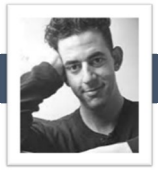

Jonathan's Case	NOTES
Phenotype This is based on the true story of Jonathan Larsen, although his specific genetic variant is not known. He died, as described, in the early morning hours before the first preview performance of his eventual Tony award winning musical "Rent".	A 35 year old, Caucasian male was found unresponsive on his kitchen floor and pronounced dead on the scene by EMS, who delivered the body to the Medical Examiner's Office. Tox screen was negative with no evidence of trauma. Cause of death was determined to be thoracic aortic dissection. The cause of death as well as other typical clinical features present in the body that are commonly associated with Marfan Syndrome (tall and lanky stature, long and narrow face with deeply set eyes, and pectus excavatum) concerned the family - who requested additional investigative measures due to misdiagnosis in two separate emergency room visits in the three days prior to death.
Preliminary Diagnosis	Marfan Syndrome
Genetic Variation(s)	Arg1790 & Arg1790Ter
Laboratory Assertion(s)	pathogenic
Variant Information: • Asserted interpretation listed in **ClinVar**	pathogenic
• HGVS names from **ClinVar**	NG_008805.2:g.194098C>T NP_000129.3:p.Arg1790Ter
• Is population data available in **dbSNP**?	rs113249837 Exceedingly rare
Gene Information in NCBI Gene: • Symbol and Name	FBN1 & Fibrillin 1
• Gene Summary	This gene encodes a member of the fibrillin family of proteins. The encoded preproprotein is proteolytically processed to generate two proteins including the extracellular matrix component fibrillin-1 and the protein hormone asprosin. Fibrillin-1 is an extracellular matrix glycoprotein that serves as a structural component of calcium-binding microfibrils. These microfibrils provide force-bearing structural support in elastic and nonelastic connective tissue throughout the body…Mutations in this gene are associated with Marfan syndrome… [provided by RefSeq, Apr 2016]
• Tissue Expression information	Broad expression in tissues such as placenta, thyroid, heart, adipose, gall bladder and others.
• Gene Ontology information	Extracellular matrix structural stability and elasticity Involved in skeletal system, lung and heart development Located in collagen-containing extracellular matrix
Ultimate Impacted Biomolecule based on: • **GDV** to view the chromosome and gene region	Located in the coding region of exon 43.
• **RefSeqGene Graphics** view of gene region and transcript(s)	Located in the coding region of exon 43.
• **RefSeq Protein Graphics** view of protein and domains	Located in the middle of the protein chain in region containing a large number of Calcium ion binding sites, this termination variant prevents the expression of the full-length protein.
• **CDD or iCn3D** to view a structure, *as needed*	The lack of the full coding protein prevents effective extracellular matrix integration and cross-molecular stability in complex with other microfibril proteins, such as fibronectin and elastin.
Proposed Molecular Mechanism of Variant Impact	The prematurely truncated FBN1 protein in connective tissue prevents the development of strongly cross-linked, structurally reinforcinbg microfibrils which are critical to strengthen vasculature, particularly in regions susceptible to stress (ex: aorta). In addition, this variant also assists this shortened peptide in escaping the Nonsense-Mediated Decay (NMD) protective pathway. Thus, it serves as a dominant

	negative aggravator for further impacting the weakening of connective tissue - even though this is encoded in a heterozygous genotype.
How does this relate back to the phenotype (symptoms/clinical features & diagnosis)?	The disruption of common structural connective mesh dramatically weakens vasculature wall strength. Upon prolonged or repeated, high pressure or stress – the area can deform and be readily seen in imaging as an aortic bulge or aneurysm, which can be fixed before full bursting or dissection which usually causes death.