Genetics of Inclusion Body Myositis

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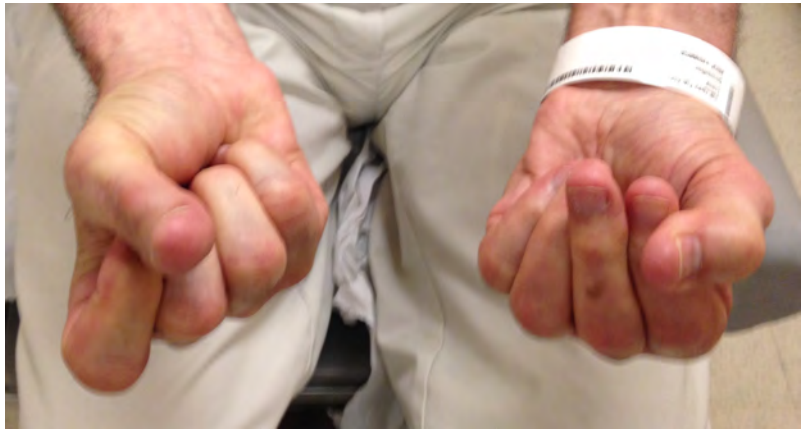
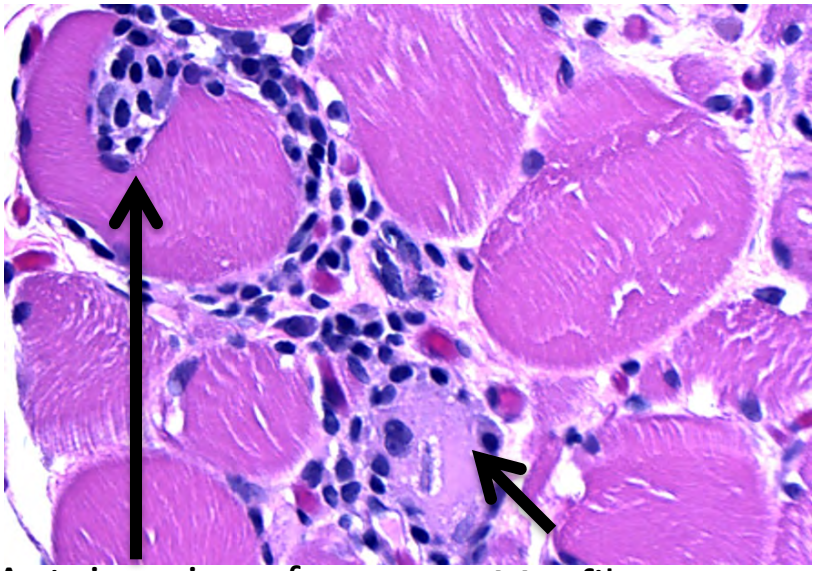
Sporadic IBM (IBM)

- Age at onset usually > 50
  - Prevalence 1 to 8 per million, 3:1 males
  - Median age of onset ~ 60 yo.
  - *Most common acquired myopathy* over age 40 yo.
- Slowly progressive muscle weakness and wasting.
  - Quadriceps (knee extensors) → frequent falls
  - Finger flexors → inability to grip
  - Dysphagia common
- Cause is unknown
  - Autoimmune and Degenerative features
- Refractory to immunosuppressive treatment

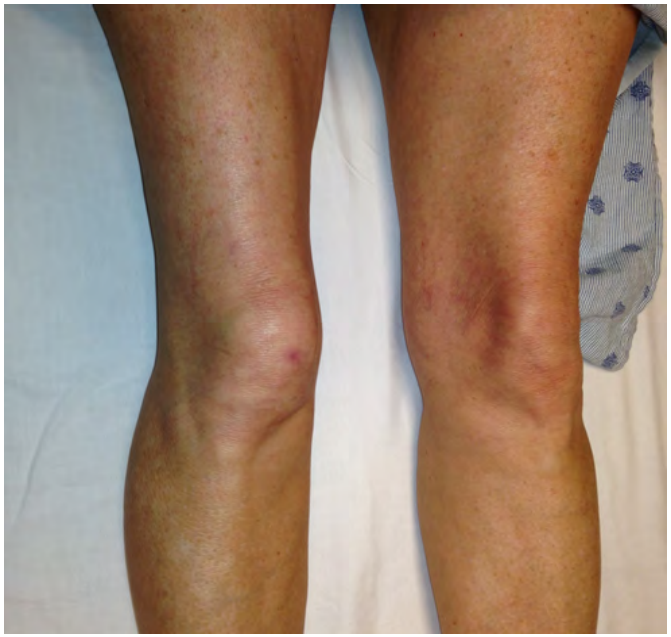
Sporadic IBM clinical features

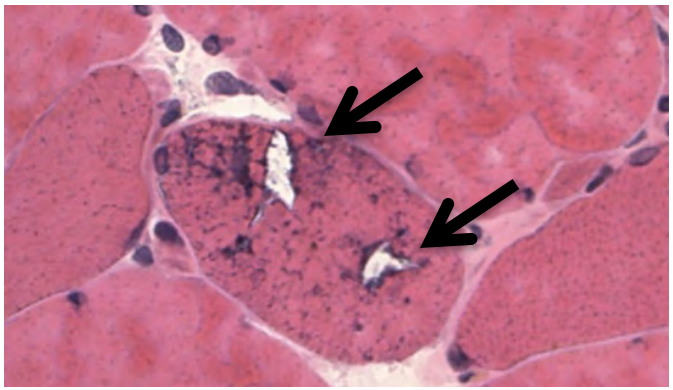




Autoinvasion of Mononuclear Cells

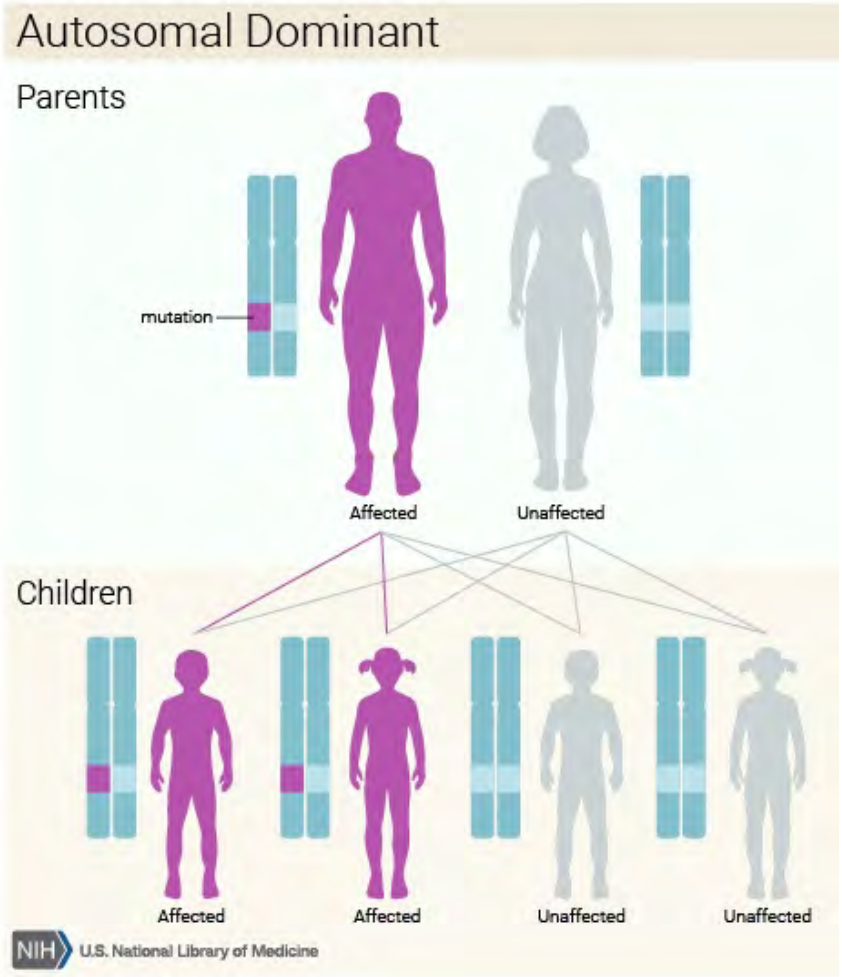
Myofiber Degeneration

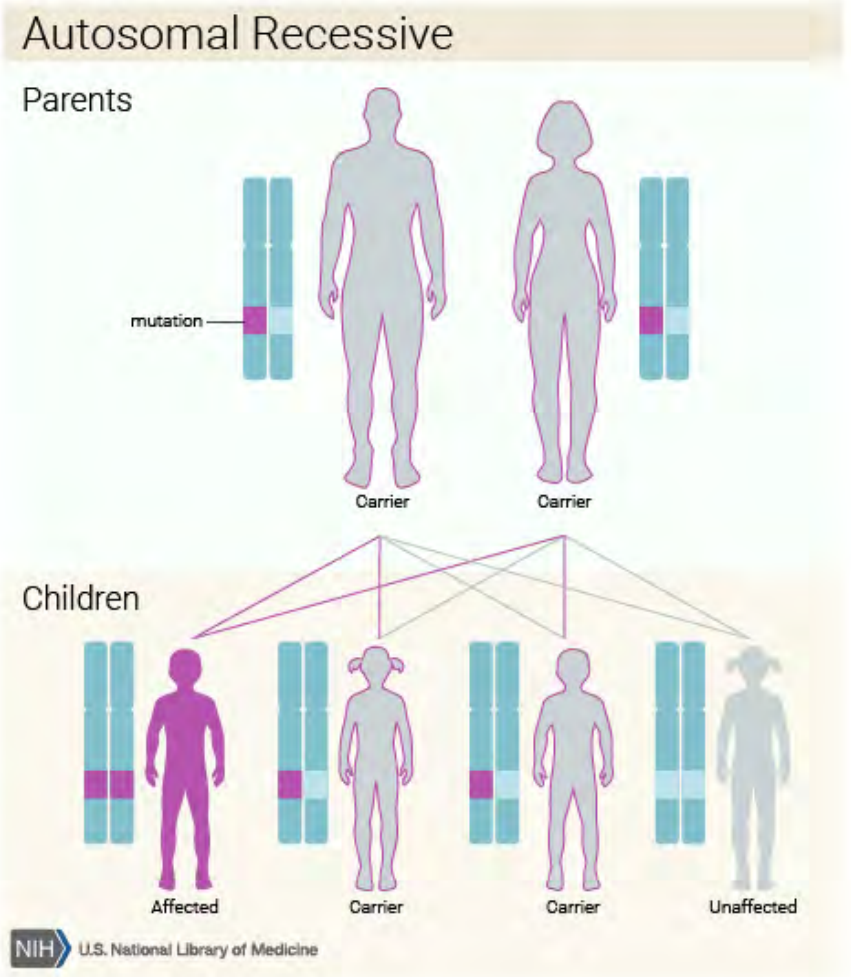




Rimmed vacuoles (RVs) and protein aggregates

Genetic Inheritance





Sporadic (sIBM/IBM) vs hIBM vs fIBM

- Hereditary IBM (hIBM) usually distinct from sporadic IBM
  - Biopsy shows RVs, inclusions, but rarely inflammation
  - Numbered based on order they were described; hIBM1 and hIBM3 extremely rare.

  - hIBM1 (Desmin, myofibrillary myopathy) – Autosomal Dominant
  - hIBM2 (GNE myopathy) – Autosomal Recessive (see curehibm.org)
    - Early onset, spares quadriceps (aka Quadriceps-Sparing Myopathy)
    - Often middle eastern or Japanese descent
  - hIBM3 (MYH2) – Autosomal Dominant
    - proximal weakness, contractures, ophthalmoplegia (eye movement abnormalities)
  - IBMPFD (VCP) – Autosomal Dominant
    - proximal + distal weakness, associated with Paget's (bone) disease, Frontotemporal Dementia
  - Other inherited muscle diseases may be associated with Rimmed Vacuoles, inflammation, or protein aggregates

- Familial IBM (fIBM) - typical sIBM present in a family

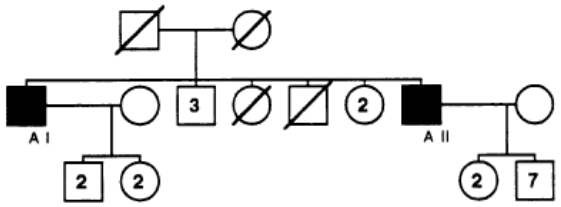
Brain (1997), **120**, 653–661

An inflammatory, familial, inclusion body myositis with autoimmune features and a phenotype identical to sporadic inclusion body myositis

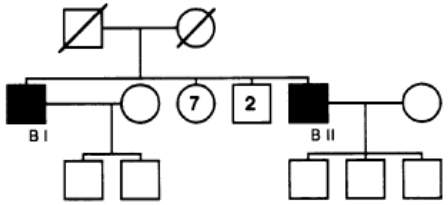
Studies in three families

Kumaraswamy Sivakumar, Christina Semino-Mora and Marinos C. Dalakas

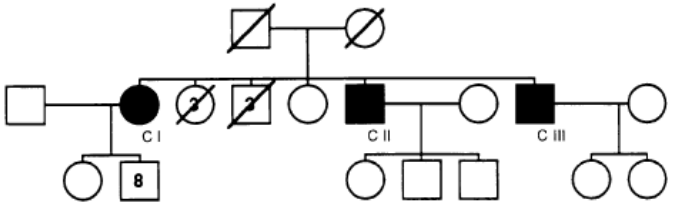
Family A



Family B



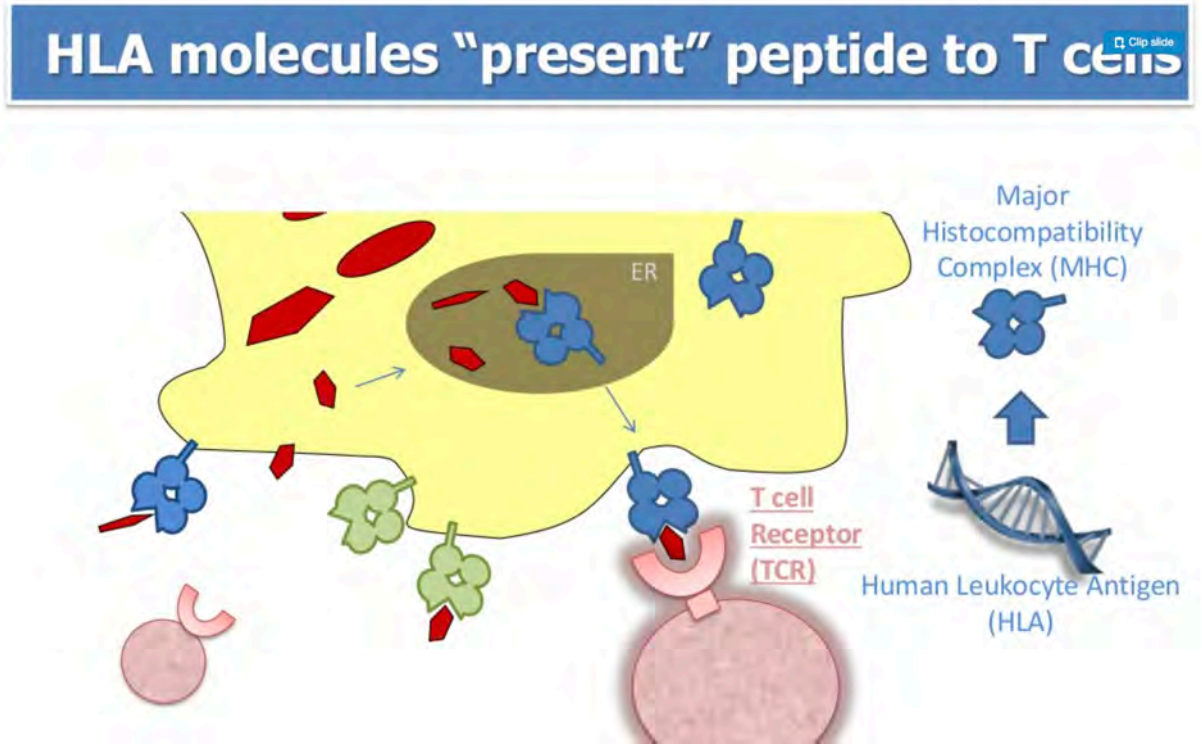
Family C



All families had at least one member that met strict sIBM criteria:

1. Onset mid-50's to 60's
2. Quad and FF
3. Muscle Bx-
    1. RVs, tubulofilaments on EM
    2. Invasion, MHC I upregulation
4. **All patients had HLA DR3 allele**

Human Leukocyte Antigen (HLA) Genetic Association in sIBM



Arguably, this is the best scientific evidence that sIBM is triggered by the immune system.

- 92% of 13 Caucasian sIBM patients have HLA-DR3 haplotype compared with 25% control (Garlepp et al Clin Exp Immuno 1994; Badrising, 2004; Mastaglia, 2009).
- HLA-DR3 allele associated with a 10-fold increased risk of IBM(Needham et al, 2009).

Next Gen Sequencing has revolutionized genetic testing

Date	Cost per Mb	Cost per Genome
Sep-01	$5,292.39	$95,263,072
Sep-02	$3,413.80	$61,448,422
Oct-03	$2,230.98	$40,157,554
Oct-04	$1,028.85	$18,519,312
Oct-05	$766.73	$13,801,124
Oct-06	$581.92	$10,474,556
Oct-07	$397.09	$7,147,571
Oct-08	$3.81	$342,502
Oct-09	$0.78	$70,333
Oct-10	$0.32	$29,092
Oct-11	$0.086	$7,743
Oct-12	$0.074	$6,618
Oct-13	$0.057	$5,096

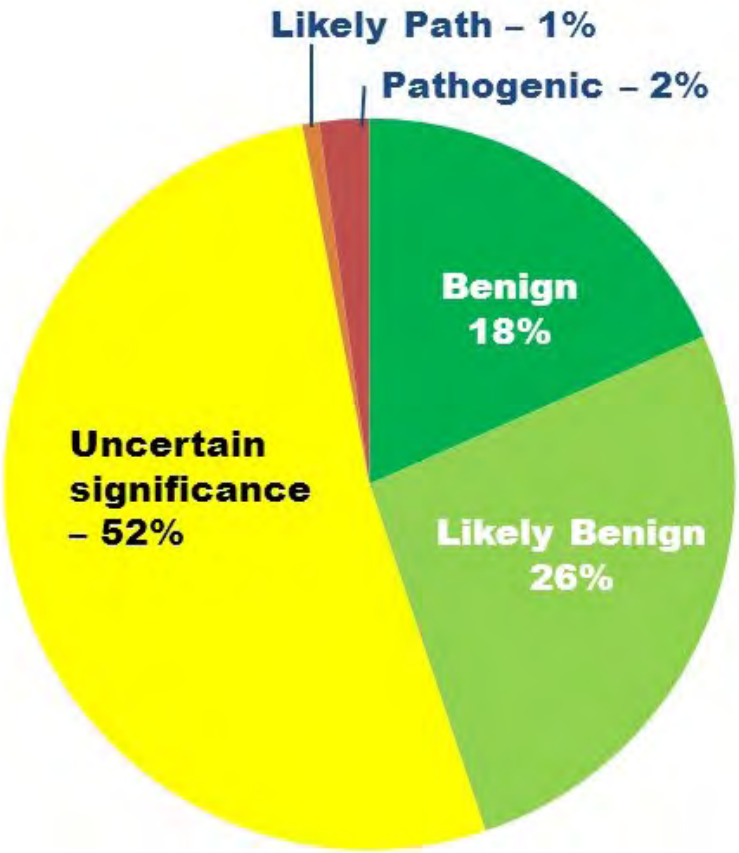
“Next Generation” Sequencing in sIBM

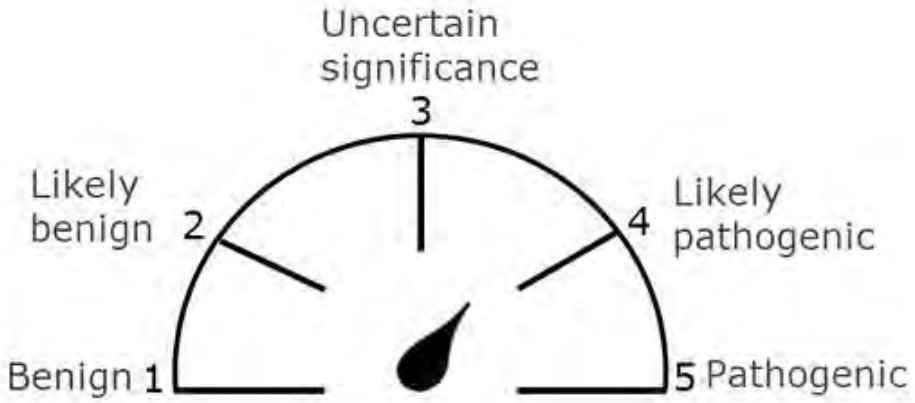
- 79 sIBM patients enrolled (many of them at TMA conference).
- “Next Generation Sequencing” panel for 38 genes known to be mutated in neuromuscular disease.
- A known IBMPFD-causing mutation in VCP found in one patient.
  - Slightly atypical pattern of weakness
  - Did have “endomysial invasion”

- 27 “rare variants” found in several genes. The variants are of uncertain signficance (VUS).

C.C. Weihl et al. / Neuromuscular Disorders 25 (2015) 289–296

Variants of Uncertain Significance





Very
Unhelpful
Statement

Case

- 62 yo woman with no family history and greater than 10 year history of progressive weakness
- Exam showed “limb-girdle” pattern of weakness and scapular winging.
- CK ~6000 IU/L.
- Negative genetic testing for FSHD.
- Diagnosed with Inclusion Body Myositis based on biceps muscle biopsy. Our review of single slide: chronic myopathy with rimmed vacuoles.
- 2012: Sent blood to Emory Genetics Lab for “Neuromuscular Disorders Panel”

Gene	Exon/Intron	Nucleotide change	Amino acid change	Zygosity	Type
CAV3	Ex2	c.233C>T	p.T78M	Heterozygous	VOUS
COL6A1	IVS29	c.1823-9C>T		Heterozygous	VOUS
RYR1	Ex29	c.4178A>G	p.K1393R	Heterozygous	VOUS
RYR1	Ex35	c.5637C>T	p.D1879D	Heterozygous	VOUS
RYR1	Ex100	c.14505G>A	p.G4835G	Heterozygous	VOUS
TTN	Ex4	c.426C>T	p.A142A	Heterozygous	VOUS
TTN	Ex7	c.1137A>G	p.R379R	Heterozygous	VOUS
TTN	IVS12	c.1938+10G>C		Heterozygous	VOUS
TTN	Ex61	c.15092A>G	p.N5031S	Heterozygous	VOUS
TTN	Ex66	c.16443A>G	p.I5481M	Heterozygous	VOUS
TTN	Ex78	c.19806C>G	p.F6602L	Heterozygous	VOUS
TTN	Ex80	c.20418C>T	p.S6806S	Heterozygous	VOUS
TTN	Ex85	c.21758G>A	p.R7253H	Heterozygous	VOUS
TTN	Ex104	c.26652T>C	p.D8884D	Heterozygous	VOUS
TTN	Ex145	c.30663A>C	p.E10221D	Heterozygous	VOUS
TTN	Ex155	c.31720C>T	p.P10574S	Heterozygous	VOUS
TTN	Ex194	c.37471G>A	p.A12491T	Heterozygous	VOUS
TTN	Ex202	c.39841C>A	p.P13281T	Heterozygous	VOUS
TTN	Ex212	c.41667A>T	p.L13889L	Heterozygous	VOUS
TTN	Ex214	c.42215G>C	p.S14072T	Heterozygous	VOUS
TTN	Ex244	c.49944C>T	p.I16648I	Heterozygous	VOUS
TTN	Ex259	c.57085G>A	p.V19029M	Heterozygous	VOUS
TTN	Ex275	c.64920A>G	p.P21640P	Heterozygous	VOUS
TTN	Ex275	c.74856C>A	p.N24952K	Heterozygous	VOUS
TTN	Ex284	c.82290G>A	p.S27430S	Heterozygous	VOUS
TTN	Ex284	c.82832G>A	p.R27611H	Heterozygous	VOUS
TTN	Ex284	c.83122T>G	p.C27708G	Heterozygous	VOUS
TTN	Ex286	c.84061G>A	p.A28021T	Heterozygous	VOUS
TTN	Ex292	c.87444C>T	p.T29148T	Heterozygous	VOUS

Continued...

Gene	Exon/Intron	Nucleotide change	Amino acid change	Zygosity	Type
TTN	Ex292	c.87593C>T	p.S29198F	Heterozygous	VOUS
TTN	Ex301	c.90795C>T	p.L30265L	Heterozygous	VOUS
TTN	Ex305	c.92355T>A	p.I30785I	Heterozygous	VOUS
TTN	Ex307	c.93702C>G	p.V31234V	Heterozygous	VOUS
TTN	Ex307	c.94187G>A	p.R31396H	Heterozygous	VOUS
TTN	Ex307	c.94891A>G	p.I31631V	Heterozygous	VOUS
TTN	Ex309	c.98934G>A	p.R32978R	Heterozygous	VOUS
TTN	Ex312	c.99996A>G	p.E33332E	Heterozygous	VOUS

Pathogenic variants in the *CAV3* gene (MIM 601253) cause limb-girdle muscular dystrophy type 1C (LGMD 1C). A single pathogenic variant in one copy of the *CAV3* gene causes disease. The c.233C>T (p.T78M) variant in *CAV3* has been previously reported in a homozygous state in an individual with LGMD 1C and dilated cardiomyopathy.[1] It has also been reported in individuals with long QT syndrome[2], sudden infant death syndrome[3,4], and idiopathic elevated serum creatine kinase levels[5] Additionally, the c.233C>T (p.T78M) variant has been reported in the general population[6,7]. While these studies have reported an association between the c.233C>T (p.T78M) variant and various conditions, there is currently insufficient data to prove causality for these conditions. Therefore, the c.233C>T (p.T78M) variant is classified as a variant of unknown significance (VOUS).

Pathogenic variants in the *COL6A1* gene (MIM 120220) cause the collagen type VI-related disorders Bethlem myopathy (BM) and Ullrich congenital muscular dystrophy (UCMD). BM is an autosomal dominant condition and a single pathogenic variant in one copy the *COL6A1* gene is associated with disease. UCMD can be autosomal dominant or autosomal recessive, requiring one pathogenic variant in the *COL6A1* gene in dominant cases or two pathogenic variants, one inherited from each parent, in recessive cases to cause the disease. The c.1823-9C>T intronic variant in *COL6A1* has not been reported in individuals with disease or as a variant in the general population. Therefore, the c.1823-9C>T variant is classified as a VOUS.

Pathogenic variants in the *RYR1* gene (MIM 180901) cause *RYR1*-related disorders. *RYR1*-related disorders include central core disease (CCD) and malignant hyperthermia susceptibility (MHS). CCD can be inherited in an autosomal dominant or autosomal recessive manner. Malignant hyperthermia susceptibility is an autosomal dominant disorder. A single pathogenic variant in one copy of the *RYR1* gene is associated with autosomal dominant disease. Two pathogenic variants within the *RYR1* gene, one inherited from each parent, are required to cause autosomal recessive disease.

The c.4178A>G (p.K1393R) variant in *RYR1* has been previously reported in an individual with MHS.[8] This variant has also been reported in a heterozygous state in a mother and son with late onset axial myopathy.[9] Additionally, the c.4178A>G (p.K1393R) variant has been reported in the general population.[6,7] Therefore, the c.4178A>G (p.K1393R) variant is classified as a VOUS.

The c.5637C>T (p.D1879D) and c.14505G>A (p.G4835G) variants in *RYR1* have not been previously reported as disease causing. These variants have been reported in the general population; however, the data are insufficient to determine clinical significance at this time.[6,7] Therefore, the c.5637C>T (p.D1879D) and c.14505G>A (p.G4835G) variants are classified as a VOUS.

Pathogenic variants in the *TTN* gene (MIM 188840) cause *TTN*-related disorders. *TTN*-related disorders include the autosomal dominant conditions dilated cardiomyopathy, hypertrophic cardiomyopathy, and hereditary myopathy with early respiratory failure, and the autosomal recessive conditions limb-girdle muscular dystrophy type 2J, tardive tibial muscular dystrophy, and early-onset myopathy with fatal cardiomyopathy.

Genetic Counseling and Informed Consent

Benefits

- End diagnostic odyssey
- Clarify reproductive risk
- Genetic counseling for family members
- Disease-specific management and prognosis
- Disease-specific support groups and research

Limitations

- Variable expression limits predictions
- Variants of Uncertain Significance
- Yield depends on phenotype

Risks

- Psychosocial impact
- Family impact
- Insurance (Life, disability)
- **Incidental Findings**

ACMG recommendations for incidental findings in clinical exome/genome sequencing

Whole Exome Sequencing (WES) in sporadic IBM

- 181 sIBM patients
- WES to identify rare variants in sIBM
- 7 (4%) have rare variants in VCP or SQSTM1
- **VCP**
  - Mutated in IBMPFD (Watts, 2004), ALS, FTD (Johnson, 2010; Koppers, 2012)
- **p62/SQSTM1**
  - Mutated in Paget's disease, ALS, FTD; rarely in distal myopathy (Bucelli, 2015)
  - Associates with protein aggregates in sIBM

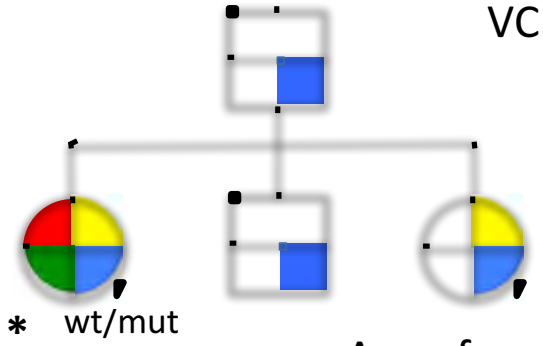
Age of onset 45 – 85 years old
None had other family members with IBM
All had prominent finger flexor weakness
All had inflammation on muscle biopsy
Most had met "definite" sIBM criteria

Gang et al, Neurobiol Aging 2016

Phenotypic heterogeneity of IBMPFD caused by VCP mutations

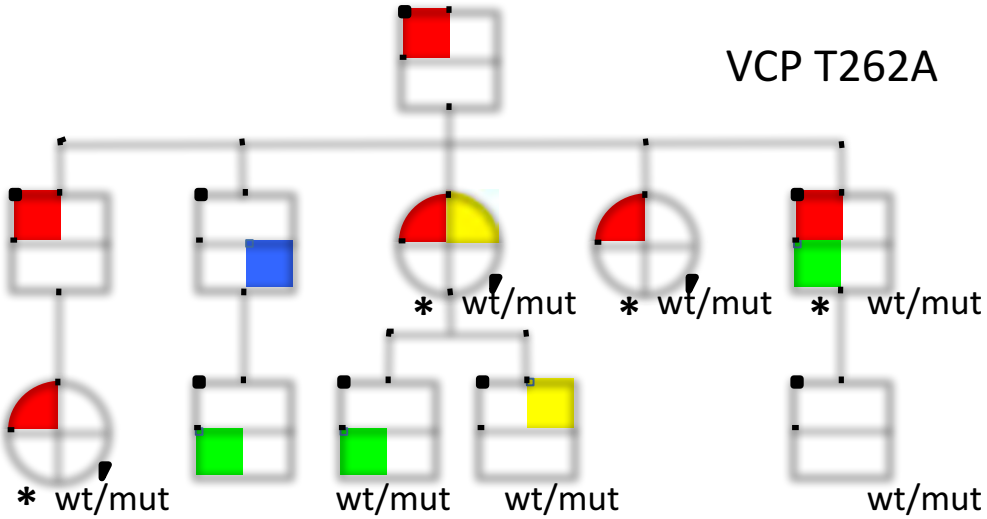
<u>Patients with VCP mutations can develop neurodegenerative disease and/or IBM</u>
Three families with VCP mutations and members with IBM and/or neurodegenerative disease

VCP R191Q

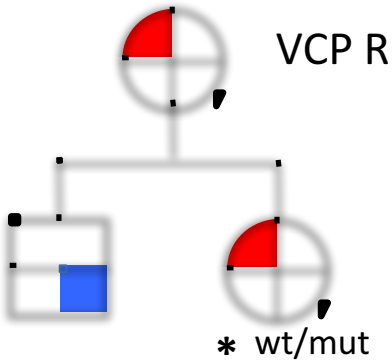


Age of onset 50-60

VCP T262A



VCP R159C



Age of onset 65-73

* Autopsy

FTD Parkinsonism ALS IBM

Adapted from Spina et al *Eur J Neurol* 2013

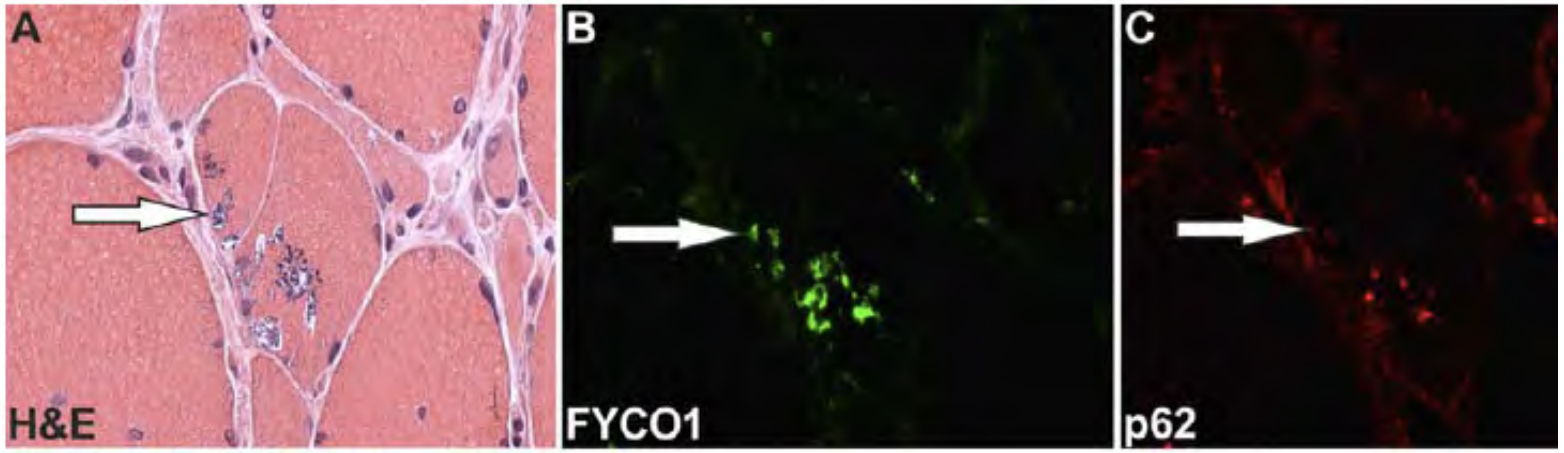
Combined proteomic and whole exome sequencing approach identifies FYCO1

- Vacuoles in sIBM enriched in proteins that function in protein degradation
- Rare missense FYCO1 variants present in 11.3% of sIBM patients (compared with 2.6% controls).
- FYCO1 variants may impair protein turnover and increase risk of sIBM

Proteomics of Rimmed Vacuoles Define New Risk Allele in Inclusion Body Myositis

Anne-Katrin Güttsches, MD,[1] Stefen Brady, MD, DPhil,[2] Kathryn Krause, MSc,[1,3] Alexandra Maerkens, MSc,[1,3] Julian Uszkoreit,[3] Martin Eisenacher, PhD,[3] Anja Schreiner,[1] Sara Galozzi, PhD,[3] Janine Mertens-Rill,[1] Martin Tegenthoff, MD,[1] Janice L. Holton, MD, PhD,[4,5] Matthew B. Harms, MD,[6] Thomas E. Lloyd, MD, PhD,[7] Matthias Vorgerd, MD,[1] Conrad C. Weihl, MD, PhD,[8] Katrin Marcus, PhD,[3] and Rudolf A. Kley, MD[1]

ANN NEUROL 2017;81:227–239



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INFLAMMATORY MUSCLE DISEASE (I LUNDBERG, SECTION EDITOR)

New Developments in the Genetics of Inclusion Body Myositis

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Published online: 2 April 2018

Abstract

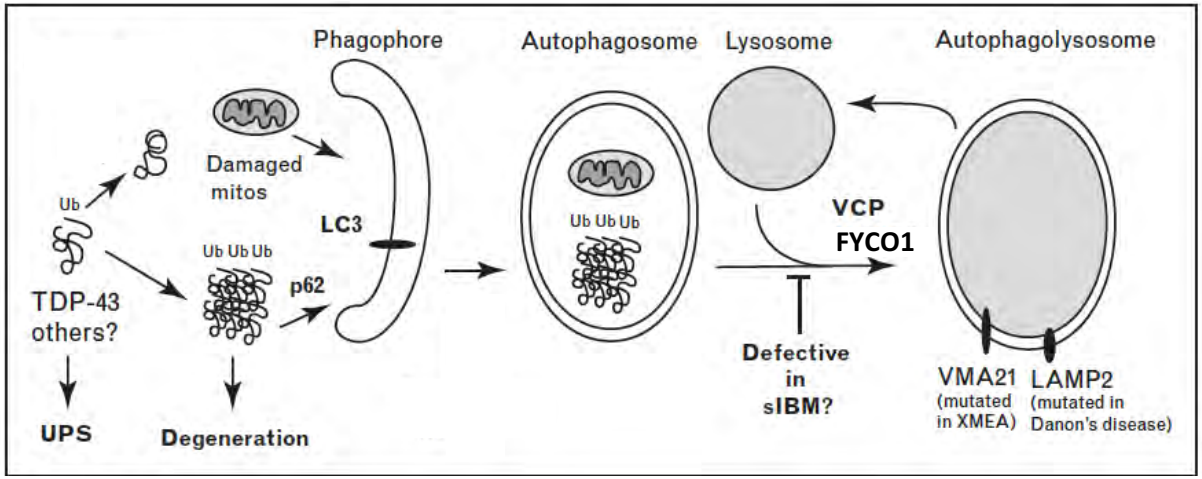
Purpose of Review Our goal is to review the recent literature pertaining to the genetics of sporadic inclusion body myositis (IBM).

Recent Findings In a study of 252 IBM patients, the class II MHC allele HLA-DRB1*03:01 showed the most significant association with IBM, and that risk could be largely attributed to amino acids within the peptide-binding pocket. Candidate gene sequencing identified rare missense variants in proteins regulating protein homeostasis including VCP and SQSTM1. An unbiased approach employing exome sequencing of genes encoding rimmed vacuole proteins identified FYCO1 variants in IBM. Ongoing GWAS approaches may shed new light on genetic risk factors for IBM.

Summary Many variants have been reported at an increased frequency in IBM in small studies; however, only HLA association has shown genome-wide significance. Future studies are needed to validate variants in larger cohorts and to understand the molecular roles these risk factors play in IBM.

Summary

- HLA locus strongly associated with sIBM risk
  - Evidence supporting autoimmune etiology
- Rare variants in known inherited myopathy and ALS/FTD genes in sIBM patients
  - Risk factor for sIBM?
    - Most variants also present in controls –more studies needed.
    - Might these patients have uncommon presentation of inherited myopathy?
  - Overlap between sIBM and neurodegenerative disease genes?



Modified from Lloyd TE, Curr Opin Rheum 2010