



**OPMD Patient and Family
Conference
November 12, 2011**

Sarah Youssof, MD



- Carol Smith and MDA staff
- Leslie Morrison, MD
- Sarah Youssof, MD
- OPMD clinic staff
 - Carol Romero-Clark



Many questions from guests:

- Treatment of swallowing problems
- Other throat and voice issues
- Mucus and phlegm
- Eyelid drooping
- Fatigue and exercise
- Genetics
- Research/stem cells
- Nutrition/general



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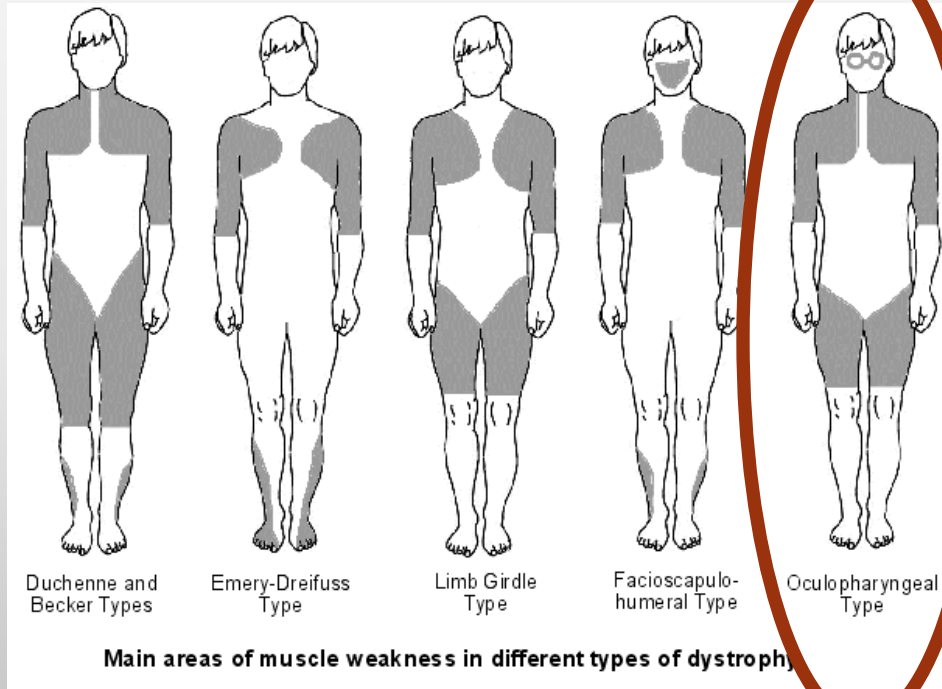
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Oculopharyngeal Muscular Dystrophy

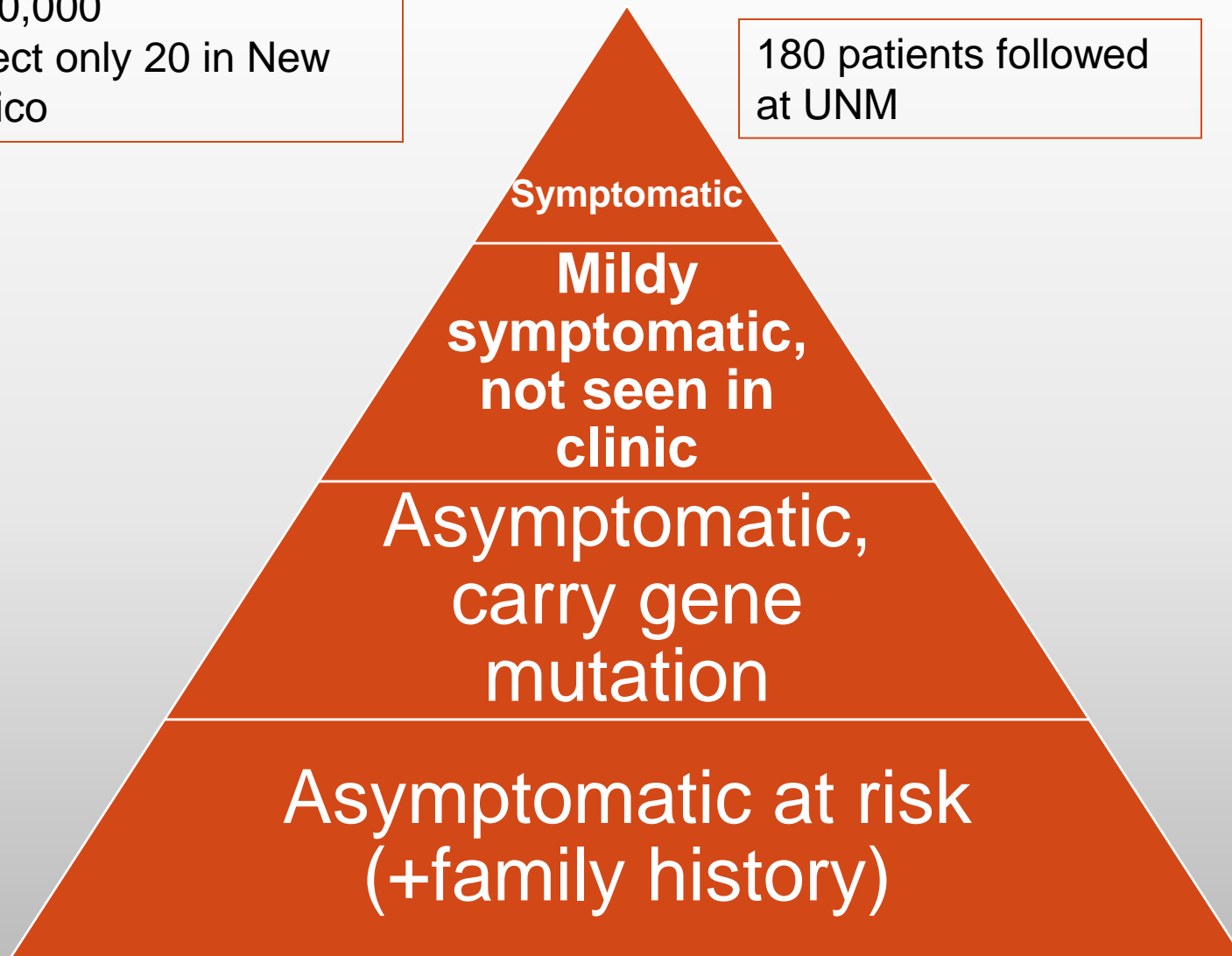
- “What does ‘**dystrophy**’ mean”?
- Dystrophy means an inherited (genetic) condition where there is breakdown of muscle
- This leads to progressive weakness
- “Dystrophy” itself is not caused by poor nutrition (although poor nutrition can also lead to muscle loss)

Muscular Dystrophy

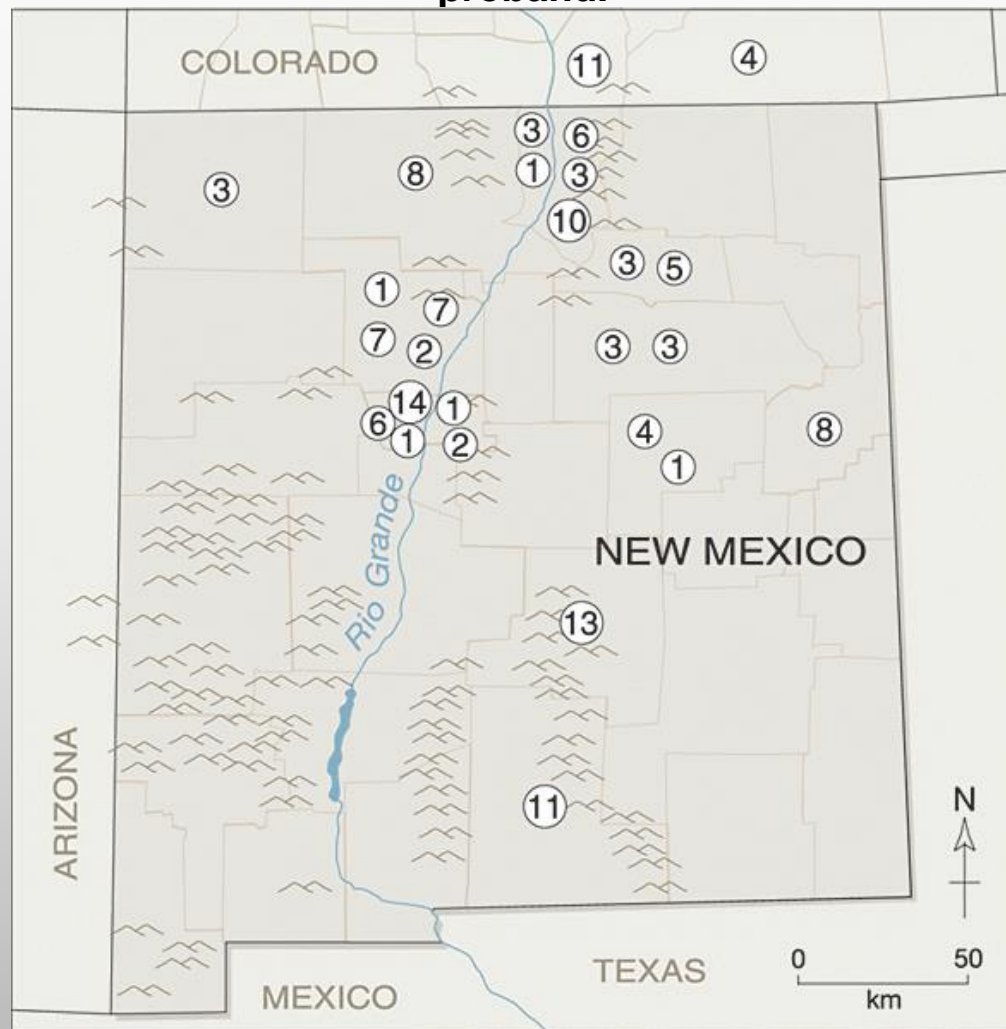


Worldwide prevalence
1:100,000
Expect only 20 in New
Mexico

180 patients followed
at UNM



Distribution of New Mexico OPMD Kindreds: Geographical distribution of 27 of the New Mexico oculopharyngeal muscular dystrophy (OPMD) kindreds by original location of proband.



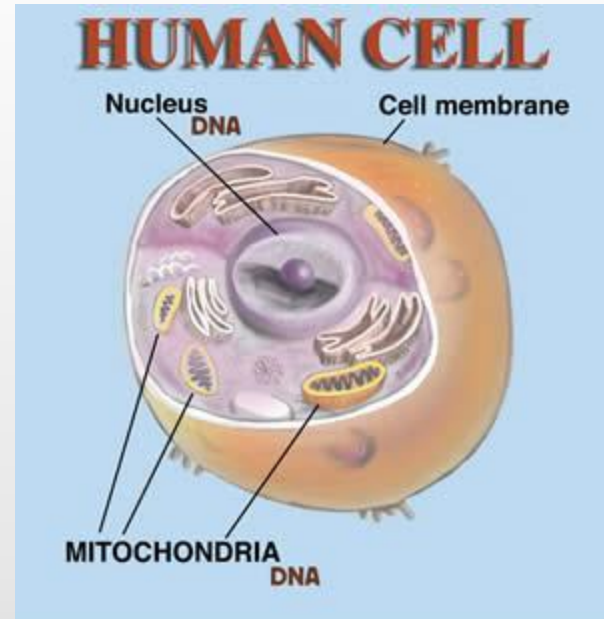
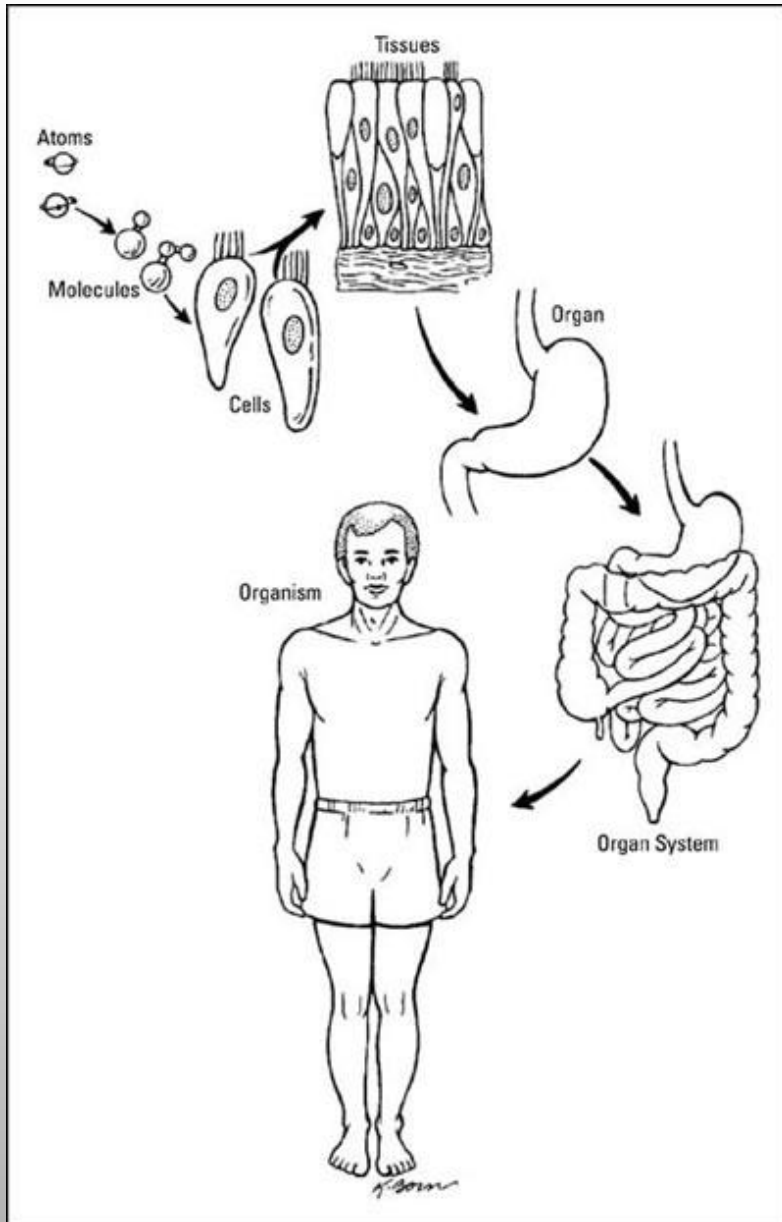
Becher, M. W. et al. JAMA 2001;286:2437-2440

Autosomal dominant form of OPMD, incidence



Genetics





Chromosomes contain DNA



14

- Chorea, hereditary benign
- Meningioma-expressed antigen
- Myopathy, distal
- Defender against cell death
- Temperature-sensitive apoptosis
- Lysinuric protein intolerance
- Ichthyosis, lamellar, autosomal recessive
- Ichthyosiform erythroderma, congenital
- Spastic paraplegia
- Deafness, autosomal recessive
- Deafness, autosomal dominant
- Meniere disease
- Arrhythmogenic right ventricular dysplasia
- Immunodeficiency
- Glycogen storage disease
- Phenylketonuria, atypical
- Dystonia, DOPA-responsive
- Leber congenital amaurosis, type III
- Tyrosinemia, type Ib
- Alzheimer disease
- Machado-Joseph disease
- Ovarian cancer
- Microphthalmia, autosomal recessive
- Cerebrovascular disease, occlusive
- Leukemia/lymphoma, T-cell
- Agammaglobulinemia
- Achromatopsia

105 million base pairs



- Basal ganglia calcification (Fahr disease)
- Multinodular goiter
- Retinitis pigmentosa, autosomal dominant
- Leukemia/lymphoma, T-cell
- Oculopharyngeal muscular dystrophy
- APEX nuclease (multifunctional DNA repair enzyme)
- Cardiomyopathy, familial hypertrophic
- Oligodontia
- Goiter, familial
- Carbohydrate-deficient glycoprotein syndrome, type II
- Elliptocytosis
- Spherocytosis
- Anemia, neonatal hemolytic, fatal and near-fatal
- Arrhythmogenic right ventricular dysplasia
- Marfan syndrome, atypical
- DNA mismatch repair gene MLH3
- Diabetes mellitus, insulin-dependent
- Krabbe disease
- Hypothyroidism, congenital
- Thyroid adenoma, hyperfunctioning
- Graves disease
- Hyperthyroidism, congenital
- Usher syndrome, autosomal recessive
- Emphysema-cirrhosis
- Hemorrhagic diathesis
- X-ray repair

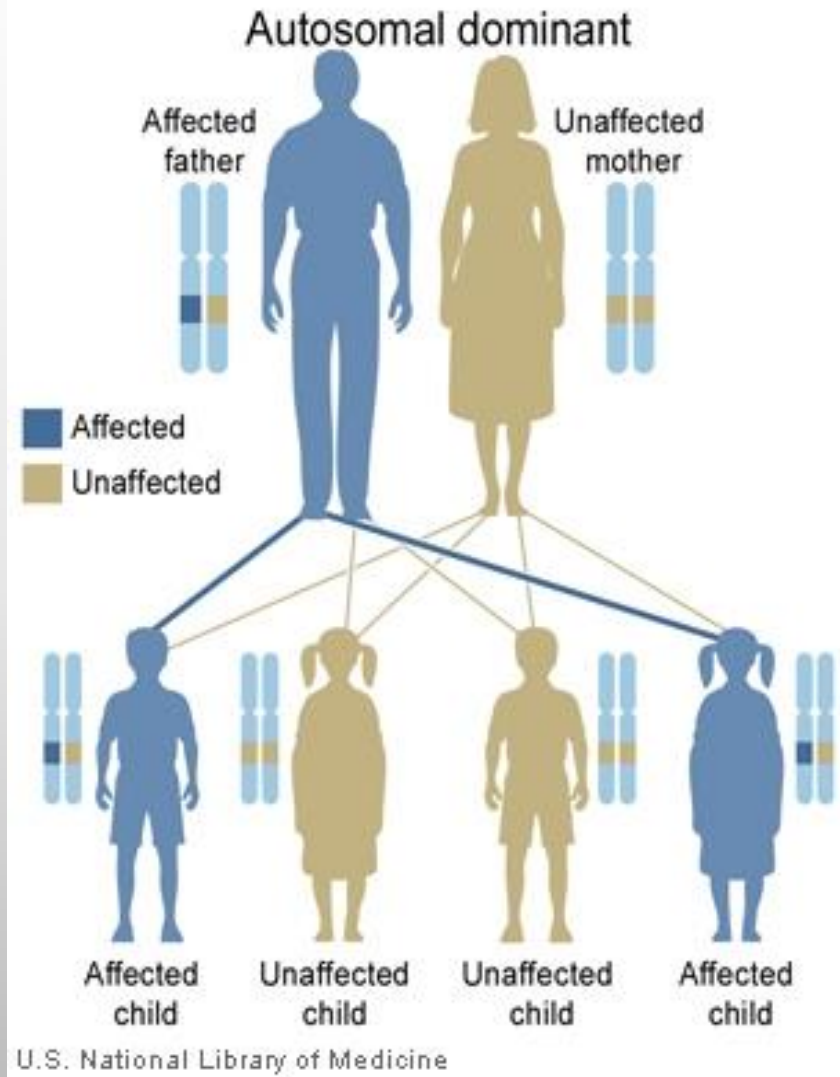
PABPN1
Gene
Chromosome
14q11

Genetics and OPMD



We have 2 copies of each gene: one inherited from our mother, and the other from our father

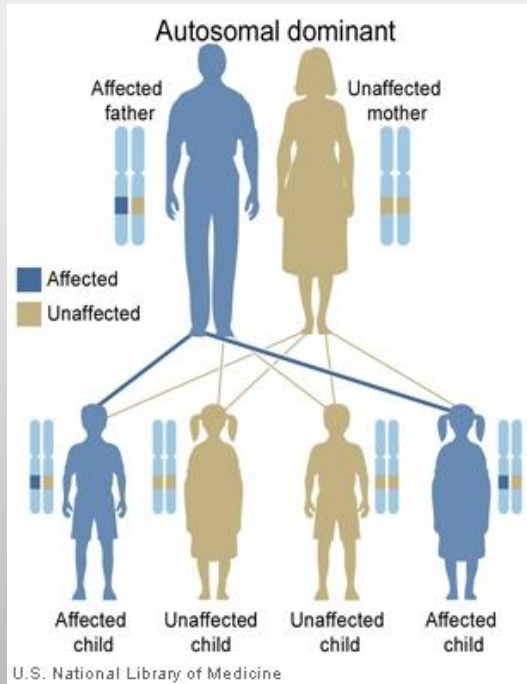
In typical OPMD, **one copy has a mutation** (and the other copy is normal)



Generally, it takes one affected parent to pass on the disease.

On average, 50% of the children will be affected

- Can OPMD be passed **by** males as well as females **to** males as well as females?



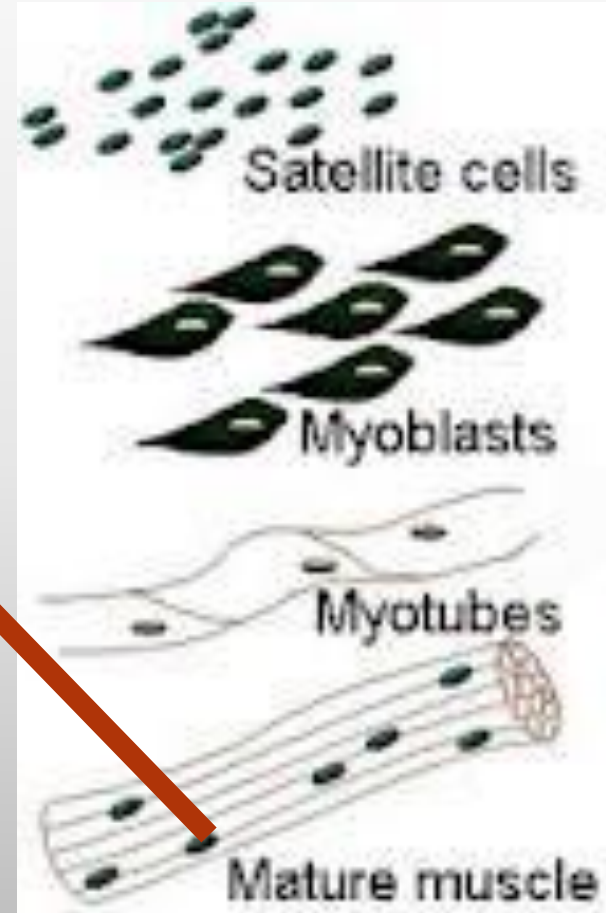
Yes – either parent (mom or dad) can pass OPMD to children (son or daughter)

- “There are eight siblings in the family, out of the eight, four had all the signs, symptoms and suffered from OPMD. The four that didn't have signs or symptoms - **can they still be carriers of the disease without showing any symptoms?**”
- A person who carries the typical mutation will develop the symptoms assuming he/she lives into their 50s/60s

- “Of the four siblings not showing any signs or symptoms, what is the possibility of their children or grandchildren getting OPMD?”

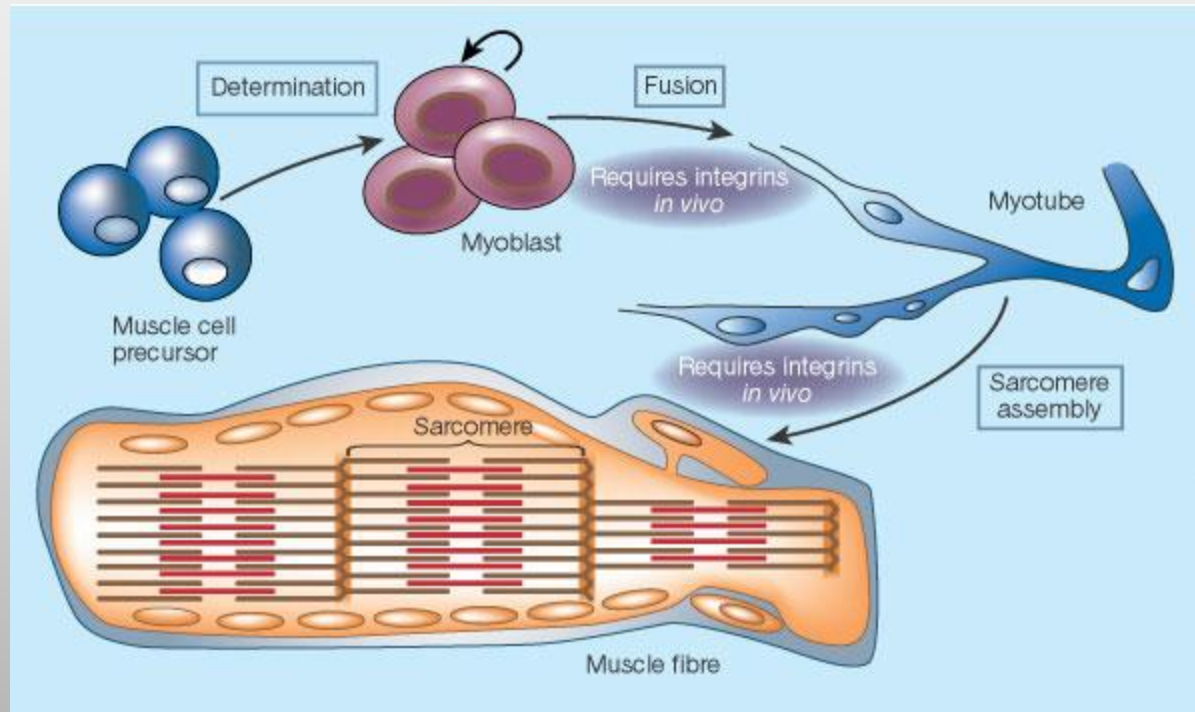
Depends on how old the 4 siblings are – if they are 50-60 yo, with no symptoms, then they probably do not have the disease, and therefore their children won't have the disease.

If the siblings are less than 50 yo, then the only way to know for sure that they don't have the disease is to get the blood test (genetic test) for OPMD. If they test negative, then their children and grandchildren won't have the disease.



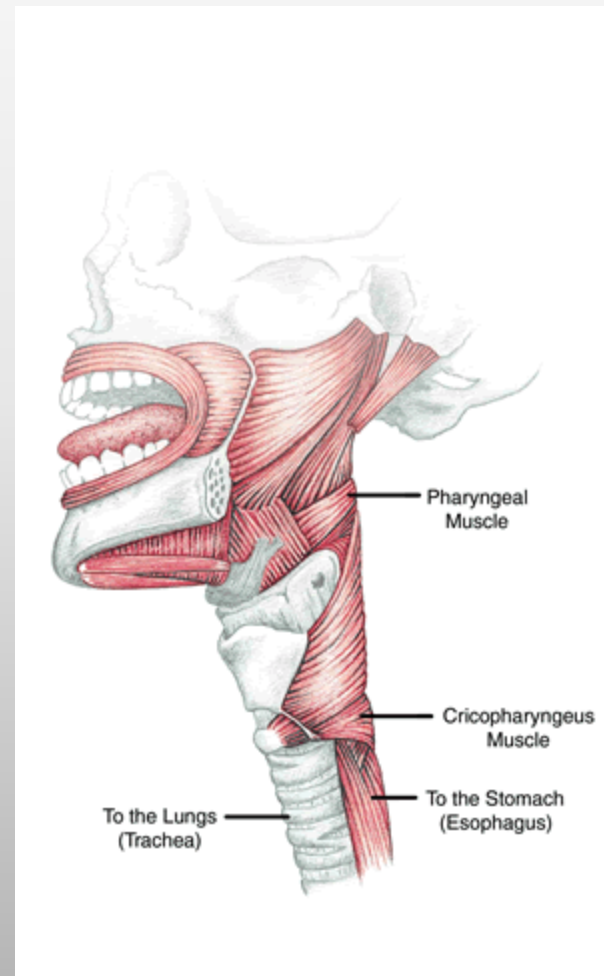
- In OPMD, muscle regeneration might **not** occur normally. This may be because **MYOBLASTS** (“baby muscles”) do not develop normally

(Apponi 2010)

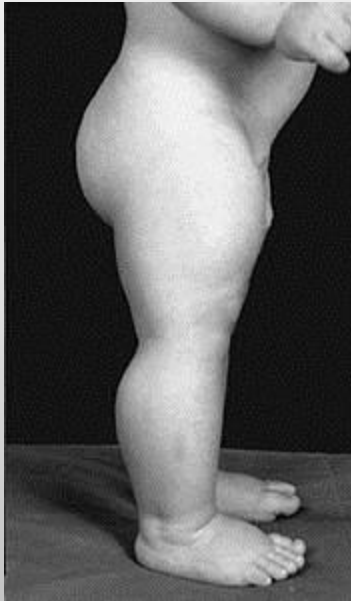


Myoblast transplantation

- Transplantation of myoblasts from a normal muscle into pharyngeal muscles
- Phase I,II clinical trial done (Paris, France)
 - Done with a cricopharyngeal myotomy
 - Results not published



Myostatin Inhibition



Long-Term Systemic Myostatin Inhibition via Liver-Targeted Gene Transfer in Golden Retriever Muscular Dystrophy

Lawrence T. Bish,^{1,*} Meg M. Sleeper,^{2,*} Sean C. Forbes,³ Kevin J. Morine,¹ Caryn Reynolds,²
Gretchen E. Singletary,² Dennis Trafny,² Jennifer Pham,¹ Janet Bogan,⁴ Joe N. Kornegay,⁴
Krista Vandeborne,³ Glenn A. Walter,⁵ and H. Lee Sweeney¹

HUMAN GENE THERAPY 22:1–12 (XXXXX 2011)





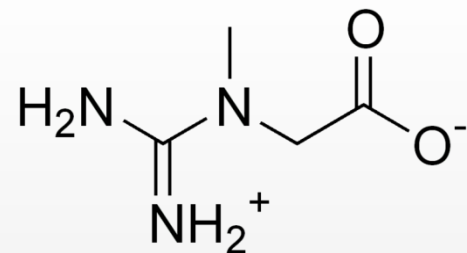
**This afternoon:
"Patient and family experiences"**

**Share your thoughts on living with
OPMD**



Question and Answer Session

Creatine



- Is there a relationship between creatine and OPMD?
- Creatine is a nitrogenous organic acid
- The body can make creatine on its own from amino acids in the diet
- Creatine also enters the body from foods, mainly meat
- It is mostly stored in skeletal muscle and helps supply energy to the muscle
- Supplements are used by athletes and body builders who want to build muscle mass. Usual daily dose is 2-5 grams per day

Coenzyme Q-10

- Found in meat (liver), fish (salmon and tuna), vegetable oils, whole grains, avocado, broccoli, grapes, and cauliflower
- Important for energy production by mitochondria
- Anti-oxidant

- Not specifically tested in OPMD
- For adults 19 years and older: recommended dose for CoQ10 supplementation is 30 - 200 mg daily

Medication safety

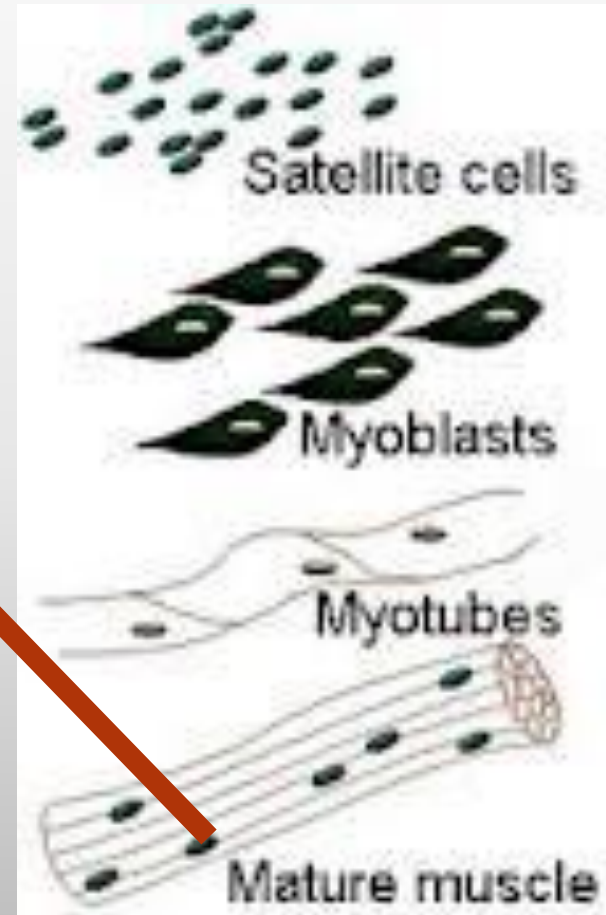
- Neurontin
- Oxycodone
- Percocet



Future Directions in OPMD

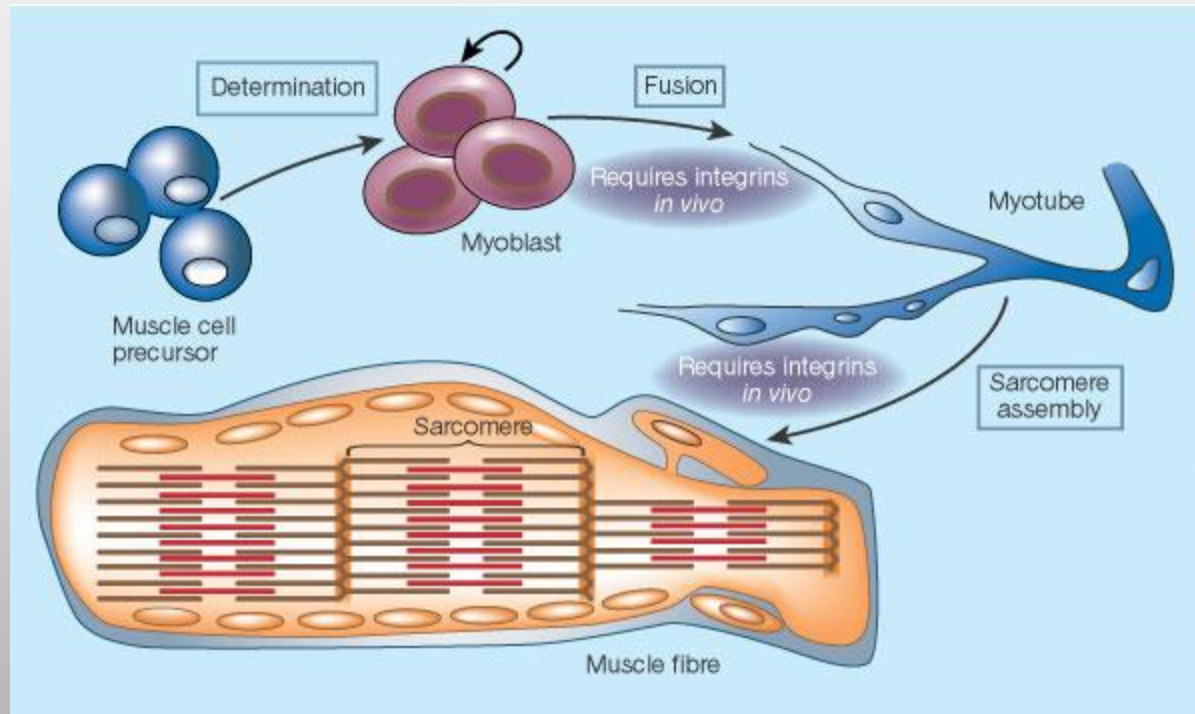
November 12, 2011

Sarah Youssof, MD



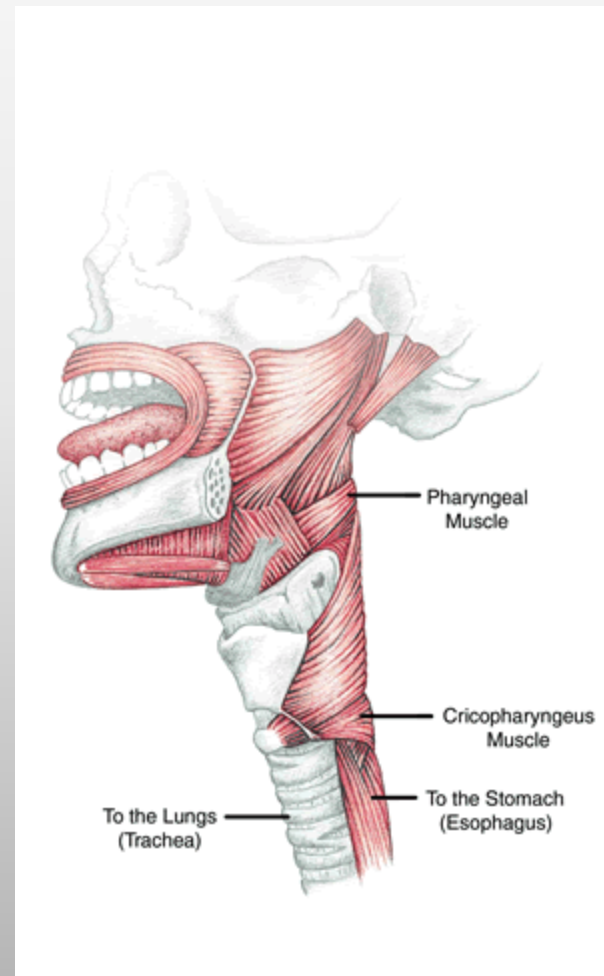
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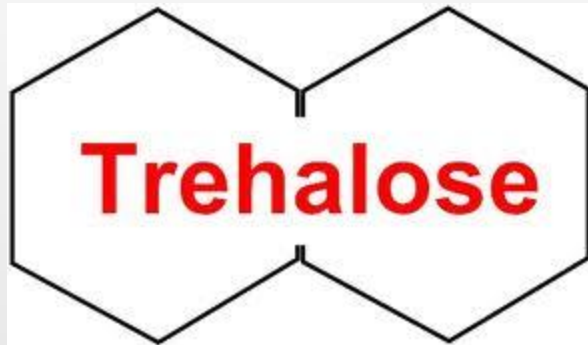


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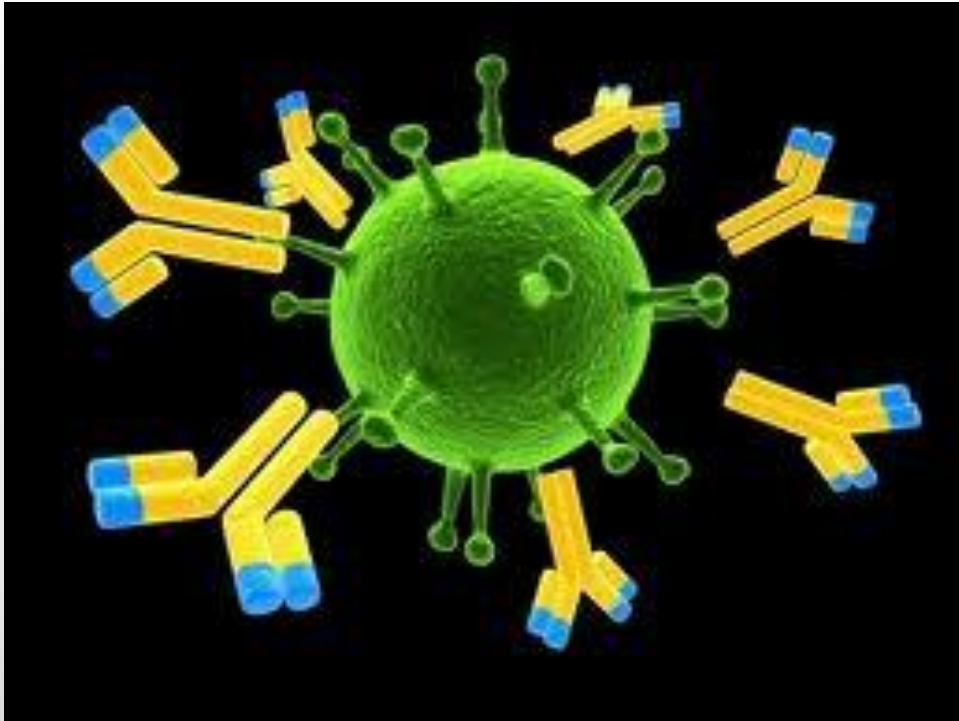
Special form of sugar

Reduced aggregate formation and delayed pathology in mouse model of OPMD (Davies et al, 2006)



Doxycycline – delayed toxicity of the OPMD mutation in mouse model (Davies et al, 2005)

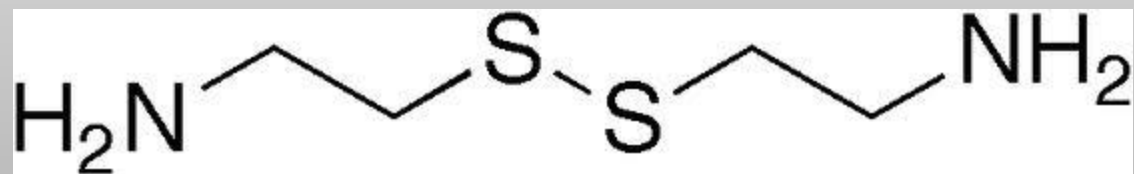
Effect may be due to reduced nuclear aggregates and reduced apoptosis



Developing intracellular single-domain antibodies (engineered from antibodies from llamas) that bind PABPN1 and prevent its aggregation in nucleus – cellular model of OPMD (Verheesen 2006, Chartier 2009)

Cystamine

- Inhibits transglutaminase 2
- Protects against the toxicity of mutant PABPN1
- Led to improvement in mice with OPMD
 - Davies (2010)



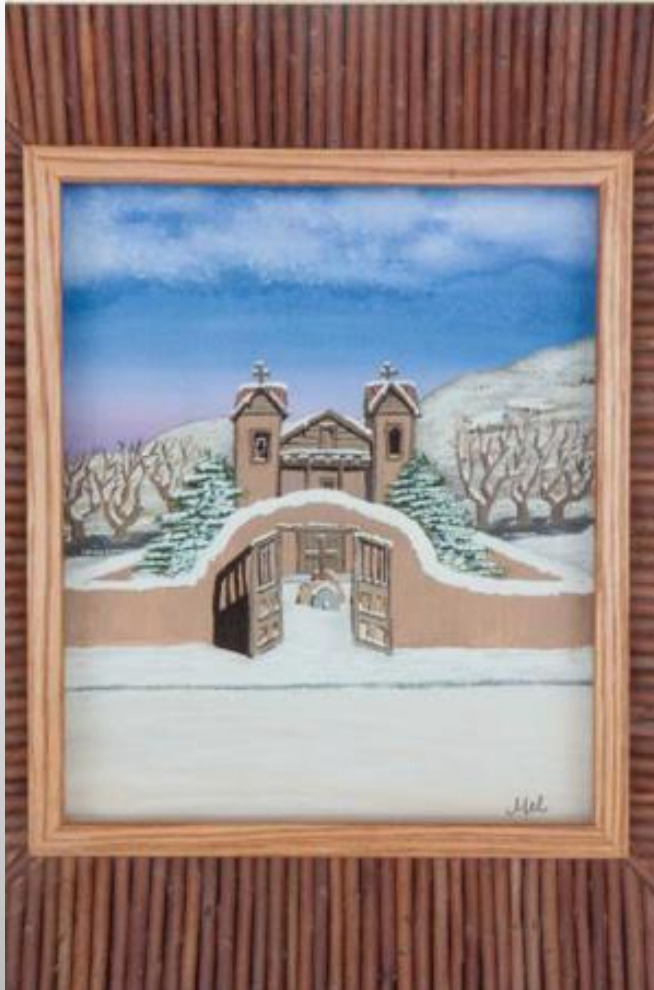
“Dysphagia in OPMD –
Evaluation, Endoscopic
Examination of Swallowing,
Treatment and Long Term
Follow-up”

Study being done in Israel

2009-present

Evaluating benefit of
cricopharyngeal myotomy





Melecio Fresquez of
(Española, N.M.)
(Suffers from FSHD)

“El Santuario de
Chimayo”

Muscular Dystrophy
Association’s Art
Collection