Genetics of Inclusion Body Myositis

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Co-director, Johns Hopkins Myositis Center
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) $\rightarrow$ frequent falls
  - Finger flexors $\rightarrow$ 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

Autosomal Dominant

Parents

Affected
Unaffected

Children
Affected
Affected
Unaffected

Autosomal Recessive

Parents

Carrier
Carrier

Children
Affected
Carrier
Carrier
Unaffected
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
    - Early onset, spares quadriceps (aka Quadriceps-Sparing Myopathy)
    - Often middle eastern or Japanese descent
  - hIBM2 (GNE myopathy) – Autosomal Recessive (see curehibm.org)
    - proximal weakness, contractures, ophthalmoplegia (eye movement abnormalities)
  - hIBM3 (MYH2) – Autosomal Dominant
    - proximal + distal weakness, associated with Paget’s (bone) disease, Frontotemporal Dementia
  - 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
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

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

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“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 significance (VUS).
Variants of Uncertain Significance

- Uncertain significance: 52%
- Benign: 18%
- Likely Benign: 26%
- Likely Pathogenic: 1%
- Pathogenic: 2%
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”
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Pathogenic variants in the **C4V3** gene (MIM 601253) cause limb-girdle muscular dystrophy type 1C (LGMD 1C). A single pathogenic variant in one copy of the **C4V3** gene causes disease. The c.233C>T (p.T78M) variant in **C4V3** 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\(^3\)\(^6\), 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 (VOS).

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 of 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 VUS.

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 VUS.

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 VUS.

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

Genetic liberitarians

“Return comprehensive data”
- Patient has the right to know
- Return all data on known, unknown risk variants

ACMG recommendations 2013

“Return data on a limited number of conditions & genes”

~20 diseases
~60 genes

Spectrum of opinions

Genetic empiricists

“Only return data that is truly significant”
- Penetrance for most variants unknown
- Don’t create burden of “patient in waiting”
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

Patients with VCP mutations can develop neurodegenerative disease and/or IBM

Three families with VCP mutations and members with IBM and/or neurodegenerative disease

VCP R159C

Age of onset 65-73

VCP R191Q

Age of onset 50-60

VCP T262A

* wt/mut

**Autopsy

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
New Developments in the Genetics of Inclusion Body Myositis

Kyla A. Britson\textsuperscript{1,2} · Stephanie Y. Yang\textsuperscript{1,3} · Thomas E. Lloyd\textsuperscript{1}

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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?