



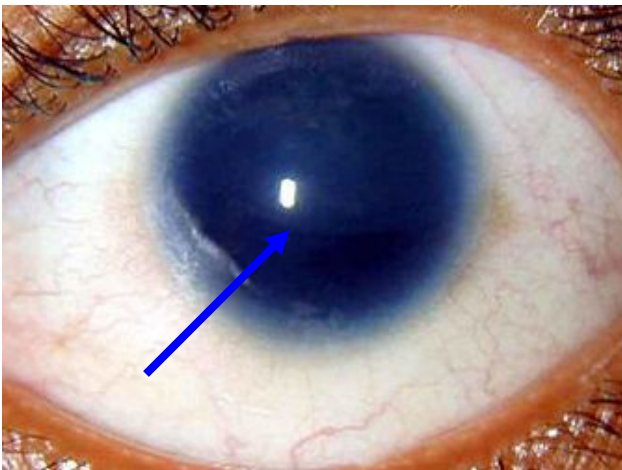
# HOLY C.O.W.!

## IT'S...

Clinical Question of the Week #5  
August 4th, 2008 through August 11th,  
2008

Please e-mail your answers to Kuo, Tim, Wendy, and Kevin ([klian@mednet.ucla.edu](mailto:klian@mednet.ucla.edu); [tprovias@mednet.ucla.edu](mailto:tprovias@mednet.ucla.edu); [wsimon@mednet.ucla.edu](mailto:wsimon@mednet.ucla.edu); [kbreger@mednet.ucla.edu](mailto:kbreger@mednet.ucla.edu)) by 0800 on Monday, August 11<sup>th</sup>, 2008. The resident or intern with the most correct answers at the end of each month will receive a prize!

**Case:** A 24-year-old woman presents to you for evaluation after failing the vision test required for obtaining a California driver's license, despite scoring enough to pass the written DMV exam using her glasses. She's had regular ophthalmologic follow up since she was a child, although she says she's had to wear glasses for several years and has had problems with her eyes in the past. Her development was relatively normal and she played high school basketball without incident (they won the state super-sectionals) despite her old pediatrician telling her to "take it easy out there." Examination reveals a well developed, tall slender woman in no distress. Her eye exam revealed a visual acuity of 20/40 on the right, and 20/80 on the left (shown below). Extraocular motions were intact, and the remainder of her exam was notable only for flow murmur on cardiac auscultation.



### Questions:

1. **What is the diagnosis?**

Marfan syndrome (MFS), one of the most common inherited disorders of connective tissue, is an autosomal dominant condition affecting approximately 1 out of every 3000-5000 individuals with a wide range of clinical severity. Most commonly, it is associated

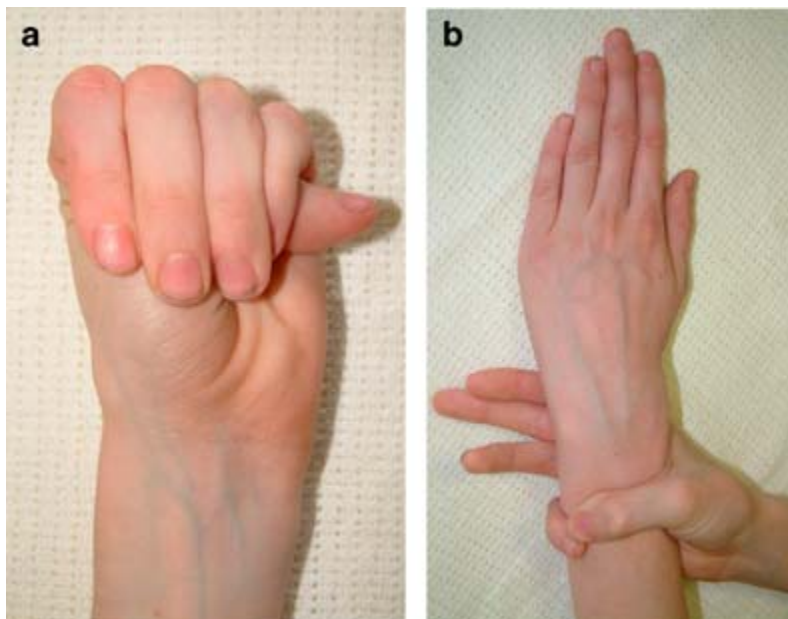
with a mutation in the fibrillin-1 gene (FBN-1) or less commonly TGFBR2 mutation (see below).

Classic features of MFS include abnormalities involving the skeletal, cardiovascular, and ocular systems. Less common systems involved include pulmonary, gastrointestinal, and skin changes. Criteria for diagnosis involves at least one major finding (see below), two separate systems involved, and having a first degree relative with the syndrome or genetic testing to confirm a FBN-1 mutation.

Management involves monitoring of aortic root disease with serial echocardiogram to assess for aneurysmal dilatation and dissection, which is the main cause of morbidity and mortality in MFS. Mitral valve prolapse is also monitored. Beta blockers are used to decreased myocardial contractility and pulse pressure, with possible benefit in aortic elasticity as well. Beta blockers in prophylactic use have been shown to reduce aortic dilatation, but despite this, many patients will require aortic root replacement. Ocular complications often require recurrent Ophthalmologic surgery (see below). Finally, avoidance of strenuous activity is recommended and pregnancy can be a particularly hazardous time for risk of aortic rupture/dissection. Life span is usually around 60 years in the present era of therapy. (0.5)

**2. Name three other features of this condition.**

Other features of Marfan syndrome include: reduced upper to lower body segment ratio (0.85 versus 0.93 in normals); arm span exceeding height (ratio>1.05); arachnodactyly of fingers and toes with positive thumb and wrist signs (see below); scoliosis or kyphosis, medial displacement of the medial malleolus with pes planus, reduced extension at the elbows (<170 degrees); marked degrees of pectus excavatum or carinatum; protrusio acetabuli; dilation of the aorta involving the sinuses of Valsalva associated with AR; mitral valve prolapse/mitral regurgitation; ascending aortic dissection; ectopia lentis; dural ectasia; and finally, family history of first degree relative that meets diagnostic criteria or confirmed by genetic testing. (1)



Arachnodactyly (a) positive thumb sign: entire thumbnail protrudes beyond ulnar border of hand. (b) Positive wrist sign: thumb and fifth finger overlap when encircling the wrist.

**3. What is the ophthalmologic finding depicted above?**

Ectopia lentis, with classic upper and lateral displacement of the lens (blue arrow, above), occurs in up to 65-80% of individuals and is commonly bilateral. Occasionally, lens

dislocation may be complete with the lens floating in the vitreous. Other ocular findings may include angle anomaly with glaucoma (up to 35% lifetime incidence), severe axial myopia (due to elongation of the globe), flattened corneal curvature, amblyopia, strabismus, cataracts, iritis, hypoplasia of the dilator muscle, and retinal detachment (also frequently bilateral, and commonly resulting in proliferative retinopathy), which occurs at a much higher incidence than baseline population. The risk for lens dislocation and retinal detachment are the reasons why Marfan patients are counseled not to participate in contact or strenuous sports. Aniridia is a very rare finding. Iridodonesis is increased tremulousness of the lens and may be detected on EOM examination. (0.5)

**4. What is the genetic basis of this condition, and who discovered it?**

Most patients with Marfan syndrome harbor one or more mutations in the large fibrillin-1 (FBN-1) gene, with a minority of patients having an inactivating mutation in TGF- $\beta$  receptor 2. These varying mutations may contribute to the varying clinical severity of phenotypes seen. Fibrillin-1 is an important component of both elastic and nonelastic connective tissues.

While Marfan syndrome was initially described by Antoine Bernard-Jean Marfan, who described the physical syndrome in 1896, three groups (Lee et al., Maslen et al., and Dietz et al.) simultaneously presented the finding of the defect in FBN-1 in the July 25<sup>th</sup>, 1991 issue of *Nature*. A comment was also made by Victor A. McKusick in the same issue on the discovery – he also thought that Abraham Lincoln had a 50/50 chance of having Marfan syndrome.

McKusick is regarded as the father of medical genetics, and began the first database of gene functions, now listing more than 18,000 genes. He also established the first medical genetics department at Johns Hopkins in 1957, and was the originating author of *Mendelian Inheritance in Man*, a publication that he chief edited until his death. He initially trained as a Cardiologist and his early work focused on acoustic spectography with Bell Telephone Laboratory, where he described heart murmurs in more detail than had ever been possible. He also had an identical twin, Vincent, who went on to serve in the Maine Supreme Court. Victor A. McKusick was born October 21<sup>st</sup>, 1921, and recently died on July 22<sup>nd</sup>, 2008. (0.5 for FBN-1, 0.5 for any of the Nature 1991 authors, 0.5 extra for McKusick)