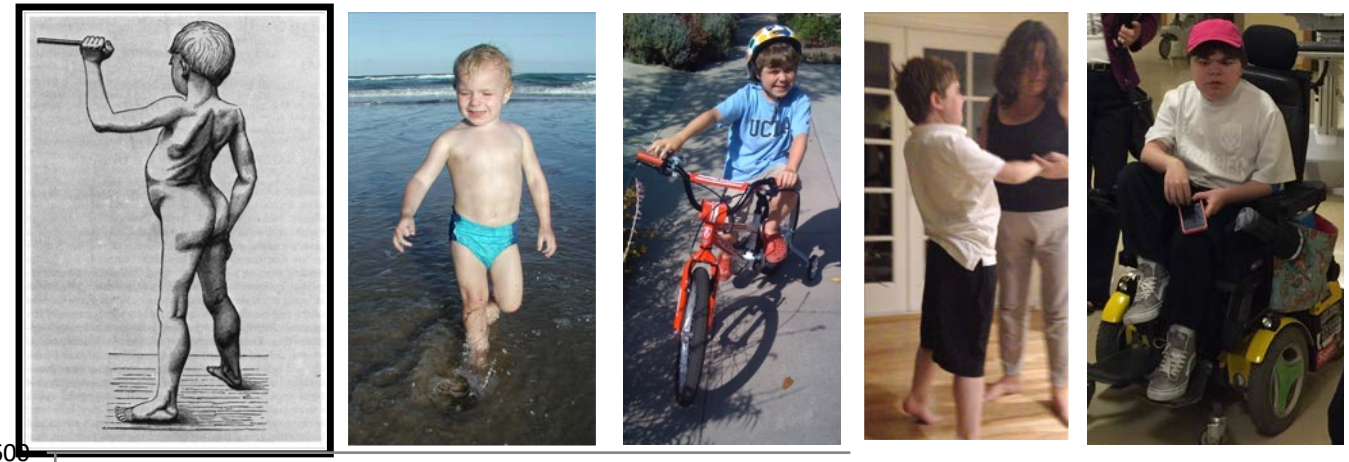
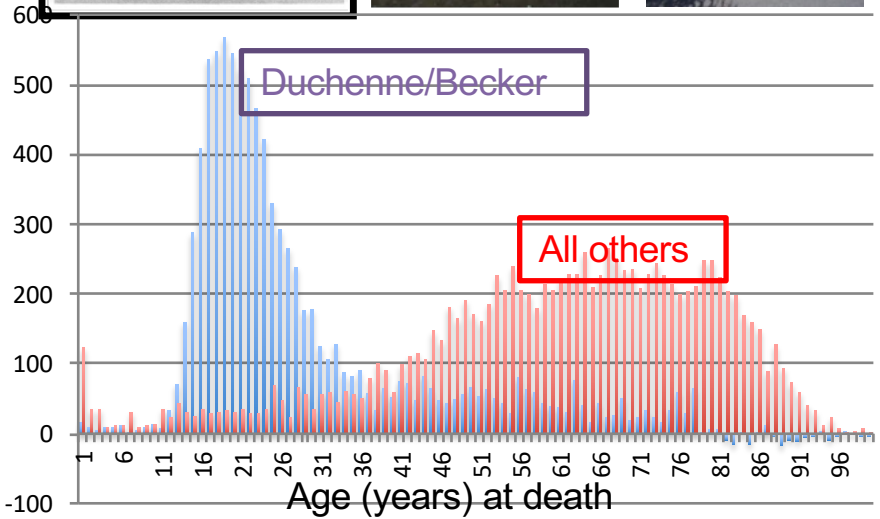
Duchenne is a multisystem disease

Parent Project Muscular Dystrophy
JOIN THE FIGHT. END DUCHENNE.

Stanley F. Nelson, MD
June 27, 2019

Duchenne muscular dystrophy





X-linked recessive:

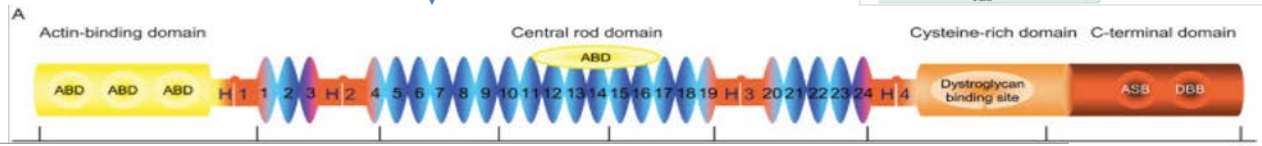
1/ 5000 male births

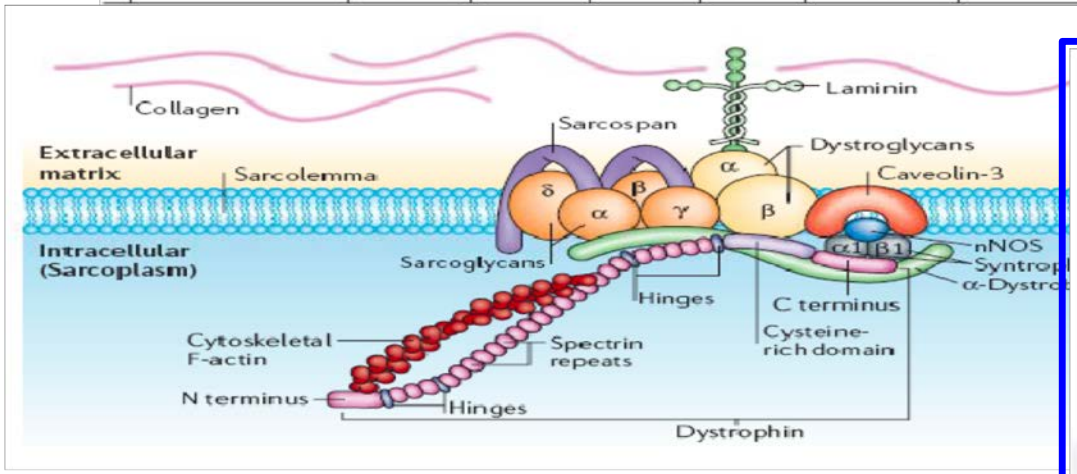
Common muscular dystrophy

Resp/cardiac failure

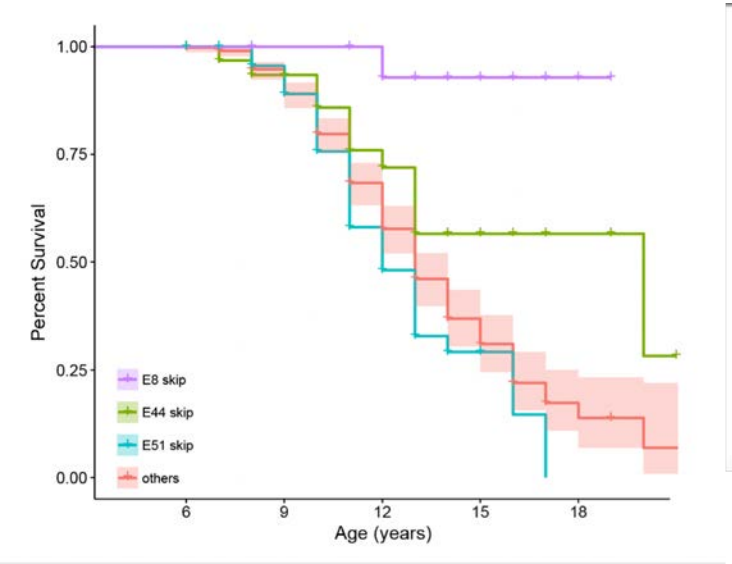
2.5mb *DMD* gene in 79exons

encodes dystrophin protein





Duchenne can progress differently in different boys



LTBP4 Genotype Predicts Age of Ambulatory Loss in Duchenne Muscular Dystrophy

Kevin M. Flanigan, MD,[1,2,3] Ermelinda Ceco, BS,[4] Kay-Marie Lamar, BS,[4] Yuuki Kaminoh, BS,[1] Diane M. Dunn, BS,[5] Jerry R. Mendell, MD,[1,2,3] Wendy M. King, PT,[3] Alan Pestronk, MD,[6] Julaine M. Florence, DPT,[6] Katherine D. Mathews, MD,[7] Richard S. Finkel, MD,[8] Kathryn J. Swoboda, MD,[9] Eduard Gappmaier, PhD,[10] Michael T. Howard, PhD,[5] John W. Day, MD, PhD,[11] Craig McDonald, MD,[12] Elizabeth M. McNally, MD, PhD,[4] and Robert B. Weiss, PhD[5] for the United Dystrophinopathy Project

Objective: Duchenne muscular dystrophy (DMD) displays a clinical range that is not fully explained by the primary *DMD* mutations. *Ltbp4*, encoding latent transforming growth factor-*β* binding protein 4, was previously discovered in a genome-wide scan as a modifier of murine muscular dystrophy. We sought to determine whether *LTBP4* genotype influenced DMD severity in a large patient cohort.
Methods: We analyzed nonsynonymous single nucleotide polymorphisms (SNPs) from human *LTBP4* in 254 nonambulatory subjects with known *DMD* mutations. These SNPs, V194I, T787A, T820A, and T1140M, form the VTTT and IAAM *LTBP4* haplotypes.
Results: Individuals homozygous for the IAAM *LTBP4* haplotype remained ambulatory significantly longer than those heterozygous or homozygous for the VTTT haplotype. Glucocorticoid-treated patients who were IAAM homozygotes lost ambulation at 12.5 ± 3.3 years compared to 10.7 ± 2.1 years for treated VTTT heterozygotes or homozygotes. IAAM fibroblasts exposed to transforming growth factor (TGF) *β* displayed reduced phospho-SMAD signaling compared to VTTT fibroblasts, consistent with LTBP4's role as a regulator of TGF*β*.
Interpretation: *LTBP4* haplotype influences age at loss of ambulation, and should be considered in the management of DMD patients.

ANN NEUROL 2013;73:481–488

Duchenne/Becker Genetic Modifier Study

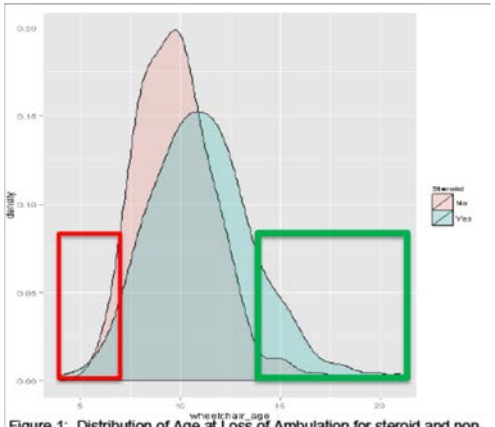
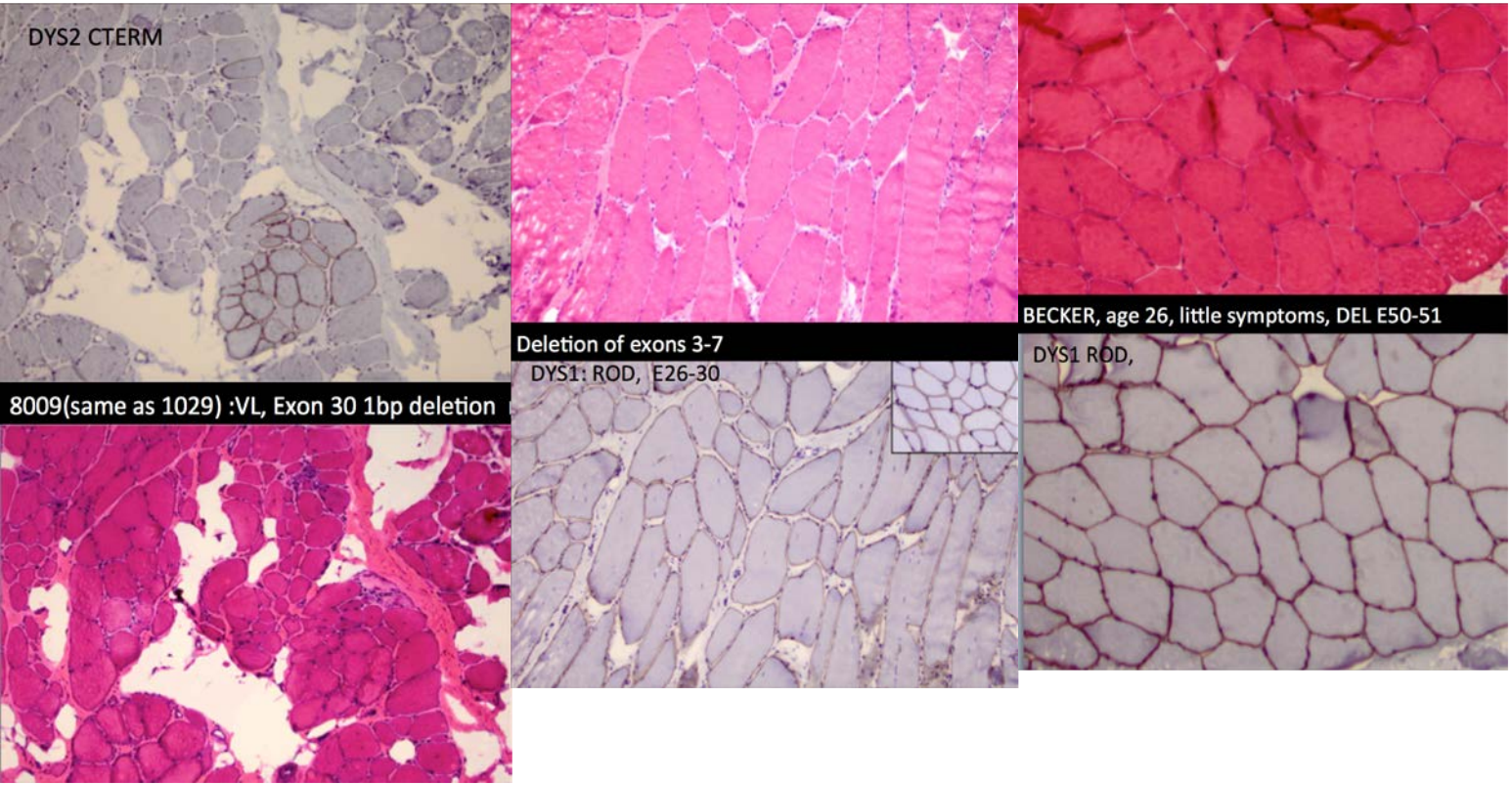
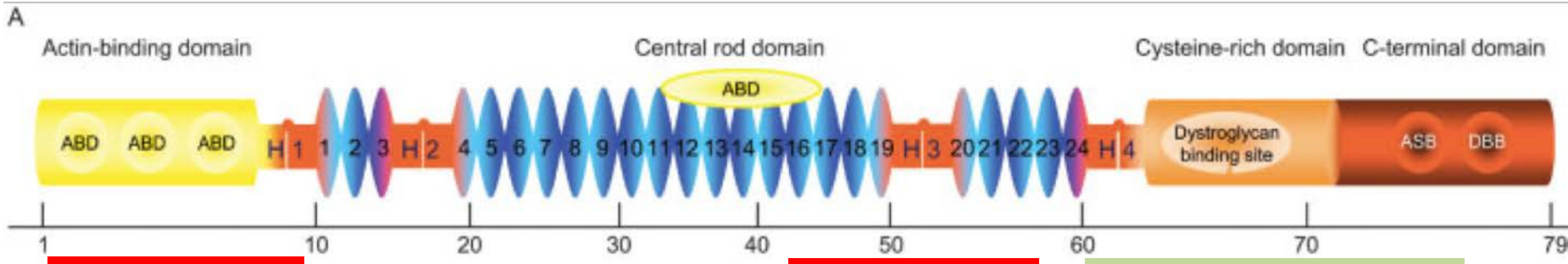


Figure 1: Distribution of Age at Loss of Ambulation for steroid and non

DMD Mutation can predict dystrophin amount contribution to disease severity



Exceptions to readingframe rule



HOT SPOT

HOT SPOT

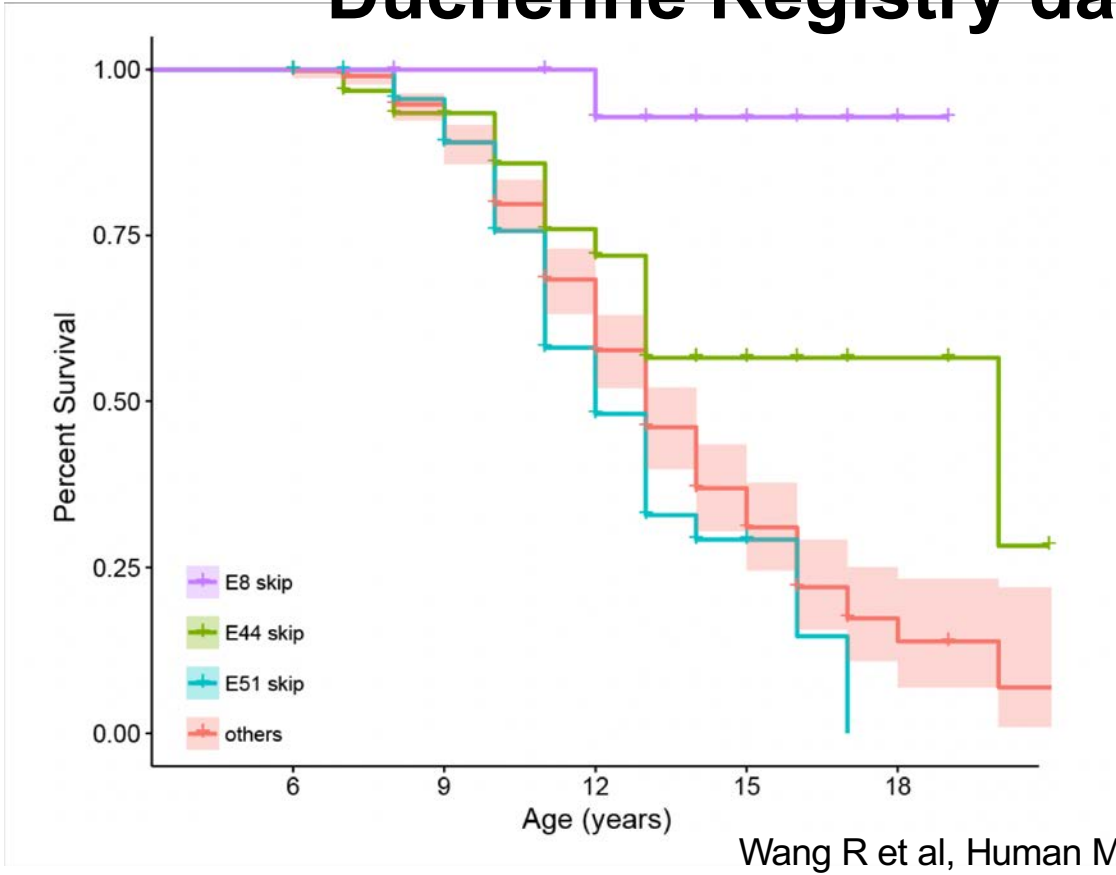
In frame mutations can be severe

In frame mutations can be severe

Exon 45 deletion can be more mild

Out of frame mutations can be mild

Variation in age at loss of ambulation from Duchenne Registry data



Wang R et al, Human Mutation, 2018

Muscle

- Lack of dystrophin at muscle cell membrane: leads to progressive damage to skeletal muscle
- High blood CK, High ALT/AST (so called liver function tests)
- Progressive weakness: Center of body weaker than distal
- Mild weakness > Loss of ability to rise from floor > Loss of ambulation > Loss of ability to transfer > Loss of ability to bring hands to mouth
- Contractures
  - Daily stretching/standing PWC/ROM exercise
- Mobility/Medical Equipment Needs
  - scooter > wheelchair

Lungs

- Due to weak muscles of breathing
- Weak cough
  - Cough Assist
- Pneumonia
  - Antibiotics
  - Vaccines
- Chronic hypoventilation at night initially
  - BIPAP/AVAPS/Vent

Heart

- High lifetime risk of some degree of heart failure
- Arythmias
- Observable at younger ages with more sensitive heart measures
- Progressive
- Treatable

Bone

- Often low Vitamin D at diagnosis
- Steroids and less physical activity induce low bone mineral density>>Osteopenia/osteoporosis
  - Monitor/medications
- Fracture risk (about 40%)
  - Treatment depends on stage of disease
- Spinal Compression Fractures
- FAT EMBOLISM SYNDROME
- Scoliosis
  - Spinal fusion surgery

Endocrine

- Steroids: Adrenal insufficiency
  - Stress dosing/replacement/slow wean
- Steroids: Slowed growth
  - Growth hormone
- Steroids/Lack of mobility: Obesity
  - Diet/metformin
- Steroids: hyperglycemia
  - medications
- Delayed puberty
  - testosterone

Brain

- Some different forms of dystrophin expressed highly in brain cells
- Increased risk of affect on brain development, highly variable
  - Delayed speech
  - Social isolation
  - Rigidity
  - Easy frustration
- Learning disabilities in language and math
- Mild increase in seizure risk (?)

GI

- Nutritional Assessment
- Reflux
  - medications
- Swallowing difficulty
  - Modifications/G tube
- Chronic constipation
  - Stool softener; Maintain daily soft stools
- Bowel distension risk
- Toxic megacolon (atonic bowel/sepsis)

Takeaways

Duchenne has affects on many organs

Comprehensive care team needed


Questions?

Thank you!

Acknowledgements

- UCLA
  - R. Wang
  - E. Douine
  - M. C. Miceli
  - F. Barthelemy
  - N. Khanlou
  - A. Eskin
  - R. M. Cantor
- The Duchenne Registry
  - Holly Peah
  - Ann Martin
  - Jenifer Lavigne