Marfan Syndrome

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Physiology

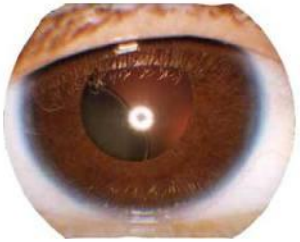


Fig 1

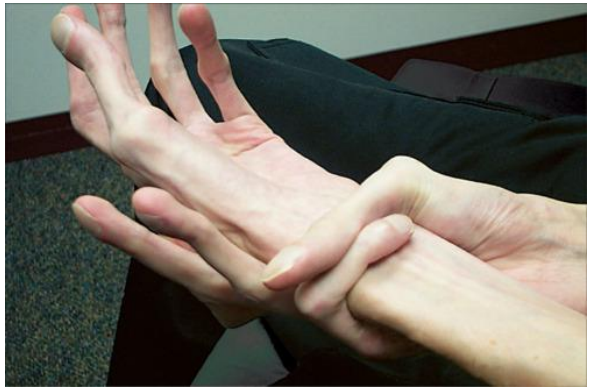


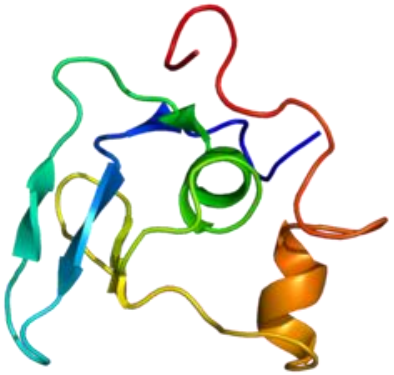
Fig 2

- Affects ~ 1/15,000 people
- Early onset: childhood
- Multisystem disorder; Occurs with variable expressivity
  - Symptoms/severity vary from person to person
  - Symptoms (usually) stay relatively consistent within a family, but severity may still vary
- Symptoms worsen with age; may eventually lead to early death
- Some common symptoms include:
  - Cardiovascular: Aortic dissection(tearing in the aortic wall), Mitral valve prolapse (Valve does not close properly)
  - Pulmonary: Spontaneous pneumothorax (Air escapes from lungs into chest cavity)
  - Ocular: Ectopia lentis (Dislocation of the lens), Myopia(Near-sightedness)
  - Skeletal: Tall, arm span : height ratio > 1.05, Arachnodactyly (long fingers), Scoliosis (Curved spine)
  - Dural: Dural Ectasia (Enlargement of the Dura)

Fig 3

Molecular Cause

Fig 4



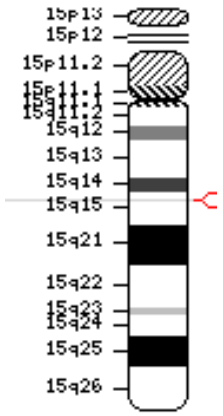


Fig 5

- Autosomal Dominant
  - Any child with one affected parent has a 50% chance of inheritance
  - Those with two have a 75% chance, and a more severe case if they do
  - Up to 30% of cases can be sporadic
- Mutation in chromosome 15, at point **15q21.1**
  - Encodes for FBN1 gene, which produces fibrillin-1
  - Affects synthesis, processing, secretion, polymerization, or stability of fibrillin-1
- Fibrillin-1 polymerizes to form micro fibrils
- Altered fibrillin-1 leads to altered microfibrils, which make up connective tissue, thus affecting stability
- Microfibrils also inactivate excess TGF-ß (Transforming Growth Factor-Beta) , which regulate cell functions
- Over expression in TGF-ß causes a decrease in elasticity of connective tissue
- No definitive genotype –phenotype correlations
  - Many responsible mutations: In one study, “We detected 49 different FBN1 mutations, 30 (62%) of which were novel. The mutations comprised 38 substitutions (78%), 10 deletions (20%), and one duplication (2%). There were 28 missense (57%), nine frameshift (18%), eight splice site (16%), and four nonsense mutations (8 %) “(Biggin).

Current Treatments

- No conclusive blood diagnosis
- Diagnosis by symptoms
  - Having multiple defining symptoms of marfans is the only definitive diagnosis, however, it can be confused with other similar connective tissue disorders.
- No cure; as treatments improved, survival rates did as well.
- Frequent check ups
  - Catch new/ worsening symptoms early- start treatment early
- Treatment individualized as per symptoms shown
  - ie. If one patient showed scoliosis, they would be given a brace, but those that do not show this symptom, do not need one.
- Beta / calcium channel blockers –Lowers blood pressure, which lowers the chances for aortic damage
- Surgery- can repair/ replace most effected parts.
  - Heart, eye, spinal, etc. , depending on the symptoms
- Limitations:
  - Only treats symptoms, not the cause
  - May need more treatment as the disease progresses
  - Surgery still has the same risks: infections, rejection of parts
- Therapies under study:
  - Losartin , an angiotensin II type 1 receptor (AT1) blocker used to lower blood pressure, has been tested in mice with with Marfans and heart defects, to promising results.(Negates TGF-ß receptors, thereby negating excess TGF-ß)

Proposed Cure

- My proposal is to treat both parts of the defected microfibrils; excess TGF-ß as well as the decrease in strength and elasticity of connective tissue
- Use Losartin, small dosages at young age
  - Safe for children, original use is as hypertension medication
- Early onset- increase dosage as age increases
- Use of Elastin and Collagen to replace elasticity and strength, respectively, in connective tissues
  - Other proteins found in connective tissues
  - Used often in plastic surgeries ; relatively easy to obtain
- Orally taken, hydrolyzed proteins.
  - Future: Replace with gene therapy for elastin ; currently under study (body production stops after 13)
- Limitations:
  - Losartin may cause hypotension in a normal body-Hypotension deprives brain of oxygen- dangerous
  - No guarantee that Elastin or Collagen will actually replace fibrillin-1's job
  - Elastin/Collagen probably from birds/ cows- Some believe it increases susceptibility to avian flu or mad cow disease

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IMAGES

Degenerated Aortic Valve(Fig 3):
http://upload.wikimedia.org/wikipedia/commons/thumb/4/4e/Myxomatous_aortic_valve.jpg/800px-Myxomatous_aortic_valve.jpg

Ectopia Lentis(Fig 1):
https://encrypted-tbn2.gstatic.com/images?q=tbn:ANd9GcSOwgUh5EWHXD6inXJ_FuagkZirgQ0Ih9b3lRO3Yu4gjIm_dnqE

Arachnodactyly (Fig 2):
http://24.media.tumblr.com/tumblr_m0e2weabjH1r8vrhxo1_500.jpg

Chromosome 15(Fig 5):
http://www.ncbi.nlm.nih.gov/projects/sviewer/ncfetch.cgi?key=NCID_1_6847267_130.14.22.10_9145_1369712394_2603521953

Fibrillin-1(Fig 4):
http://upload.wikimedia.org/wikipedia/commons/thumb/9/95/Protein_FBN1_PDB_1apj.png/250px-Protein_FBN1_PDB_1apj.png