sequence Alteration	
MPZ Sequencing	No Sequence Alteration	
PMP-22 Sequencing	No Sequence Alteration	
EGR2 Sequencing	No Sequence Alteration	
NF-L Sequencing	No Sequence Alteration	
PRX Sequencing	*Sequence Alteration	Carrier

*Sequence alteration details given below:

PRX allele 1: Sequence alteration detected: transition C -> T
Nucleotide position: 3502
Codon position: 1168
Amino acid change: glutamine --> Amber (stop codon)
DNA variant type: Predicted disease-associated mutation

Sent by: M.I.N.D. 248 553 0100; 05/04/2004 15:05 #544; Page 2 / 1
Received: 10/30/2002 10:30:02 PM; -M.I.N.D.; #315; Page 2
10/30/02 15:38 FAX 508 753 5601 ATHENA DIAGNOSTICS



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Worcester, Massachusetts 01605
(800) 394-4493 • (508) 756-2886

Diagnosis Service Re

Patient _____

Date of Birth _____ Sex _____ Social Security Number _____

Specimen Type
Whole Blood

Test Category
Diagnostic (Symptomatic)

Test Requested
Connexin32 DNA Sequencing Test

Requesting Physician
Michael Shy, MD

Report to
Michael Shy, MD/Dmc/Wayne State Univ.

Address
421 E. Canfield

Elliman Bldg RM 3217

Detroit, MI 48201

Additional Reports to: _____

Accession Number _____

Family Number/Kindred Number _____

Patient Number _____

Specimen Collection Date
NO Date

Accession Date _____

Report Date _____

Interpretation

This individual does not possess a DNA sequence alteration in the coding region of the Cx32 gene. Therefore, this individual is unlikely to be affected with, or predisposed to developing, X-linked CMT due to Cx32 gene sequence alterations.¹⁻³ This result does not rule out peripheral neuropathy due to mutations in other genes or due to noncoding mutations in Cx32.^{1,2} Please see the comments section for further details.

Technical Results

Connexin32 allele 1: No sequence alteration detected
Connexin32 allele 2: No sequence alteration detected

Methods

Direct testing for Cx32 gene sequence alterations was performed by PCR amplification and automated sequencing of both genomic DNA strands which code for the entire mature protein. The technical analysis, as performed here, is greater than 99% accurate.

Abbreviation: CMT1 - Charcot-Marie-Tooth disease Type 1; CMT1A - Charcot-Marie-Tooth disease Type 1A; HNPP - Hereditary Neuropathy with liability to Pressure Palsies; CMTX1 - X-linked Charcot-Marie-Tooth disease Type 1; CMT1B - Charcot-Marie-Tooth disease Type 1B; DSS - Dejerine-Sottas Syndrome; CHN - Congenital Hypomyelination; Cx32 - Connexin 32; PMP-22 - Peripheral Myelin Protein; MPZ - Myelin Protein Zero; EGR2 - Early Growth Response 2.

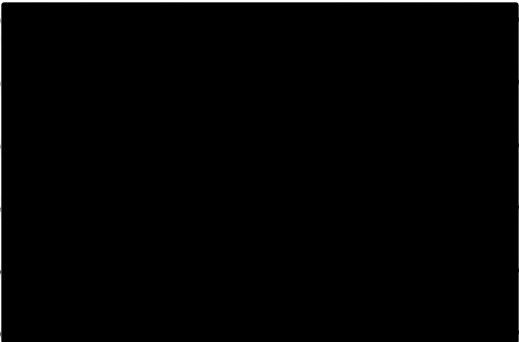
This testing service is performed pursuant to a PCR license agreement with Roche Molecular Systems, Inc. The Cx32 DNA sequencing test is protected by U.S. Patent No 5,691,144.

Comments

This individual does not possess a DNA sequence alteration in the coding region of the Cx32 gene. Therefore, this individual is unlikely to be affected with, or predisposed to developing, a peripheral neuropathy due to Cx32 gene sequence alterations.¹⁻⁴

Several genes (PMP22, Cx32, MPZ, and EGR2) have been implicated in causing peripheral neuropathy. In addition to sequence alterations within these genes, duplication or deletion of a chromosomal region containing the PMP22 gene causes disease due to an altered PMP22 gene dosage. Collectively, mutations in these genes account for up to 85% of CMT1.^{1,2}

Over 200 different mutations have been described in the Cx32 gene, accounting for approximately 90% of X-linked CMT (CMTX1).^{1,2} In general, males affected by CMT1 due to a Cx32 mutation are more severely affected than females, but the severity of phenotype can vary markedly.^{1,2} Cx32 mutations have also been identified in a small number of females with a CMT2 diagnosis.^{1,2} Two noncoding mutations have been reported in Cx32^{1,2} and would not be detected in the Cx32 DNA sequencing test performed here. CMTX1 is considered to be the second

Patient	Requesting Physician		Accession Number
Date of Birth	Sex	Social Security Number	Family Number/Kindred Number
Specimen Type Whole Blood			Patient Number
Test Category Diagnostic (Symptomatic)			Specimen Collection Date
Test Required Partial CMT - Axonal Only			Accession Date
			Report Date

Interpretation

This individual possesses a DNA sequence variant in one or more genes tested in this panel, whose significance is unknown (**amino acid change of unknown significance**). The significance of this new sequence variant may be clarified by careful reconciliation of this molecular data with this patient's clinical symptoms and family member testing if appropriate. Please refer to the Technical Results and Comments sections of this report for further information.

Codon position: 298
 Amino acid change: Glycine > Arginine
 DNA variant type: Variant of unknown significance, heterozygous
 Inheritance: Unknown

No other abnormal DNA sequence variants were identified in the remainder of the coding sequence or intron/exon junctions of this gene.

Comments

Most Significant result: Analysis of this individual's DNA identified a DNA sequence variant in one or more genes tested in this panel, whose significance is unknown (**amino acid change of unknown significance**). Since this type of sequence variant is similar to those observed in both disease-associated mutations and benign polymorphisms, the nature of this variation precludes clear interpretation. While methodologically accurate, the results of this analysis cannot be definitively interpreted due to the absence of published studies correlating these variant(s) with clinical presentation and/or pathology. Therefore, it is not possible to conclude with any reasonable degree of clinical certainty at this time whether or not this variant is associated with the phenotype in question.

Possible outcomes: Although the clinical significance of this test result is not certain, several outcomes are possible:
Normal -- the variant is a benign polymorphism that has not been previously detected or reported and it is very unlikely that this mutation

Technical Results

Test	Result	Alert
Cx32 Sequencing	No Sequence Alteration	
MPZ Sequencing	No Sequence Alteration	
NFL Sequencing	No Sequence Alteration	
GDAP1 Sequencing	No Sequence Alteration	
MFN2 Sequencing	*Sequence Alteration	Unknown Variant

*Sequence alteration details given below:

MFN2 Variant 1: Transition G > A
 Nucleotide position: 892

Send this to us here



Clinical and electrophysiologic features of CMT2A with mutations in the mitofusin 2 gene

Victoria H. Lawson, MD; Brad V. Graham, BS; and Kevin M. Flanigan, MD

NEUROLOGY 2005;65:197-204

in exon 9 of the control population. One (c.956C>T) represented a synonymous amino acid change and was present in 1% of controls. The other (c.891G>A) was found in 3% of controls and resulted in a non-synonymous, G to R substitution at amino acid position 298.

The remainder of the family members had no mutations.

Patient	Requesting Physician	
Date of Birth	Sex	Social Security #
Specimen Type	Whole Blood	
Test Category	Diagnostic (Symptomatic)	
Test Required	Complete CMT Evaluation	

Accession Number
Family Number/Kindred Number
Patient Number
Specimen Collection Date
Accession Date
Report Date

Interpretation

This individual's testing yielded **inconclusive** results for one or more analytic segments of one or more genes tested in this panel. Therefore, this testing is incomplete and the clinical utility of this analysis is limited. Athena recommends sending a follow-up specimen at no additional cost to resolve these inconclusive test results. Please refer to the Technical Results and Comments section of this report for further information.

Technical Results

Test	Result	Alert
PMP22 dup/del	No duplication/deletion	
Cx32 Sequencing	<u>Inconclusive</u>	Inconclusive
MPZ Sequencing	No Sequence Alteration	
PMP22 Sequencing	No Sequence Alteration	
EGR2 Sequencing	No Sequence Alteration	
NFL Sequencing	No Sequence Alteration	
PRX Sequencing	No Sequence Alteration	
GDAP1 Sequencing	No Sequence Alteration	
LITAF Sequencing	No Sequence Alteration	
MFN2 Sequencing	No Sequence Alteration	

HMSE Results 15;8;15;15;15;15;15;15;15;

Comments

*Hand To Speak Follow-Up
Symptoms*

Most Significant result: Analysis of this individual's DNA yielded inconclusive test results for one or more analytic segments of one or more genes tested in this panel. Completed analyses of all other analytic segments and genes tested in this panel did not detect any known, predicted or clinically informative variants. Inconclusive test results are results for one or more segments of a specific gene that cannot be interpreted as either normal or abnormal due to analytical uncertainty. Please note that this testing is incomplete and therefore the clinical utility of this analysis is limited. Any conclusions based upon this limited information may differ significantly from a completed test analysis.

Possible reasons for inconclusive results: these generally include (1) test results which fall outside of the established quality control criteria, (2) an insufficient quantity of DNA to yield required amounts of PCR amplified products, or (3) factors within the DNA specimen that interfere with PCR and/or sequencing for all sequencing assays in this panel. An insufficient number of white blood cell count to yield required amount of agarose plugs and/or factors within the DNA specimen that interfere with restriction digestions and southern hybridizations for the PMP22 dup/del analysis component of this profile can lead to inconclusive results. Typically, inconclusive results are resolved by analysis of a repeat specimen.

Course of action for possible resolution: A repeat specimen is recommended to resolve the inconclusive test results. There will be no charge for the repeat analysis. Please indicate "REPEAT SPECIMEN" along with the above Athena Accession Number on the requisition.

(MON) SEP 8 2008 9:22/No. 7500000461 P 1



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Diagnosis Service

Patient	Requesting Physician	
Date of Birth	Sex	Social Security Number
Specimen Type	Whole Blood	
Test Category	Diagnostic (Symptomatic)	
Test Requested	Connexin32 DNA Sequencing Test	

Accession Number
Family Number/Kindred Number
Patient Number
Specimen Collection Date
Accession Date
Report Date

Interpretation

This individual's testing yielded inconclusive results. Please refer to the Comments section of this report for further information.

Technical Results

Connexin32 allele 1: Inconclusive
Connexin32 allele 2: Inconclusive

Methods

Direct testing for Cx32 gene sequence alterations was performed by PCR amplification and automated sequencing of both genomic DNA strands which code for the entire mature protein. The technical analysis, as performed here, is greater than 99% accurate.

Abbreviation: CMT1 - Charcot-Marie-Tooth disease Type 1; CMT1A - Charcot-Marie-Tooth disease Type 1A; HNPP - Hereditary Neuropathy with liability to Pressure Palsies; CMTX1 - X-linked Charcot-Marie-Tooth disease Type 1; CMT1B - Charcot-Marie-Tooth disease Type 1B; DSS - Dejerine-Sottas Syndrome; CHN - Congenital Hypomyelination; Cx32 - Connexin 32; PMP-22 - Peripheral Myelin Protein; MPZ - Myelin Protein Zero; EGR2 - Early Growth Response 2.

This testing service is performed pursuant to a PCR license agreement with Roche Molecular Systems, Inc. The Cx32 DNA sequencing test is protected by U.S. Patent No 5,691,144.

*No full sequence at No
addition cost*

Comments

Inconclusive test results cannot be interpreted as either negative or positive due to a technical problem. The results do not indicate the presence or absence of abnormalities in the coding region of the gene.

The reasons for failure to reach a conclusive test result generally (1) test results which fall outside of the established quality criteria, (2) an insufficient quantity of DNA to yield required amount of PCR amplified products, or (3) factors within the DNA specimen interfere with PCR and/or sequencing. Typically, inconclusive results are resolved by analysis of a repeat specimen.

Athena recommends a follow-up specimen to be tested to resolve inconclusive test results. There will be no charge for the repeat analysis. Please indicate "REPEAT SPECIMEN" along with the above Accession Number on the requisition. Please contact Athena Diagnostics Services at 800-394-4493 if you have any questions.

References

1. Lupski, J.R. and C. A. Garcia(2000) Charcot-Marie-Tooth peripheral neuropathies and related disorders. Chapter 227, In Metabolic and Molecular Bases of Inherited Disease, C Scriver, ed., Eighth Edition.
2. Nelis, E., et al.(1999) Human Mutation 13: 11-28
3. Bergoffen, J. et al.(1993) Science 262: 2039-2041
4. The Mutation Database of Inherited Peripheral Neuropathies



Four Biotech Park • 377 Plantation Street
 Worcester, Massachusetts 01605
 (800) 394-4493 • (508) 756-2886

Diagnosis Service

Patient

Date of Birth Sex Social Security Number

Specimen Type
Whole Blood

Test Category
Diagnostic (Symptomatic)

Test Requested
CX32 (GJB1) Evaluation

Requesting Physician
Michael Shy, MD

Report to
Michael Shy, MD/Dmc/Wayne State Univ.

Address
421 E. Canfield

Elliman Bldg RM 3217

Detroit, MI 48201

Additional Reports to:

Accession Number

Family Number/Kindred Number

Patient Number

Specimen Collection Date
NO Date

Accession Date

Report Date

Interpretation
POSITIVE

Analysis of this individual's *GJB1* gene identified one reported or predicted disease-associated mutation. This result is consistent with a diagnosis of, or a predisposition to developing X-linked Charcot-Marie-Tooth (CMTX1) disease associated with *GJB1* mutations. Please refer to the Technical Results and Comments sections of this report for further information.

Technical Results

GJB1 Del Result: Deletion of all copies of exon detected
 Exons deleted: 2

GJB1 Sequencing Variants:

3 of 3 analytic segments could not be analyzed. (**Inconclusive**)

All other analytic segments analyzed were normal.

Comments

Most Significant result: This individual possesses one known or predicted disease-associated mutation in the *GJB1* gene. The mutation has been reported in the literature to be associated with X-linked Charcot-Marie-Tooth (CMTX1) disease, or is predicted to significantly disrupt the structure and function of the protein. Therefore, this result is consistent with a diagnosis of, or a predisposition to developing X-linked

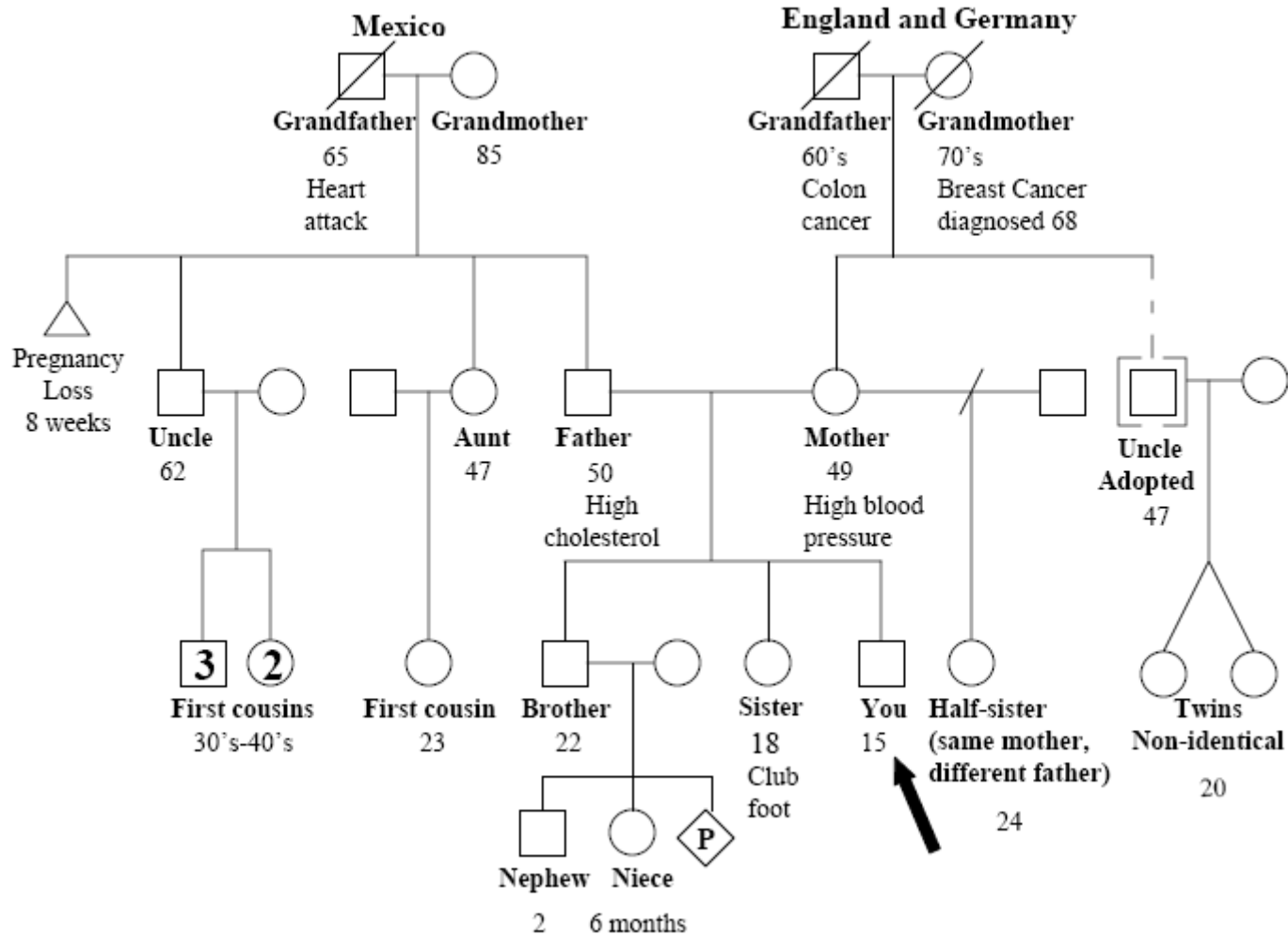
Charcot-Marie-Tooth (CMTX1) disease, associated with *GJB1* mutations. Please contact Athena Client Services at 1-800-394-4493 if you wish to consult with a Laboratory Director or a Test Counselor regarding this result.

Other variants of less significance: This analysis may also have detected other types of sequence variants as listed in the Technical Results section, a common occurrence for an analysis of this gene. However, in the context of the results reported here, the presence of additional sequence variants is generally of reduced significance. Benign polymorphisms, if identified, are considered normal sequence variants and are not reported here, but are available upon request. Please consult the Glossary for a detailed explanation of "DNA Variant Types" indicated in the Technical Results section of this report.

Follow up recommendations: This individual's family members are at risk for possessing or inheriting this mutation. Careful reconciliation of this molecular data with this person's clinical and family history is strongly recommended. Athena recommends genetic counseling for this patient and his or her family members, and consideration of testing for family members. Please contact Athena Client Services at 1-800-394-4493 or visit www.athenadiagnostics.com for further information on family member testing.

Background: X-linked Charcot-Marie-Tooth (CMTX1) disease is the second most common form of CMT, accounting for approximately 5% of CMT patients (1). It has been reported to follow an X-linked dominant mode of inheritance with variable penetrance (1), or incompletely

The Pedigree



The Pedigree

- Step one: Draw the family
- Step two: Draw an arrow to yourself
- Step three: Label ages, deaths, age at death, any chronic medical conditions, including the condition of interest
- Step four: Note maternal and paternal ethnicities
- Step five: Chronicle if there is any:
 - mental retardation, developmental delay, learning disabilities
 - birth defects
 - multiple miscarriages, infant deaths, stillbirths
 - other known genetic conditions

Questions?

Genetic Information Nondiscrimination Act (GINA)

• What does GINA do?

- Title I: Health Insurers can not:
 - Require individual/family genetic information for eligibility, coverage, underwriting, or premium-setting decisions
 - Collect genetic information to make enrollment or coverage decision
 - Require individual/family to undergo genetic testing
 - Use genetic information as a preexisting condition *
- Title II: Employers can not:
 - Use genetic information in hiring, promotion, compensation, or termination decisions
 - Use genetic information to aid in determining accessibility to training programs
 - Limit, segregate or classify an employee on the basis of genetic information
 - Request or require genetic information

• What does GINA not do?

– GINA does not regulate:

- Life Insurers
- Disability Insurers
- Long-Term Care Insurers



– GINA does not protect:

- Patients manifesting a condition:
 - If they are experiencing symptoms
 - Being treated for a condition
 - Or, if a condition has been diagnosed
- Members of the US military
- Veterans obtaining insurance through VA
- Indian Health Service



Health Insurance Portability and Accountability Act (HIPAA)

- What does HIPAA do?

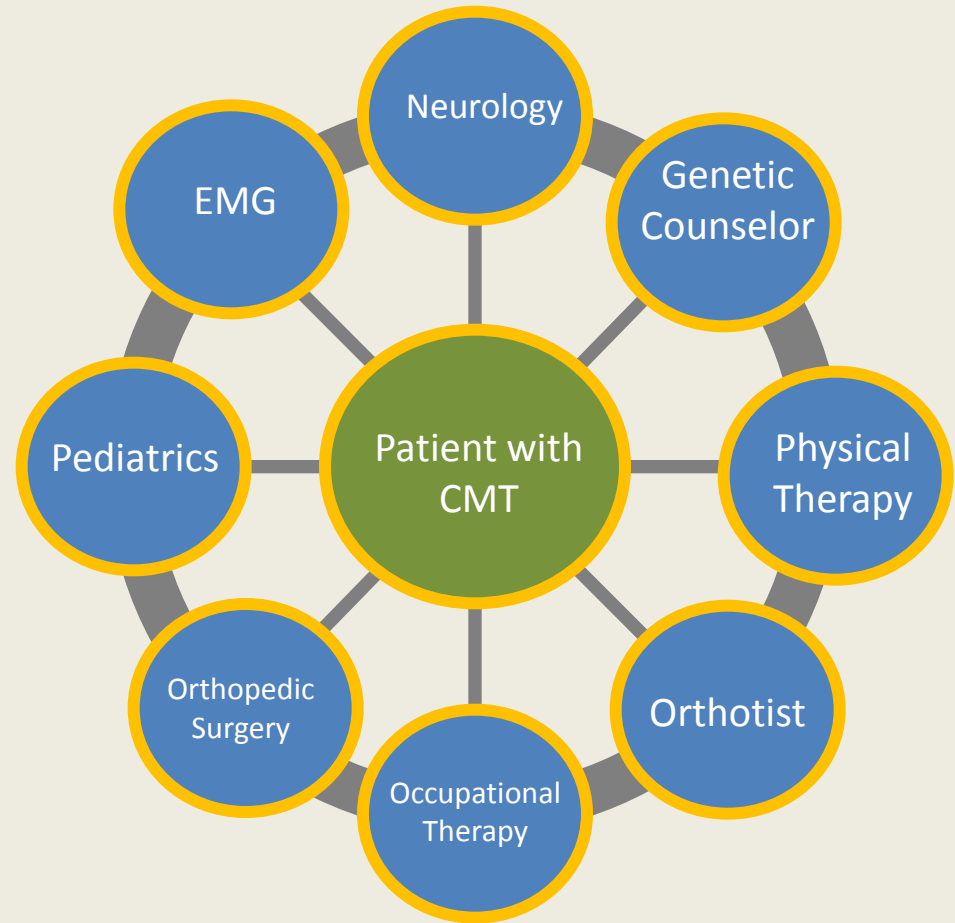
- Helps those with a preexisting condition get health coverage
 - Group Health Insurers can only use preexisting conditions to deny health coverage for up to 6 months
 - If patients did not receive medical advice, diagnosis, care, or treatment within the past 6 months, then the Health Insurer can not use that condition for exclusion
- Helps to prevent a preexisting condition from being excluded from health coverage
 - Group Health Insurers can only exclude a preexisting condition from health coverage plan for up to 12 months
 - A preexisting condition exclusion relates only to benefits for a patient's preexisting condition; patients will receive coverage for the plan's other benefits during that time
- Protects applying a preexisting condition exclusion to pregnancy, genetic information, and certain children
- Prevents Health Insurer from charging more than similarly situated individuals based on any health factors

- What does HIPAA not do?

- Does not require that employers offer health coverage
- Does not guarantee that ANY condition patients have or have had are covered
- Does not prohibit an employer from imposing a preexisting condition exclusion period if treatment for a condition has occurred during the past 6 months
- No protections for Life, Disability, or Long-Term Care Insurances

What is the CMT Clinic?

- Primary Goal: To Provide Excellent care for people with CMT
 - Diagnosis
 - Multidisciplinary care
 - Recommendations for clinical management



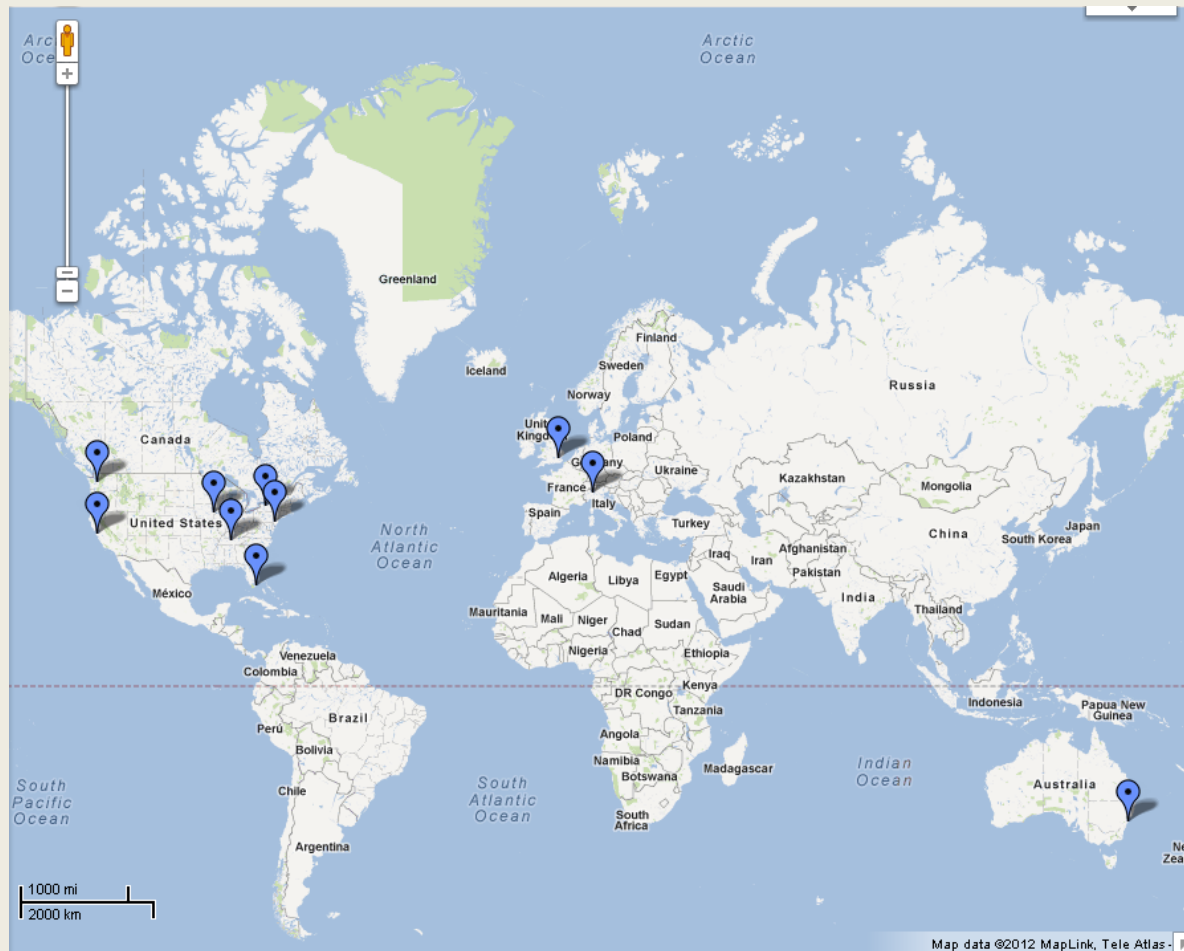
What is the CMT Clinic?

- Secondary Goal: To learn more about CMT by conducting research
 - Lead site for Inherited Neuropathy Consortium – Rare Disease Clinical Research Consortium (INC-RDCRC)
- INC-RDCRC Goals include:
 - Enrollment of patients with CMT into natural history studies
 - Conduct clinical trials of promising new drugs for the treatment of CMT
 - Establish a patient contact registry
 - Discover new laboratory markers of disease
 - Develop improved methods for studying CMT (outcome measures)
 - Work with CMT support organizations (CMTA, MDA)
 - Support other researchers by providing specimens and clinical data
 - Train new young investigators in the field of CMT
 - Construct and maintain an electronic website resource with significant information for clinicians, researchers, and patients

INC-RDCRC

<http://rarediseasesnetwork.epi.usf.edu/INC>

- Joins together 14 Sites from around the world doing research on CMT
- Collaboration of clinical data and samples to help further research
- Ultimately, improve patient care and treatment options



INC-RDCRC

<http://rarediseasesnetwork.epi.usf.edu/INC>


Inherited Neuropathies Consortium - Windows Internet Explorer

File Edit View Favorites Tools Help

http://rarediseasesnetwork.epi.usf.edu/INC/index.htm

Favorites primary, secondary, - Goo... Inherited Neuropathies ... x


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Powered by the National Institutes of Health



you can help
Rare disease research cannot move forward without the necessary participation of our patients

Inherited Neuropathies Consortium

INFORMATION FOR Patients and Families




Learn
about Inherited Neuropathies

Diseases Defined:
Charcot-Marie-Tooth Disease

Patient Glossary
Frequently Asked Questions

INFORMATION FOR Professionals



Get Involved
In INC Research

Join a Study
Find Information About Current Research

Get Involved - Stay informed of INC research studies by Joining the Contact Registry!

Physicians, Clinicians & Researchers

Diseases In Depth:
Disease Descriptions for the Medical Community

Refer patients to the Contact Registry
Participating Clinical Centers
INC Opportunities: Inherited Neuropathy Training Fellowship

