EMERY-DREIFUSS MUSCULAR DYSTROPHY (EDMD): GENETIC COUNSELING ASPECT

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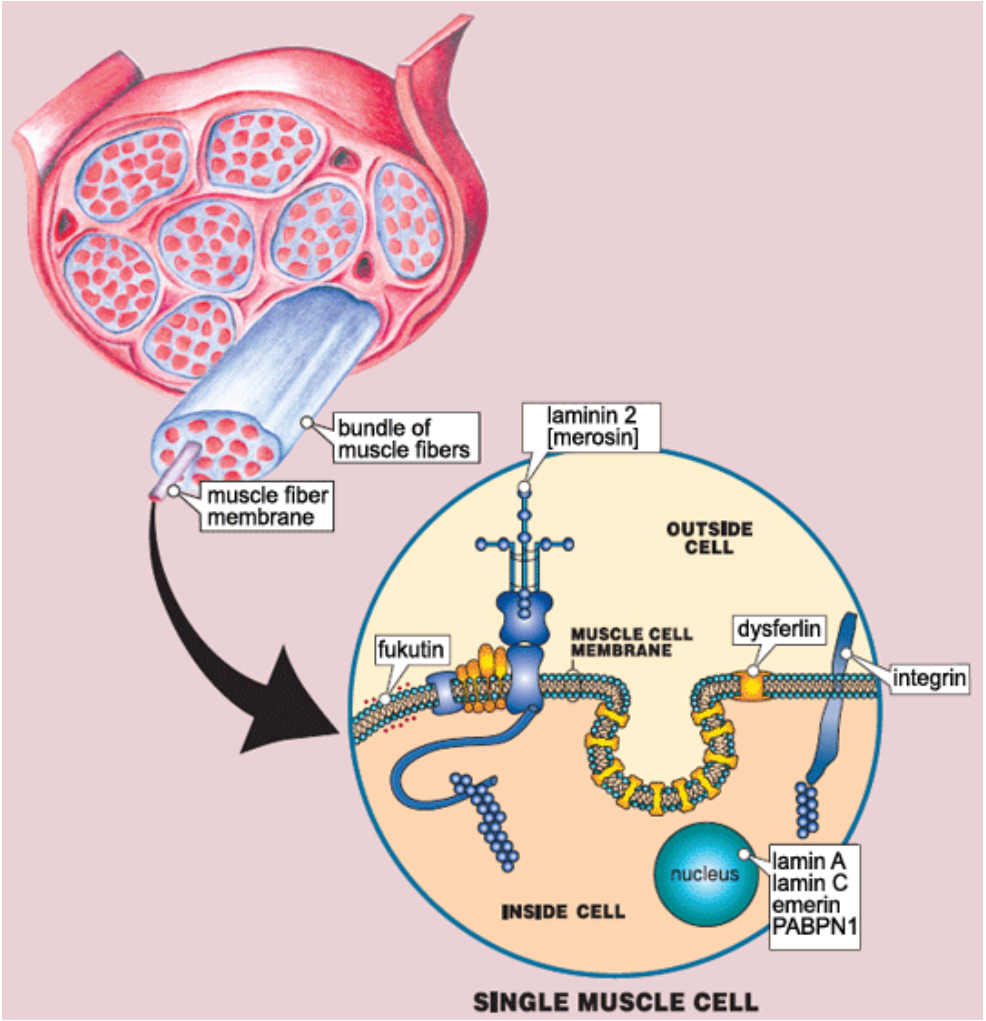
EMERY-DREIFUSS MUSCULAR DYSTROPHY (EDMD)

- EDMD is rare muscular dystrophy with variable phenotype
- Prevalence in all age groups was 0.39/100,000
- EMD (Emerin) and LMNA (Lamin A/C) is the two most causative gene

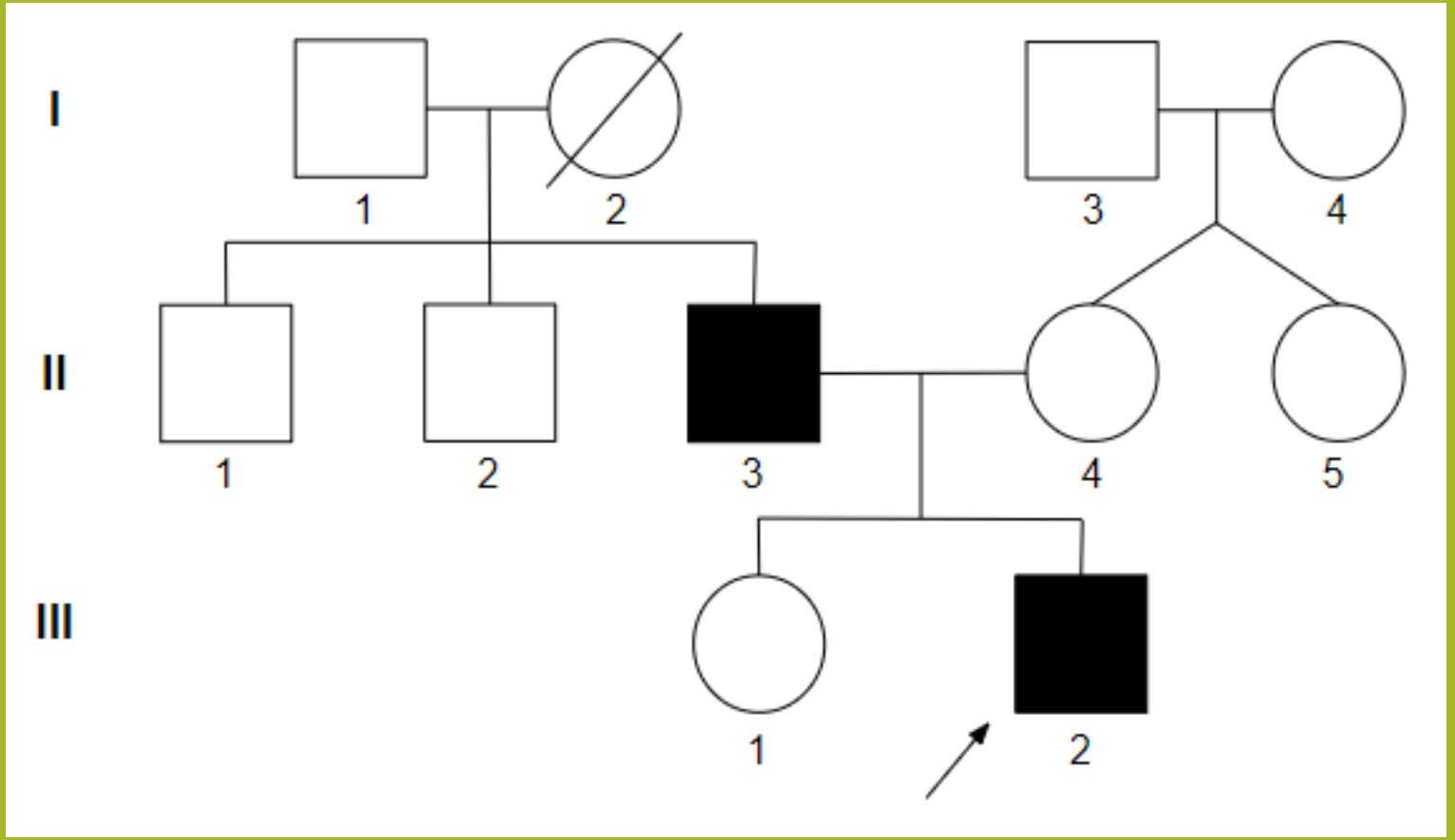


[1]Lee Y, Lee JH, Park HJ, Choi YC. Early-Onset LMNA-Associated Muscular Dystrophy with Later Involvement of Contracture. J Clin Neurol. 2017;13(4):405-410. doi:10.3988/jcn.2017.13.4.405
[2]Heller SA, Shih R, Kalra R, Kang PB. Emery-Dreifuss muscular dystrophy. *Muscle Nerve*. 2020;61(4):436-448. doi:10.1002/mus.26782

CASE PRESENTATION

- A 2 years 10-month-old boy presented with lower extremities weakness.
- No cognitive impairment, seizure, visual nor auditory impairment, and no bowel or bladder dysfunction.
- He walked at 12 months. Other developmental milestones are also unremarkable.
- Muscle strength was 4/5 for upper and lower limb. Gower sign (+)
- Cardiorespiratory examination was unremarkable

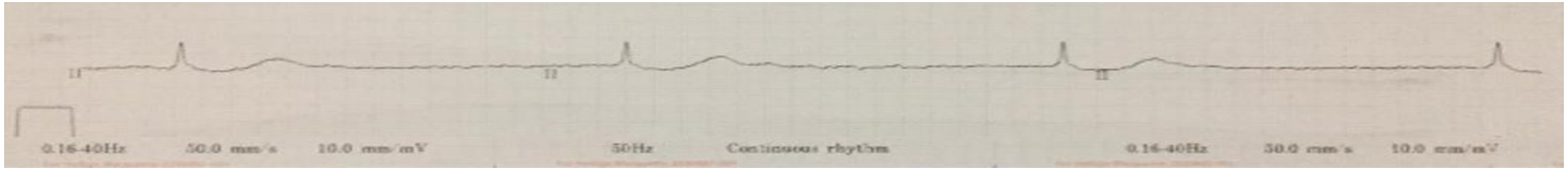
FAMILY HISTORY



FAMILY HISTORY

The father:

- Toe walking
- Rigid neck
- Elbow and ankle contracture
- Since 8-year-old
- HR 53 bpm (bradycardia)
- **Echo**: hypokinetic, dilatation of heart muscles, thrombus suspicion in the left ventricle.



SUPPORTING EXAMINATION

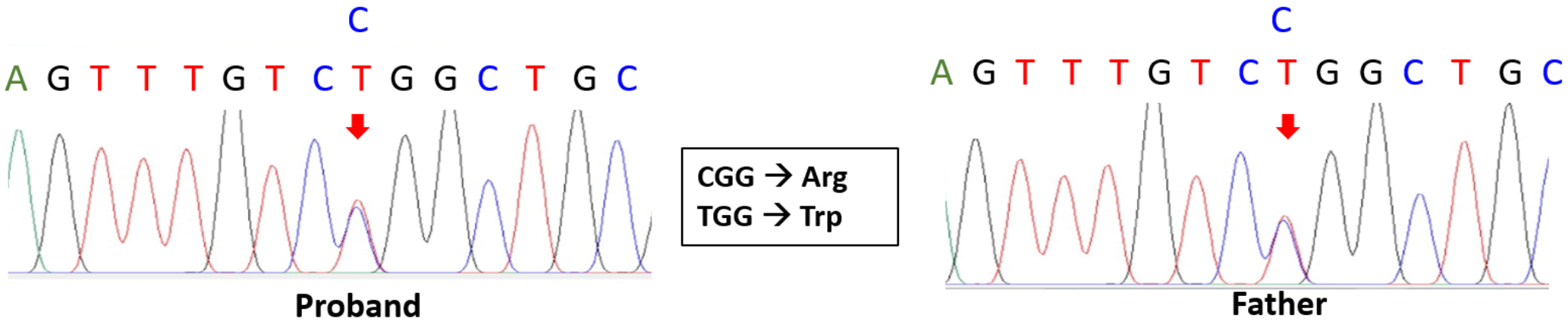
- **Laboratory**:
  - Increased creatinine kinase = 2,485 IU/L
  - Increased LDH = 1,078 IU/L
- **ECG**: no abnormalities
- **Echocardiography**: normal structure and function of heart

Whole Exome Sequencing Result

- Variant coordinates LMNA 150330.0002 Chr 1:156106204
- variant description c.1357C>T
- p.Arg453Trp
- heterozygous (exon 7)

AD Emery Dreifuss Muscular Dystrophy

Sanger Sequencing Result



Mutation detection by DNA sequencing. Heterozygosity is revealed as two overlapping peaks (red arrow)

DISCUSSION

- Triad classic form of EDMD are early contractures, progressive muscle weakness and atrophy, and cardiac abnormalities
- The pattern of contractures most prominently involves neck extension, elbow flexion, and heel cord tightening

INHERITANCE PATTERN

- Autosomal dominant
  - LMNA mutation ~28%
- Autosomal recessive
  - LMNA-associated have been reported
- X-linked recessive
  - EMD gene (8%)
  - FHL1 gene (2%)

Heller SA, Shih R, Kalra R, Kang PB. Emery-Dreifuss muscular dystrophy. *Muscle Nerve*. 2020;61(4):436-448. doi:10.1002/mus.26782
Kovalchuk T, Yakovleva E, Fetisova S, Vershinina T, Lebedeva V, Lyubimtseva T, *et al*. (2021) Case Reports: Emery-Dreifuss Muscular Dystrophy Presenting as a Heart Rhythm Disorders in Children. Front. Cardiovasc. Med. 8:668231. doi: 10.3389/fcvm.2021.668231

TABLE 1 EDMD subtypes

Subtype	Gene	Protein	Inheritance	Age of onset	Muscle weakness	Contractures	Cardiac Involvement
1	*EMD*	Emerin	X-linked recessive	4–5 years	-Develops early in course -Usually slowly progressive -Often humeroperoneal distribution in early stages	-Typically the *initial* symptom -Most often involving the elbows, Achilles tendons, cervical spinal muscles	-Typically emerges *after* skeletal muscle weakness and contractures -Includes conduction defects, arrhythmias, *hypertrophic* cardiomyopathy
2	*LMNA*	LMNA	Autosomal Dominant	Usually 3–6 years, but rarely before age 3	-May be the *initial* symptom -Unpredictable severity, but frequently severe enough to result in loss of ambulation -Preferential involvement of biceps brachii may be a feature	Develop *after* muscle weakness	-Often the *initial* manifestation of disease -Includes conduction defects, arrhythmias, *dilated* cardiomyopathy
3	*LMNA*	LMNA	Autosomal Recessive	-Variable -Can range from 14 months to 24 years	-Variable pattern, including limb-girdle or diffuse muscle involvement -Variable severity, but can be severe enough to lead to immobilization	Present, with variable involvement of Achilles tendons, elbows, neck	-Variable -If present, can include supraventricular and/or ventricular arrhythmias
4	**SYNE1*	Nesprin-1	Autosomal Dominant	11 years old	Gradually progressive	Present	Variable
5	*SYNE2*	Nesprin-2	Autosomal Dominant	Childhood	Proximal muscle weakness	Usually *not* present	-Usually present -Includes arrhythmias, *dilated* cardiomyopathy, heart failure
6	*FHL1*	FHL1	X-linked recessive	Most range from 4 to 14 years, rarely in adulthood	-Variable pattern -Typically involves some combination of scapular, humeral, pelvic, peroneal, and/or axial regions -May have facial, bulbar, or respiratory involvement	-Usually present -May include rigid spine	-Usually present -Occurs *after* skeletal muscle manifestations -Includes conduction defects, arrhythmias, *hypertrophic* cardiomyopathy
7	*TMEM43*	LUMA	Autosomal Dominant	Adulthood	Proximal muscle weakness and atrophy	Not present in reported cases	Cardiac conduction defects
N/A	**SUN1*	SUN domain-containing protein 1	Autosomal Recessive	10 years old	Mild	Spine rigidity	None
N/A	***SUN2*	SUN domain-containing protein 2	NA	NA	NA	NA	NA
N/A	*TTN*	Titin	Autosomal Recessive	Infantile or childhood	-Limb-girdle pattern -Severe and progressive, leading to permanent loss of ambulation	Develop early in course	Variable

*Clinical features associated with a primary mutation of these genes causing an EDMD phenotype are based on a single reported case.
**Not well-established.

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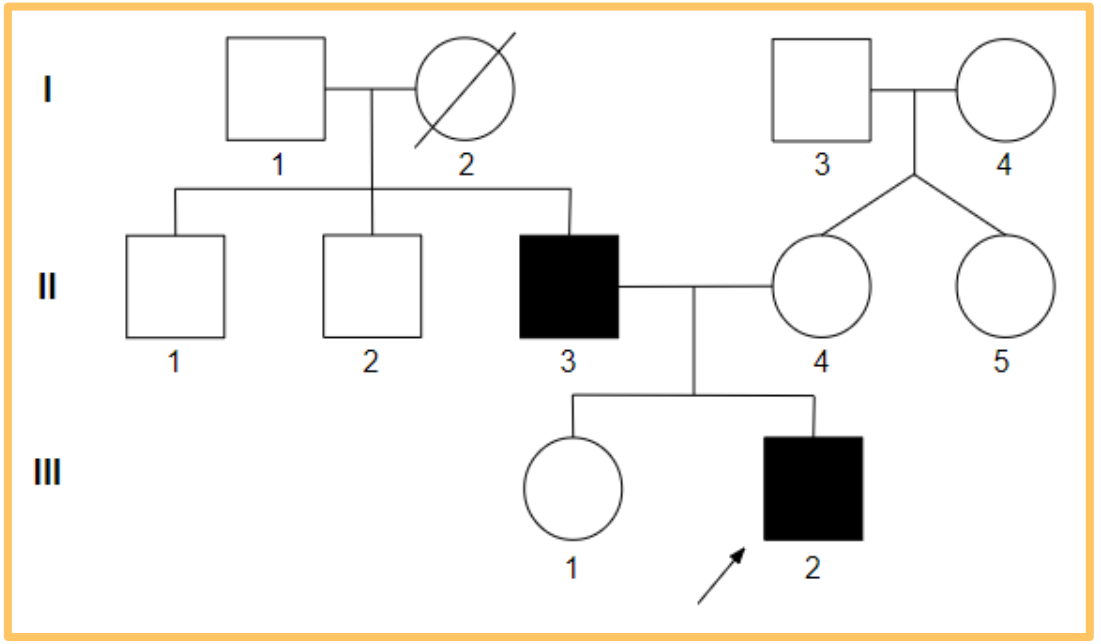
GENETIC COUNSELING

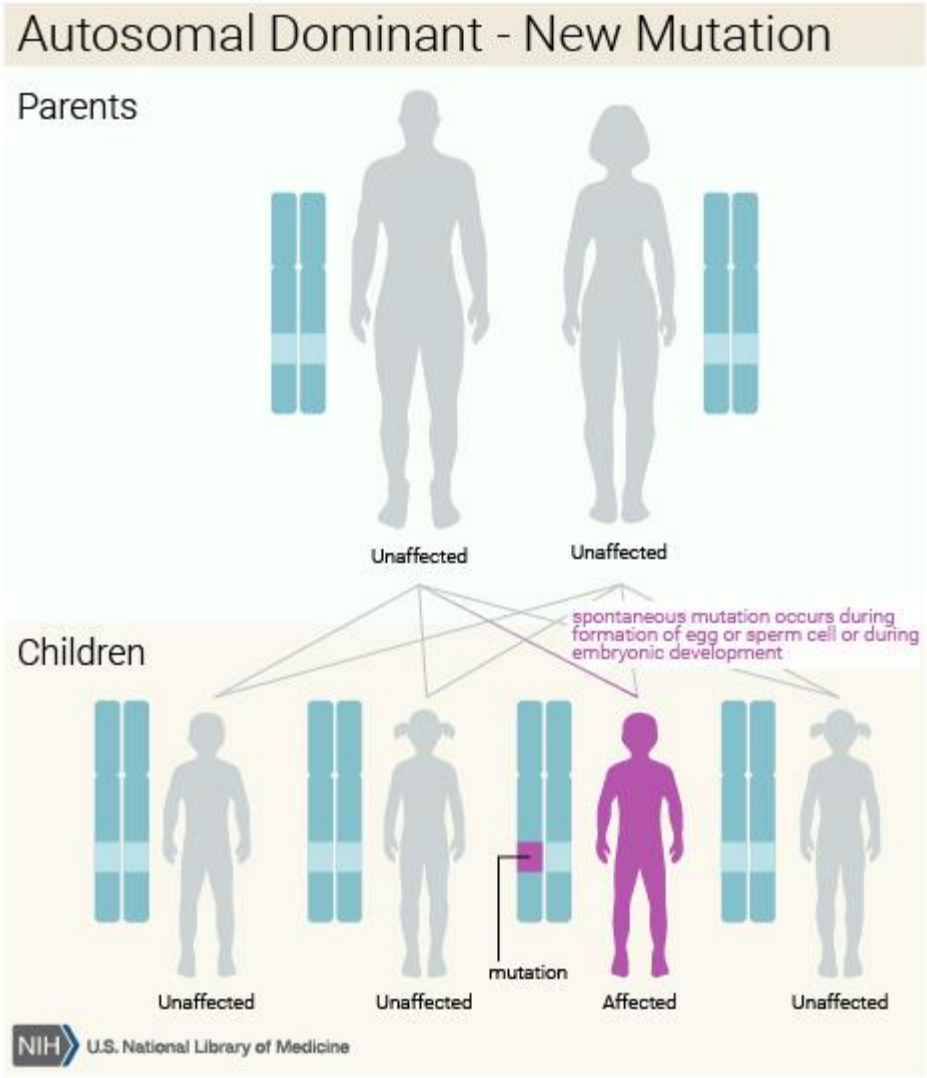
- Family history
- Modes of inheritance
- Pretest counseling
- Post-test counseling

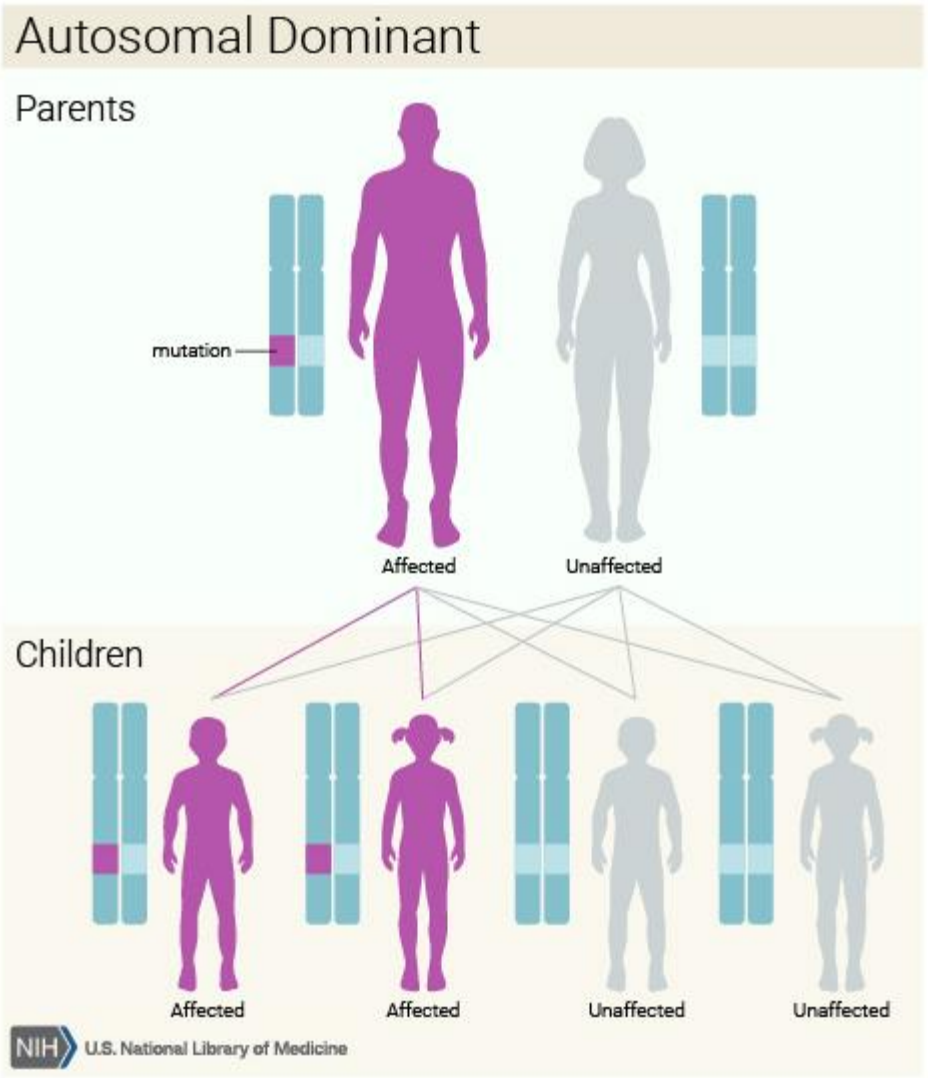


INHERITANCE PATTERN
- Patient has an affected parent
- Male-male transmission

→ Autosomal dominant

Sadat, R., & Emrick, L. (2021). Genetic Testing and Counseling in Child Neurology. Neurologic Clinics, 39(3), 705–717. doi:10.1016/j.ncl.2021.05.003





65% AD EDMD caused by new mutations

PRETEST COUNSELING

- Description of the test and its purpose
- What type of sampe is needed
- Possible test result
- When and to whom result will be reported
- Genetic counselor referral is considered if the health care provider does not have knowledge or expertise

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POST-TEST COUNSELING

- Management options
- Implication for relatives and reproductive risks
- Emotional impact of results and additional counseling referrals
- Discussion of additional testing or screening if applicable

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SUMMARY

<u>Genetic counseling for patient with EDMD include:</u>

- Family history and inheritance pattern of the disease
- Information about genetic testing, purpose, and possible result, before the genetic testing was done
- Management option:
  - Aggressive supportive management is essential
  - Cardiologist consultation is mandatory
  - Surgical management is also considered
- Emotional support is considered for the patient and the family

THANKYOU