

Titinopathies: The Dallas Experience

**Natasha Varughese, BS; Molly Snyder, MS;
Chunyu Cai, MD PhD; Diana Castro, MD; Susan Iannaccone, MD**

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TTN (Titin): A History

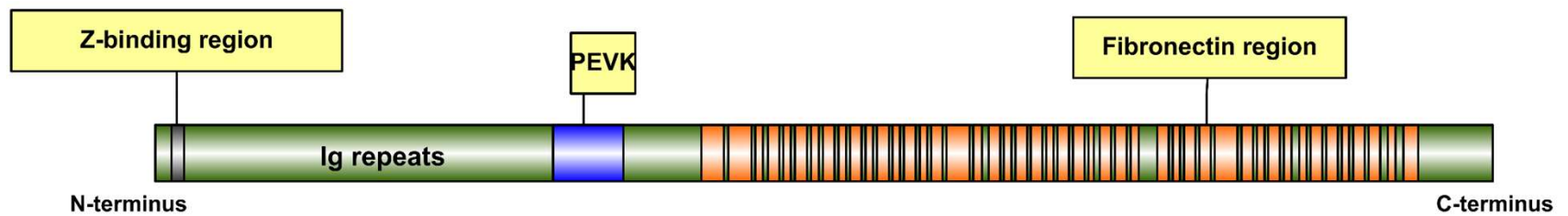
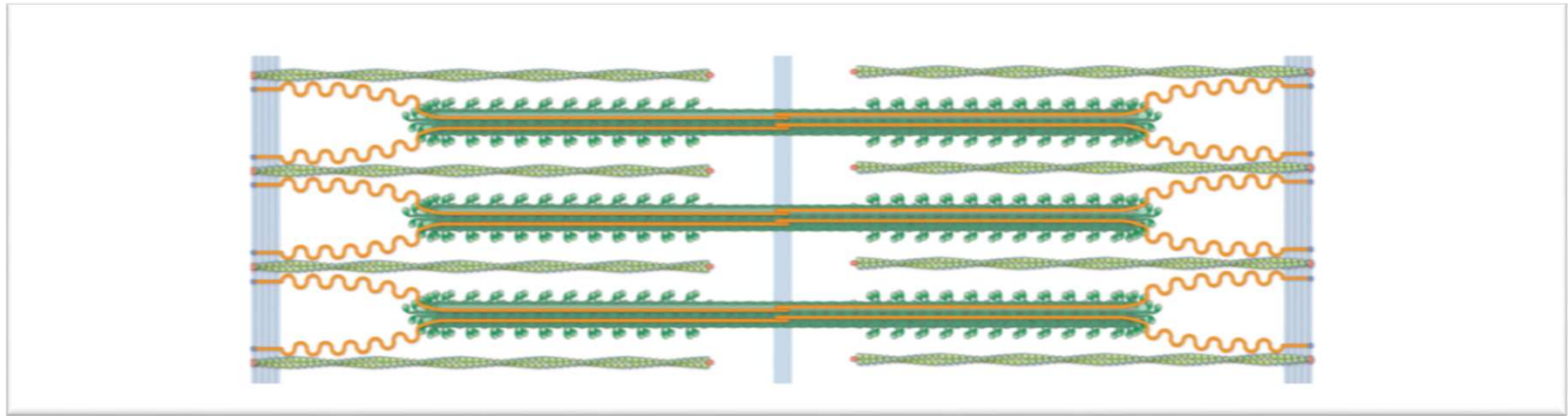
- **Structural framework of the sarcomere**
- **Largest known protein with 363 exons**
- **1977: Originally isolated as top band in gel electrophoresis of skeletal muscle in multiple animals (1,2)**
- **2002: First linked to human myopathy case (3)**
 - **Adult tibial muscular dystrophy**

1. Maruyama, K. Connectin/titin, giant elastic protein of muscle. FASEB J. 1997. 11(5):341-5.

2. Maruyama, K. et al. Connectin, an Elastic Protein of Muscle Characterization and Function. J Biochem. 1977. 82(2):317-37.

3. Hackman, P. et al. Tibial muscular dystrophy is a titinopathy caused by mutations in TTN, the gene encoding the giant skeletal-muscle protein titin. Am J Hum Genet. 2002. 71(3):492-500.

Titin Structure



1. Herman DS et al. N Engl J Med 2012;366:619-628.
2. IBS: an illustrator for the presentation and visualization of biological sequences. Liu, W. et al. *Bioinformatics* (2015) 31(20):3359-3361.
3. UniProtKB - Q8WZ42 (TITIN_HUMAN). The UniProt Consortium. UniProt: the universal protein knowledgebase. *Nucleic Acids Res.* (2017). 45: D158-D169 .

Core Myopathies and TTN

- **1956: Core myopathy was the first well-described congenital myopathy in the literature (1)**
- **Unknown incidence (2)**
 - All congenital myopathies: ~1:26,000
 - UK study (5): Half are core myopathies on biopsy
- **2014: TTN identified as a significant cause of core myopathies (3)**
 - 5/29 families with unknown myopathy identified with TTN mutations
- **2018: Currently 16 case reports of congenital titinopathies and one study with 30 patients**

1. Magee, K. et al. A new congenital non-progressive myopathy. *Brain*. 1956. 79(4): 610-21

2. Heinz, J. et al. Chapter 93 - The Congenital Myopathies, *Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease (5th Edition)*, ed. R. N. Rosenberg and J. M. Pascual, Academic Press, Boston 2015 p.1121-1129.

3. Chauveau, C. et al. Recessive *TTN* truncating mutations define novel forms of core myopathy with heart disease. *Hum Mol Genet*. 2014. 23(4):980-91.

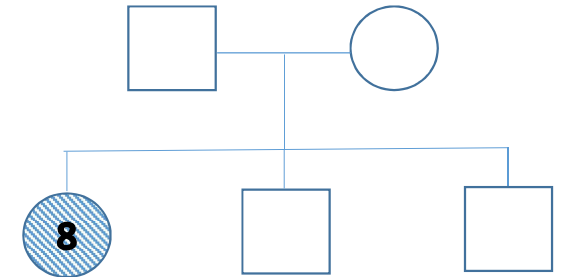
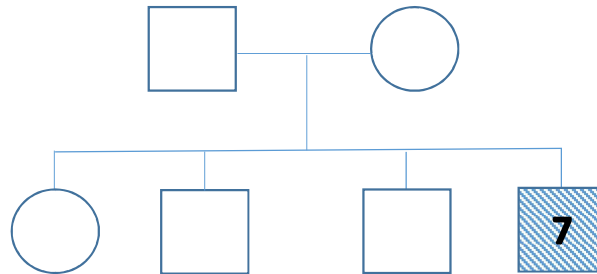
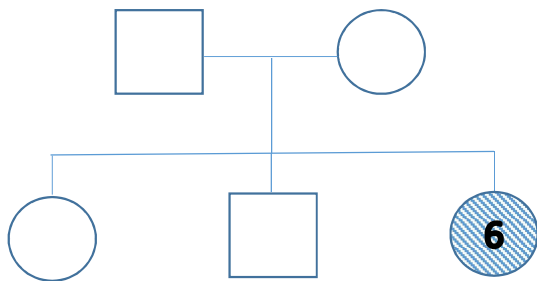
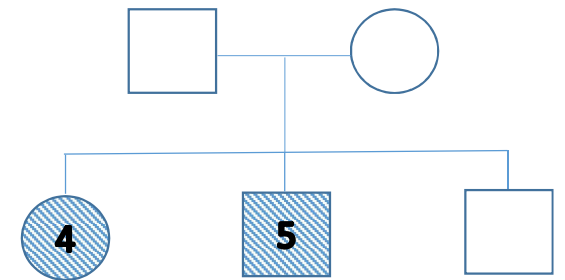
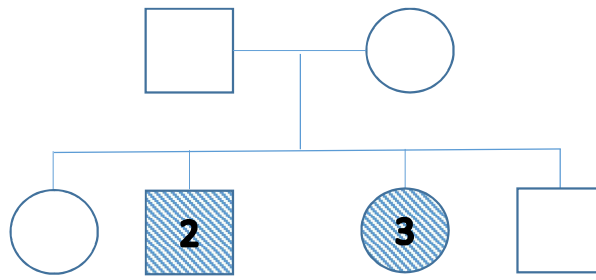
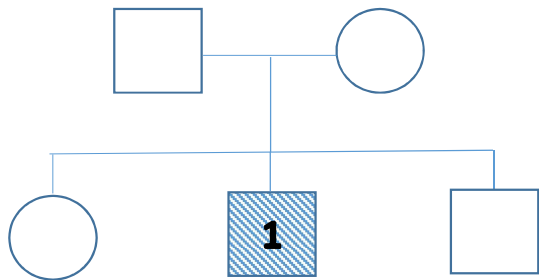
4. Dowling, J. et al. Chapter 28 - Congenital and Other Structural Myopathies, *Neuromuscular Disorders of Infancy, Childhood, and Adolescence (2nd Edition)*, ed. B. T. Darras, H. R. Jones, M. M. Ryan & D. C. De Vivo, Academic Press, San Diego 2015 p. 499-537.

5. Maggie, L. et al. Congenital myopathies – Clinical features and frequency of individual subtypes diagnosed over a 5-year period in the United Kingdom. *Neuromusc Dis*. 2013. 23(3). P. 195-205.

Methods

- **Reviewed all myopathy patients tested for TTN mutations**
 - **2008-2018**
 - **Children's Medical Center and Texas Scottish Rite Hospital (Dallas, TX)**
- **Retrospective chart review**
 - **Pedigrees**
 - **Demographics**
 - **Clinical features**
 - **Muscle biopsies**
 - **DNA**

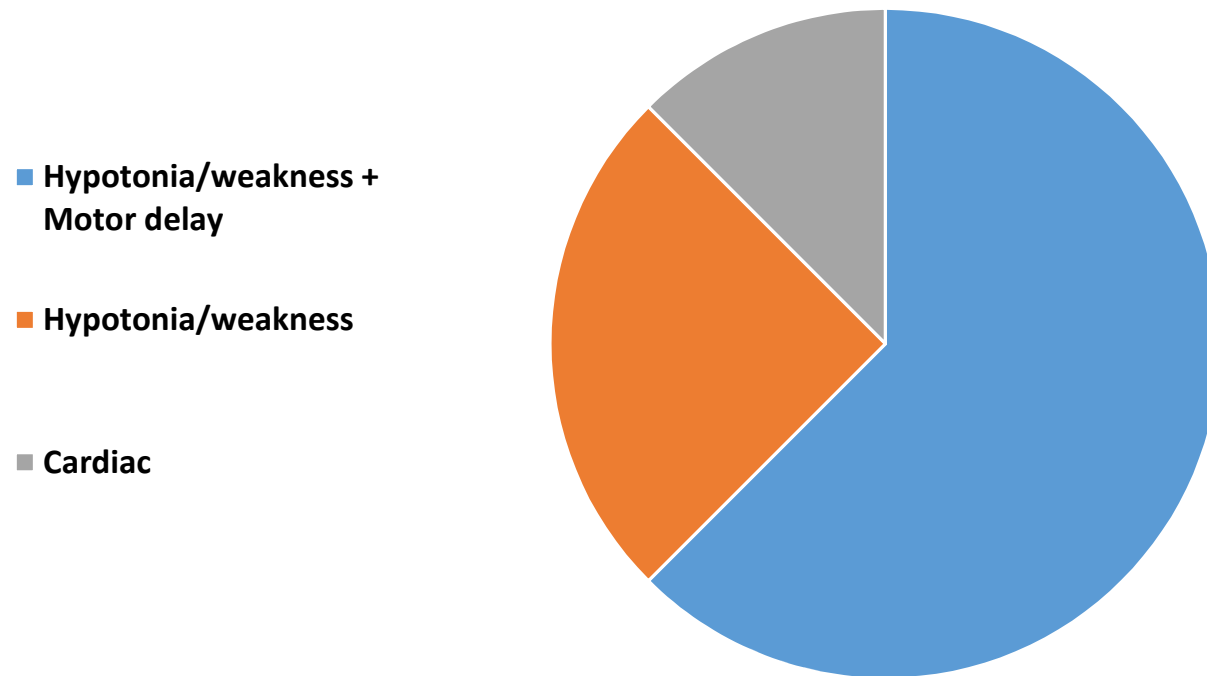
Pedigrees



Demographics

	Gender	Age of symptom onset	Age of diagnosis	Age at last follow-up visit	Ethnicity
1	M	3 mo	3 yrs	23	African-American
2*	M	2 yrs	6 yrs	19	Hispanic
3*	F	7 yrs	8 yrs	17	Hispanic
4**	F	Birth	4 yrs	17	Hispanic
5**	M	Birth-3 mo	5 yrs	12	Hispanic
6	F	Birth	8 wks	5	White
7	M	3 mo	2 yrs	3	Hispanic
8	F	Birth-3 mo	2 yrs	19	African-American

Presenting Symptoms



Creatinine Kinase

Patient	CK (U/L)
1	154
2	-
3	-
4	66
5	82
6	76
7	219
8	41

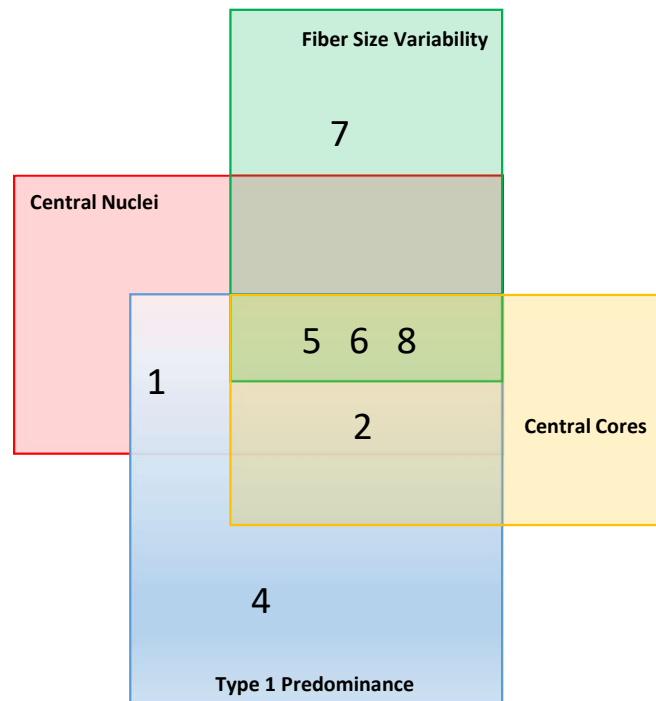
Comorbid Symptoms

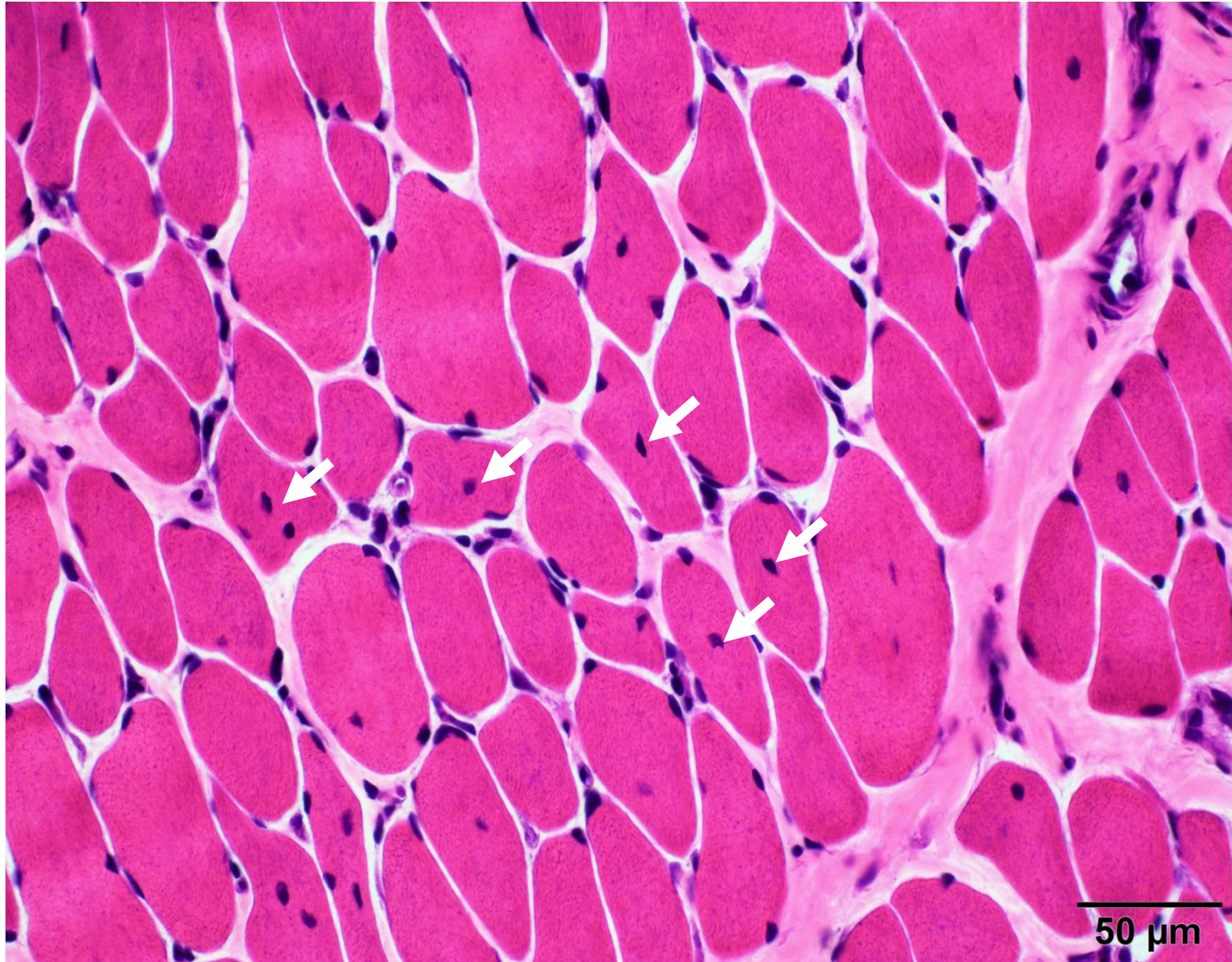
<i>Cardiac</i>		<u>Patient Case Numbers</u>
	Dilated cardiomyopathy (one transplant at age 16)	2,3
	Non-compaction cardiomyopathy	6
	Abnormal EKG	1
	Hypoplastic left heart syndrome (awaiting transplant)	5
<i>Pulmonary</i>		
	RLD	1,2,5,8
	RLD + OSA	4
	OSA	7
<i>Gastrointestinal</i>		
	Dysphagia	2,3,7
	Dysphagia + G-tube	8
	G-tube	4
	Protein-losing enteropathy	6
<i>Orthopedics</i>		
	Scoliosis	1,4,5,8
	Wheelchair-dependent	8
	Wheelchair as needed	2,3,6,7
<i>Ocular</i>		
	Mild ptosis	1
	Ophthalmoparesis	None

Muscle Biopsies

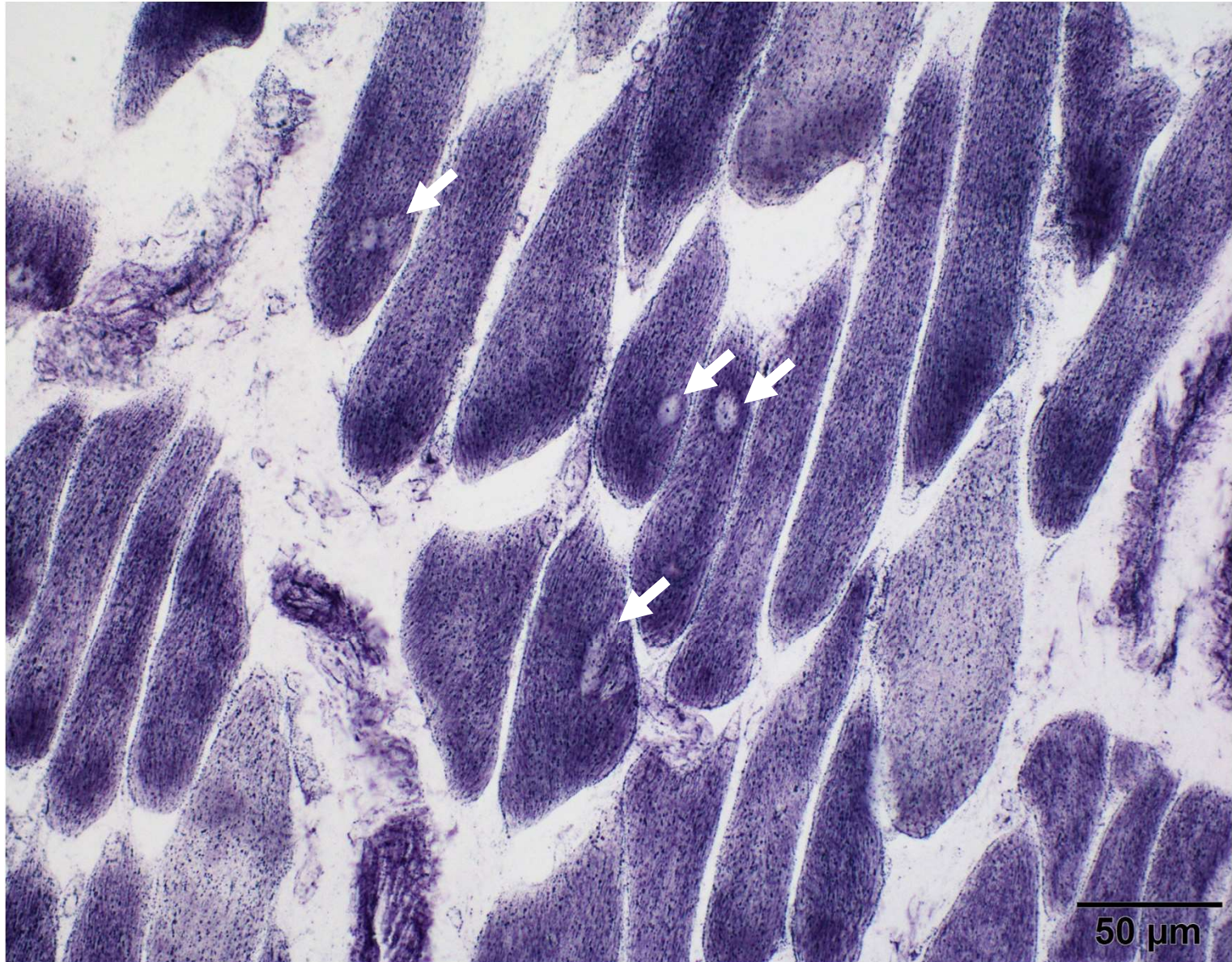
Patient	Year	Age	Lab	Fiber Size Disproportion	Central Nuclei	Category of Myopathy
1	1999	9	TSRH	Type 1 predominance	3+	-
2*	2003	6	UTSW	Type 1 predominance	numerous (in type 1 fibers)	multiminicore myopathy
3*	2007	7	ARUP	-	-	multiminicore myopathy
4**	2004	5	UTSW	Type 1 predominance	2+	nonspecific myopathy
5**	2011	5	UTSW	Type 1 predominance	some	multiminicore myopathy
6	2015	2	UTSW	Type 1 predominance	most	multiminicore myopathy
7	2016	1.5	UTSW	-		mildly chronic myopathy
8	2009	11	UTSW	Type 1 predominance	yes	chronic myopathy

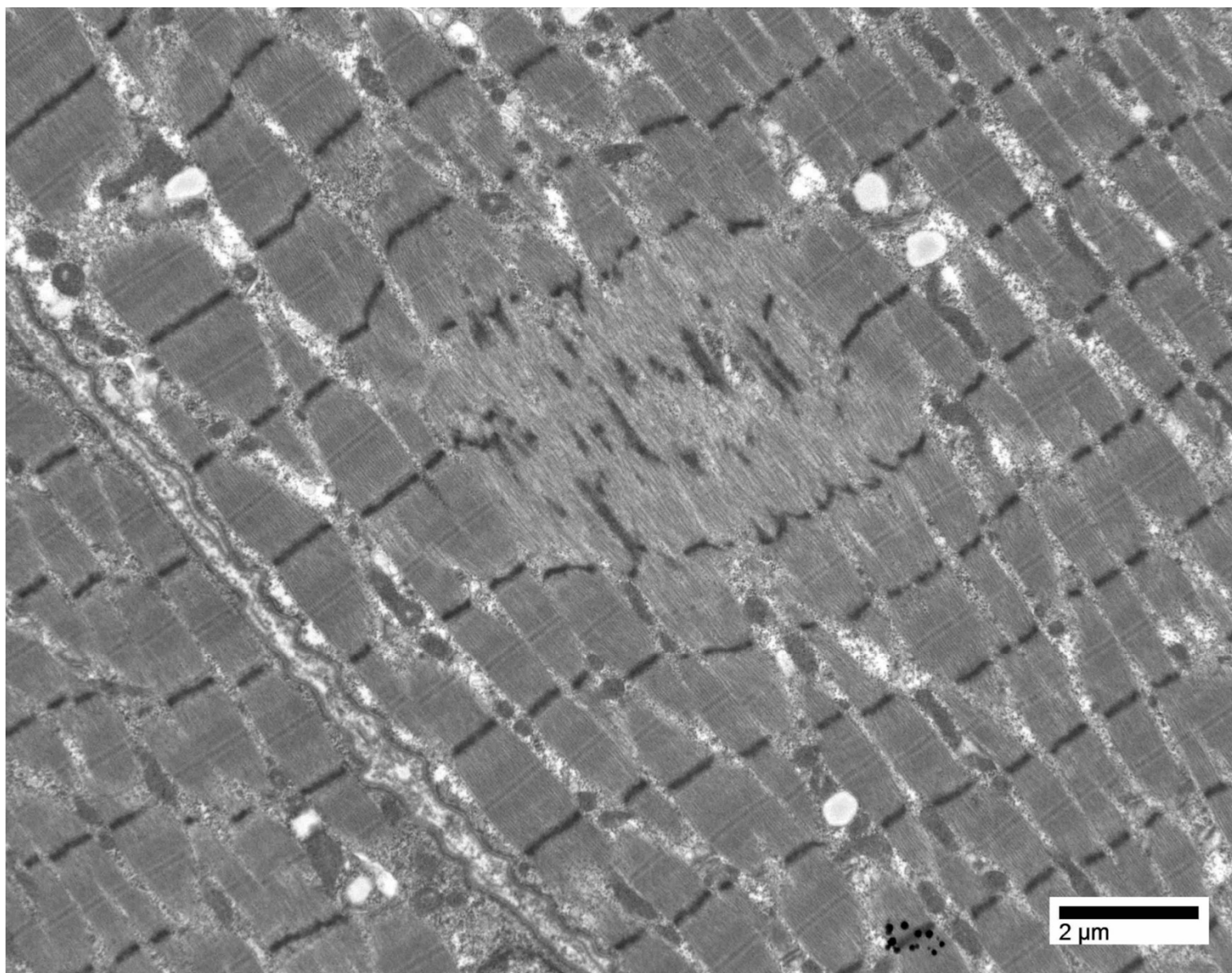
Muscle Biopsies (cont.)







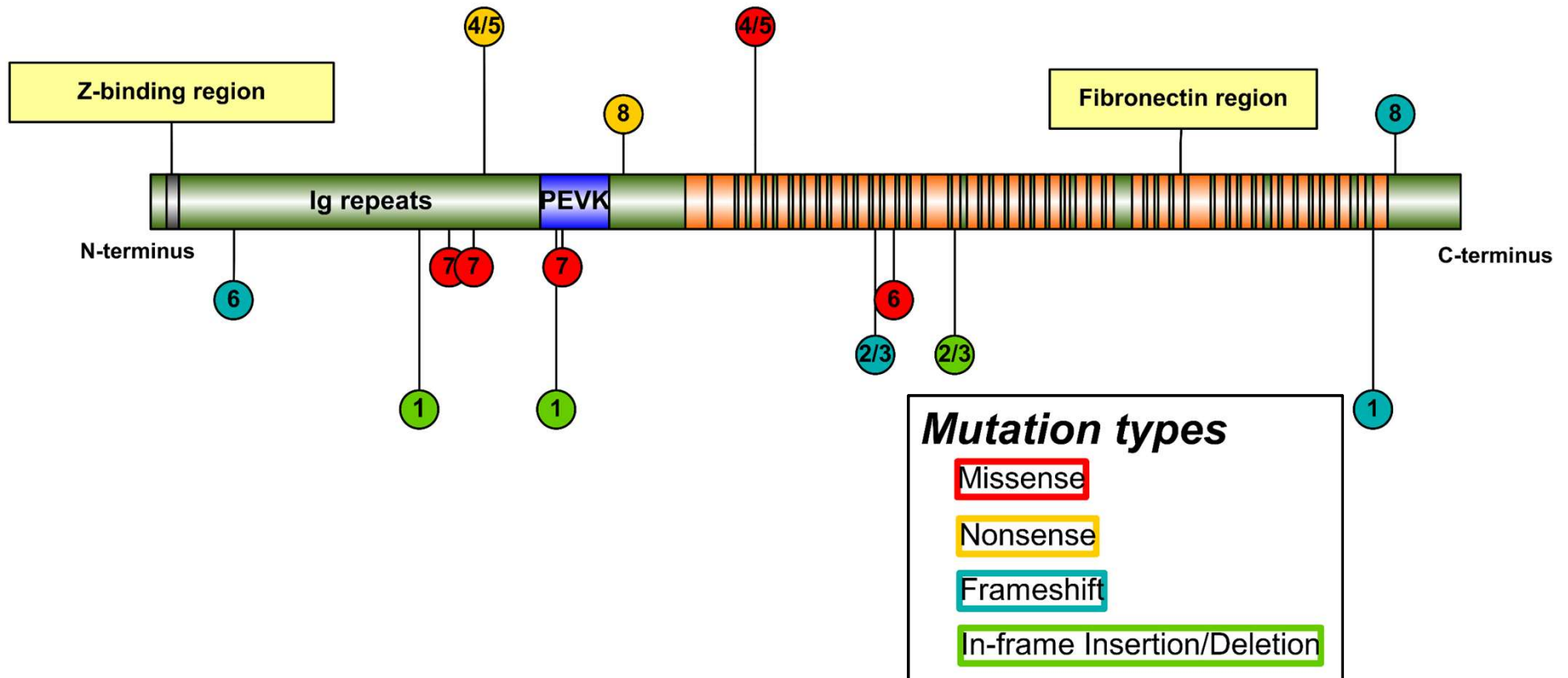




TTN Mutations

Patient	Age	Coding Variant #	Amino Acid Change #	Exon #	Parental Origin	Zygosity	Classification
1	-	c.21131_21145del	p.7044_7049del	83	Paternal	Heterozygous	VOUS
		c.31902_31903insACC	p.10634insP	157	Paternal	Heterozygous	VOUS
		c.96146_96147insAGAC	p.P32049fsX10	307	Maternal	Heterozygous	Likely Pathogenic
2/3	16/15	c.56976dupC	p.G18993RfsX8	259	-	Heterozygous	Likely Pathogenic
		c.63245_63247delACA	p.N21082del	275	-	Heterozygous	VOUS
4/5	17/10	c.26242G>T	p.E8748*	107	Maternal	Heterozygous	Likely Pathogenic
		c.47565G>C	p.K15855N	285	Paternal	Heterozygous	VOUS
6	3	c.6555_6556ins16	p.K2186CfsX15	29	Maternal	Heterozygous	VOUS
		c.58456G>T	p.D19486Y	263	Paternal	Heterozygous	VOUS
7	1	c.23480A>T	p.D7827V	-	-	Heterozygous	VOUS
		c.25412C>T	p.A8471V	-	-	Heterozygous	VOUS
		c.32387C>T	p.A10796V	-	-	Heterozygous	VOUS
8	15	c.37195C>T	p.R12399*	192	-	Heterozygous	VOUS
		c.97901_97902delTG	p. V32634GfsX5	307	-	Heterozygous	VOUS

Transcript Sequence: NM_133378.4



1. IBS: an illustrator for the presentation and visualization of biological sequences. Liu, W. et al. *Bioinformatics* (2015) 31(20):3359-3361.
 2. UniProtKB - Q8WZ42 (TITIN_HUMAN) .The UniProt Consortium. UniProt: the universal protein knowledgebase. *Nucleic Acids Res.* (2017). 45: D158-D169 .

Conclusions

- 1. Clinical phenotype for TTN-related myopathy is broad**
 - Very different clinical courses within sibling pairs
 - Majority have significant respiratory and orthopedic impairment
 - Many have related cardiac disease
- 2. Titin mutations seem to be a common cause of core myopathies**
 - Multiminicore pathology is consistent theme on muscle biopsy
- 3. Although TTN mutations are difficult to characterize, frameshift and deletion mutations are a consistent theme, and position may correlate with severity of disease presentation**