Published in final edited form as:

Curr Rheumatol Rep. ; 20(5): 26. doi:10.1007/s11926-018-0738-0.

New developments in the genetics of Inclusion Body Myositis

Kyla A. Britson^{1,2}, Stephanie Y. Yang^{1,3}, and Thomas E. Lloyd¹

¹Departments of Neurology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD

²Graduate program in Cellular and Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

³Graduate program in Human Genetics, Johns Hopkins University School of Medicine, Baltimore, MD

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.

Keywords

Inclusion Body Myositis; HLA; VCP; SQSTM1; FYCO1; follistatin

Introduction

Sporadic Inclusion Body myositis (IBM) is the most common myopathy in individuals over the age of 50, and patients typically lose the ability to ambulate 10 to 15 years after diagnosis [1–3]. IBM is characterized by slowly progressive asymmetric weakness of both proximal and distal muscles, with the finger flexors and quadriceps typically most affected

Correspondence to: Thomas E. Lloyd MD, PhD, tlloyd4@jhmi.edu.

Conflicts of Interest: The authors claim no conflict of interest.

Human and Animal Rights Statement: This article does not contain any studies with human or animal subjects performed by any of the authors.

[4]. Histological features of IBM include rimmed vacuoles, protein aggregates, cytochrome oxidase (COX)-deficient fibers, MHC-I upregulation, and an endomysial inflammatory infiltrate containing autoaggressive CD8+ T cells [4–7].

Whether IBM is primarily an autoimmune or a degenerative disease with secondary inflammation is unclear with evidence for both possibilities (Figure 1) [8,9]. The presence of CD8+ T-cells invading healthy-appearing myofibers, the association of IBM with specific HLA loci and other autoimmune disorders, and the presence of autoantibodies in IBM support an autoimmune trigger. However, the fact that immunosuppression has failed to show clinical benefit, the lack of inflammation in hereditary Inclusion Body Myopathy (hIBM) that shares other pathologic features with IBM, and the association with aging and protein inclusions found in neurodegenerative disease suggest the possibility that IBM is primarily a degenerative disease. Answering this question is essential for understanding the etiopathogenesis of IBM and developing targeted therapies.

Although rare patients with genetic muscle disease have been reported to have clinical phenotypes indistinguishable from IBM [10,11], hIBM typically presents at a younger age than IBM (before age 40), lacks inflammation, and displays a different pattern of muscle weakness [12]. For example, hIBM2 caused by autosomal recessive inheritance of mutations in the GNE gene typically spares the quadriceps, and biopsy shows rimmed vacuoles and protein inclusions but lacks inflammation. Thus, mutations in known hIBM genes cause syndromes that share degenerative features on biopsy but otherwise are clinically distinct from IBM. However, classic IBM can occasionally be present within multiple family members (“familial IBM”) [13,14], strongly supporting a role for genetic risk factors in the development of IBM. The advent of high-throughput sequencing technologies has begun to shed light on how the immune system and degenerative pathways interact in the pathogenesis of IBM.

Immune System

Robust, unbiased genome-wide association studies (GWAS) have not yet been completed in IBM due to the rarity of the disease, though a large multinational effort is underway [15]. Nonetheless, since first described by Garlepp et al in 1994, the Human Leukocyte Antigen (HLA) locus has been shown repeatedly to contain the strongest risk alleles for the development of IBM (Table 1) [16–19]. Recently, the Myositis Genetics Consortium (MYOGEN) analyzed immune-related genes in 252 Caucasian IBM patients and 1,008 ethnically-matched controls from 11 countries using the Illumina Immunochip array [19]. Variants within the HLA locus were the only single-nucleotide polymorphisms (SNPs) to reach genome-wide significance ($p < 5 \times 10^{-8}$). HLA-DRB1*03:01 showed the most significant association with IBM ($p = 5.77 \times 10^{-34}$), followed by HLA-DRB1*01:01 ($p = 1.57 \times 10^{-16}$), and HLA-DRB1*13:01 ($p = 3.28 \times 10^{-8}$). This finding is consistent with prior HLA-association studies identifying an association of IBM with the 8.1 ancestral MHC haplotype (8.1 AH) [16,20–22]. Contrary to previous results that HLA-DRB4 is protective and ameliorates the risk effect of HLA-DRB1*03:01 [17], no HLA alleles were found to modify disease onset or severity of IBM in this study. Furthermore, in agreement with a

study performed in an Australian cohort, there was no distinct HLA association with anti-cytosolic 5'-nucleotidase 1A (anti-cN1A) positivity [19,23].

To investigate whether the risk associated with these HLA-DRB1 alleles could be explained by specific amino acid positions shared between alleles, amino acid imputation was performed. A tyrosine residue at position 26 was found to be more strongly associated with IBM ($p < 5.22 \times 10^{-43}$) than the HLA-DRB1 allele alone, and an additional independent effect was seen at position 11 ($p < 3.8 \times 10^{-13}$) for serine. Of note, previous studies have associated positions 11 and 26 with other autoimmune diseases such as systemic lupus erythematosus [24]. Both of these residues are located within the β -sheet floor of DR β -chain 1 that forms part of the peptide-binding groove and may influence peptide binding and predispose individuals to autoimmunity [19]. Interestingly, although HLA-DRB1*03:01 is also a significant risk factor for Polymyositis (PM) and Dermatomyositis (DM), amino acid position 74 explains almost all of the risk within the allele for PM and DM [25].

NOTCH4, a previously identified risk gene within the HLA locus [26], was not explicitly examined in this study due to its strong linkage disequilibrium with the 8.1 AH. Three regions outside of the HLA locus that almost reached the level of genome-wide significance ($p = 2.25 \times 10^{-5}$) included a known frameshift mutation in CCR5 that causes a nonfunctional receptor [19]. CCR5 (C-C Chemokine Receptor type 5) is an important regulator of T-cell migration, suggesting a potential role for chemokines in the pathogenesis of IBM. A recent case-control study analyzing whole exome sequencing data on 30 Finnish IBM patients identified seven SNPs found at >2-fold higher frequency in IBM, and in addition to the HLA locus, implicated genes that regulate sphingolipid transport as potential IBM risk factors [18].

Overall, these recent studies have confirmed that variants within the HLA locus are risk factors for developing IBM, perhaps the strongest evidence to date that the immune system plays a causative role in IBM.

Proteostasis

Both IBM and inherited inclusion body “myopathy” syndromes share degenerative myopathic features on biopsy including rimmed vacuoles, ubiquitinated protein aggregates, and 15–18 nm tubulofilamentous “inclusions” observed with electron microscopy. A known cause of this pathology shared with many degenerative diseases is disruption of protein homeostasis, or proteostasis, as can be caused by impairment of the proteasome or autophagy. For example, Inclusion Body Myopathy with Paget’s disease and Frontotemporal Dementia (IBMPFD) is a multisystem degenerative disease caused by autosomal dominant inheritance of missense mutations in valosin-containing protein (VCP) [27]. VCP, also called p97 or cdc48, is a highly conserved homo-hexameric ATPase that functions as a “segregase” to remove ubiquitinated proteins from macromolecular complexes, and thus plays an important role in proteostasis [28].

Intriguingly, rare VCP variants have recently been implicated in IBM as well as multiple neurodegenerative diseases including Frontotemporal Dementia (FTD), Parkinson’s Disease,

Amyotrophic Lateral Sclerosis (ALS), and Charcot-Marie Tooth Disease [29–33]. Rare mutations in other genes, including HNRPA1, HNRPA2B1, and SQSTM1 have also been found to cause similar autosomal dominantly inherited degenerative diseases affecting muscle, bone, and brain, and have been termed “multisystem proteinopathy”, or MSP [34]. As with hIBM, MSP patients usually present before age 40 without the typical IBM pattern of weakness, and affected muscles in MSP display rimmed vacuoles and protein inclusions but lack inflammation. However, recent findings suggest that rare variants in these MSP genes may increase the risk for developing IBM.

Using targeted next generation sequencing, Wehl et. al. screened a cohort of 79 IBM patients for variants in 38 genes associated with muscular dystrophies, myopathies, ALS, and dementia [35]. This candidate-based approach uncovered an increased frequency of rare variants in multiple genes including VCP, SQSTM1, FLNC, ZASP, and BAG3 as well as a novel variant in HNRPA2B1. FLNC, SQSTM1, ZASP, and BAG3 are known to be mutated in rare inherited vacuolar myopathies and also play integral roles in the autophagy pathway [36–38]. SQSTM1 (Sequestosome 1, also known as p62) is a ubiquitin-binding autophagy adaptor that has been shown to label protein inclusions in IBM muscle [39–41]. The two rare variants identified in VCP were previously reported as putative disease-associated variants [31,42,43], and expression of these variants in cell culture causes an accumulation of the autophagosome markers p62 and LC3-II, suggestive of a disruption in autophagy [44]. Similarly, other candidate-based whole exome sequencing (WES) approaches have also identified rare VCP variants in IBM in addition to SQSTM1 [45] and ZASP [46]. The majority of these variants are in evolutionarily conserved regions, suggesting that they may have functional consequences and increase risk for disease. However, given the selection bias inherent in candidate-based approaches, further studies are necessary to determine whether these variants significantly alter protein function and play a role in IBM pathogenesis.

Rather than starting with genes previously implicated in muscle disease, Güttches et. al. performed an unbiased proteomics approach to identify proteins enriched in rimmed vacuoles (RVs) [47]. This method led to the identification of 213 proteins, 40 of which had been previously described in IBM including VCP and p62, validating this approach. Interestingly, proteins involved in protein quality control were among the most abundantly overrepresented proteins. To look for novel genetic contributors to IBM, WES was used to identify variants in genes encoding proteins found in RVs. When comparing the burden of these variants to an ALS cohort, only variants in the FYCO1 gene were statistically enriched in IBM patients (11.3% vs. 2.6% in controls). FYCO1 has been implicated in microtubule transport of autophagosomes, consistent with a role for autophagy impairment in the pathogenesis of IBM [48].

These recent studies all suggest that rare variants in proteins regulating autophagy and protein degradation may contribute to IBM risk. A recent study evaluated the therapeutic potential of targeting protein aggregation in IBM with Arimoclomol [49]. Arimoclomol is a small molecule thought to upregulate chaperone expression in stressed cells, thereby reducing the formation of protein aggregates. In myoblast cells and mice expressing mutant VCP protein, Arimoclomol improved IBM-like pathology, and in a small proof-of-concept

clinical study, there was a trend toward reduced decline in muscle strength and physical function in IBM patients taking Arimoclomol compared to placebo. A multisite phase II clinical trial is underway to evaluate the efficacy of this drug in IBM.

Mitochondria

Mitochondrial pathology has long been recognized as a prominent feature of IBM, including myofibers that accumulate abnormal mitochondria, COX-deficient fibers, and mitochondrial DNA (mtDNA) deletions [50–52]. Using real-time PCR, COX-deficient fibers from IBM patients were shown to have higher mtDNA deletion loads when compared to COX-normal fibers [50], supporting previous work that correlated mtDNA deletion load and COX-deficient fiber proportion. Interestingly, the fraction of COX-deficient fibers correlated with the amount of infiltrating T lymphocytes, suggesting an interaction between the mitochondrial defect and the autoimmune component of IBM [53].

Another mitochondrial protein that has been investigated in IBM is the Translocase of Outer Mitochondrial Membrane 40 (TOMM40). TOMM40 lies adjacent to apolipoprotein E (ApoE) in the genome, and thus ApoE and TOMM40 alleles are co-inherited. Prior studies have shown that the ApoE and TOMM40 genotype combination can be used as a predictor of age-dependent risk in Alzheimer's Disease (AD) [54]. Given reported β -amyloid deposition in both IBM and AD, Mastaglia et al investigated ApoE and TOMM40 polymorphisms in IBM [55]. In a study of 90 Caucasian patients, they found that carriers of APOE ϵ 3 who also contained the very long (VL) poly-T repeat allele of TOMM40 had a reduced risk of developing IBM as well as a later age of onset. Recently, Gang et. al. investigated this further in a larger cohort of 158 IBM patients obtained through the International IBM Genetics Consortium [56]. In contrast to the previous study, they did not find an association between any particular APOE-TOMM40 genotype and the risk of developing IBM, but did find that individuals carrying the VL TOMM40 allele had a later age of onset [56]. Since both studies found that the TOMM40 VL allele delays IBM disease onset, these findings suggest that further investigation into how the VL allele alters TOMM40 and mitochondrial function may shed insight into IBM pathogenesis.

Gene Therapy

Recent success in clinical trials of gene therapy in Spinal Muscular Atrophy (SMA) [57,58], an inherited motor neuron disease, in addition to excitement around genome editing technologies such as CRISPR [59] has led to the consideration of gene therapy for IBM. Since muscle atrophy is a major part of IBM pathology, Greenberg and colleagues analyzed the myostatin signaling pathway in IBM muscle. Myostatin is a tumor growth factor beta (TGF- β) family member that has a well-defined role as a negative regulator of muscle mass, making it a promising therapeutic target for muscle wasting disorders [60]. In particular, gene therapy using follistatin, a natural inhibitor of the myostatin receptor, has been reported to be safe and cause muscle hypertrophy in mice and primates [61]. Since the Myostatin signaling pathway was reported to be upregulated in IBM [62], follistatin gene therapy has been tested to determine if it improves muscle strength and function in IBM.

In a recent phase 1/2a clinical trial, adeno-associated viral (AAV) delivery of follistatin isoform 344 (FS344) via intramuscular quadriceps injection was reported to modestly improve the distance traveled for a 6 minute walk test (6MWT) in a small cohort of Becker muscular dystrophy (BMD) patients [63]. Promising histological changes were also observed including reduced endomysial fibrosis, fewer centralized nuclei, and normalization of fiber size. In a ‘proof-of-principle’ trial, 6 male IBM patients received bilateral intramuscular quadriceps injections of AAV1 vectors carrying FS344 [64]. One noteworthy change from the BMD study is that the IBM study included an exercise regimen for each participant as it had been demonstrated that exercise increased plasma levels of follistatin [65]. This study observed an improvement in the distance traveled for a 6MWT, and all post-treatment biopsies showed increased number of muscle fibers [64]. However, significant concerns have been raised in regards to the design of this trial and the authors’ claim of efficacy [66]. Most importantly, the lack of a control group makes it difficult to determine how much of the improvement was a result of exercise and/or placebo effect. Although previously it had been thought that exercise did not significantly alter the natural history of IBM, several studies suggest beneficial effects of endurance exercise in IBM patients [67–70].

Conclusion

IBM is a multifactorial disease with both inflammatory and degenerative characteristics. New high-throughput sequencing methods have revolutionized genetic analyses of complex disease, allowing for identification of genetic variants that are associated with an increased risk of developing IBM. Recent studies have confirmed and refined the major role the HLA locus plays in IBM susceptibility, strongly implicating autoimmunity in disease pathogenesis. In addition, multiple studies have identified rare variants within genes known to regulate protein quality control including autophagy, suggesting that one’s ability to prevent protein aggregate formation may partially underlie disease risk. While intriguing, the rare nature of IBM and the presence of most of these variants at low levels in the population make the significance of these findings unclear.

The identification of both immune and proteostasis-related genes in disease susceptibility of IBM further implicates both processes in IBM pathogenesis (Figure 1). In the degenerative model, a combination of genetic and environmental factors during aging may lead to defects in proteostasis (A) resulting in abnormal antigen presentation by muscle cells. This, in turn, may trigger an inflammatory response with T-cell invasion (B), and inflammation may or may not contribute to muscle degeneration and atrophy. In the autoimmune model, these same initial factors may first trigger autoimmunity (C), and the persistent inflammatory milieu may then lead to the development of protein aggregation (D), which may or may not contribute to muscle degeneration and atrophy. It’s entirely possible that both models are correct, and that the initiating process may vary in different patients. Since both inflammatory and degenerative processes interact in IBM, therapeutically targeting both may ultimately prove most successful.

References:

1. Needham M, Corbett A, Day T, Christiansen F, Fabian V, Mastaglia FL. Prevalence of sporadic inclusion body myositis and factors contributing to delayed diagnosis. *J. Clin. Neurosci.* Elsevier Ltd; 2008;15:1350–3.
2. Cortese A, Machado P, Morrow J, Dewar L, Hiscock A, Miller A, et al. Longitudinal observational study of sporadic inclusion body myositis: Implications for clinical trials. *Neuromuscul. Disord.* Elsevier B.V; 2013;23:404–12.
3. Cox FM, Titulaer MJ, Sont JK, Wintzen AR, Verschuuren JJGM, Badrising UA. A 12-year follow-up in sporadic inclusion body myositis: An end stage with major disabilities. *Brain* 2011;134:3167–75. [PubMed: 21908393]
4. Griggs RC, Askanas V, DiMauro S, Engel a, Karpati G, Mendell JR, et al. Inclusion body myositis and myopathies. *Ann. Neurol* 1995;38:705–13. [PubMed: 7486861]
5. Benveniste O, Guiguet M, Freebody J, Dubourg O, Squier W, Maisonnobe T, et al. Long-term observational study of sporadic inclusion body myositis. *Brain* 2011;134:3176–84. [PubMed: 21994327]
6. Needham M, Mastaglia FL. Inclusion body myositis: current pathogenetic concepts and diagnostic and therapeutic approaches. *Lancet Neurol* 2007;6:620–31. [PubMed: 17582362]
7. Dimitri D, Benveniste O, Dubourg O, Maisonnobe T, Eymard B, Amoura Z, et al. Shared blood and muscle CD8+ T-cell expansions in inclusion body myositis. *Brain* 2006;129:986–95. [PubMed: 16455793]
8. Benveniste O, Stenzel W, Hilton D, Marco J, Olivier S, Engelen BGM Van. Amyloid deposits and inflammatory infiltrates in sporadic inclusion body myositis: the inflammatory egg comes before the degenerative chicken. *Acta Neuropathol* 2015;129:611–24. [PubMed: 25579751]
9. Weihl CC, Mammen AL. Sporadic inclusion body myositis – a myodegenerative disease or an inflammatory myopathy. *Neuropathol. Appl. Neurobiol* 2017;43:82–91. [PubMed: 28111778]
10. Roda RH, Schindler AB, Blackstone C, Mammen AL, Corse AM, Lloyd TE. Laing distal myopathy pathologically resembling inclusion body myositis. *Ann. Clin. Transl. Neurol* 2014;1:1053–8. [PubMed: 25574480]
11. Leung DG, Taylor HA, Lindy AS, Basehore MJ, Mammen AL. A case of progressive quadriceps weakness and elevated creatine kinase level mimicking inclusion body myositis. *Arthritis Care Res* 2014;66:328–33.
12. Broccolini A, Gidaro T, Morosetti R, Mirabella M. Hereditary inclusion-body myopathy: Clues on pathogenesis and possible therapy. *Muscle and Nerve* 2009;40:340–9. [PubMed: 19618441]
13. Sivakumar K, Semino-Mora C, Dalakas MC. An inflammatory, familial, inclusion body myositis with autoimmune features and a phenotype identical to sporadic inclusion body myositis: Studies in three families. *Brain* 1997;120:653–61. [PubMed: 9153127]
14. Ranque-Francois B, Maisonnobe T, Dion E, Piette JC, Chauveheid MP, Amoura Z, et al. Familial inflammatory inclusion body myositis. *Ann. Rheum. Dis* 2005;64:634–7. [PubMed: 15769920]
15. Gang Q, Bettencourt C, Houlden H, Hanna MG, Machado PM. Genetic advances in sporadic inclusion body myositis. *Curr. Opin. Rheumatol* 2015;27:586–94. [PubMed: 26335925]
16. Garlepp MJ, Laing B, Zilko PJ, Ollier W, Mastaglia FL. HLA associations with inclusion body myositis. *Clin. Exp. Immunol* 1994;98:40–5. [PubMed: 7923882]
17. Rojana-udomsart A, James I, Castley A, Needham M, Scott A, Day T, et al. High-resolution HLA-DRB1 genotyping in an Australian inclusion body myositis (s-IBM) cohort: An analysis of disease-associated alleles and diplotypes. *J. Neuroimmunol* 2012;250:77–82. [PubMed: 22633068]
- 18. Johari M, Arumilli M, Palmio J, Savarese M, Tasca G, Mirabella M, et al. Association study reveals novel risk loci for sporadic inclusion body myositis. *Eur. J. Neurol* 2017;24:572–7. [PubMed: 28233382] This study identified novel variants within five genes: STARD3, SETD4, SGPL1, NOTCH4, and HLA-DQB1. The STARD3 and SGPL1 variants potentially indicate a role for sphingolipid dynamics in IBM pathology.
- 19. Rothwell S, Cooper RG, Lundberg IE, Gregersen PK, Hanna MG, Machado PM, et al. Immune-Array Analysis in Sporadic Inclusion Body Myositis Reveals HLA–DRB1 Amino Acid Heterogeneity Across the Myositis Spectrum. *Arthritis Rheumatol* 2017;69:1090–9. [PubMed:

28086002] Rothwell et. al. have accomplished the largest genetic association study of IBM to date. This study confirms the importance of the HLA-DRB1 loci in the risk of developing IBM and this risk can be explained by specific amino acid variants within the HLA-DRB1 binding pocket.

20. Badrising UA, Schreuder GM, Giphart MJ, Geleijns K, Verschuuren JJ, Wintzen AR, et al. Associations with autoimmune disorders and HLA class I and II antigens in inclusion body myositis. *Neurology* 2004;63:2396–8. [PubMed: 15623710]
21. Mastaglia FL. Sporadic inclusion body myositis: Variability in prevalence and phenotype and influence of the MHC. *Acta Myol* 2009;28:66–71. [PubMed: 20128139]
22. Needham M, James I, Corbett A, Day T, Christiansen F, Phillips B, et al. Sporadic inclusion body myositis: Phenotypic variability and influence of HLA-DR3 in a cohort of 57 Australian cases. *J. Neurol. Neurosurg. Psychiatry* 2008;79:1056–60. [PubMed: 18258695]
23. Limaye VS, Lester S, Blumbergs P, Greenberg SA. anti-cN1A Antibodies in South Australian Patients with Inclusion Body Myositis. *Muscle and Nerve* 2016;53:653–4. [PubMed: 26566215]
24. Kim K, Bang SY, Lee HS, Okada Y, Han B, Saw WY, et al. The HLA-DRB1 amino acid positions 11–13-26 explain the majority of SLE-MHC associations. *Nat. Commun* 2014;5:5902. [PubMed: 25533202]
- 25. Rothwell S, Cooper RG, Lundberg IE, Miller FW, Gregersen PK, Bowes J, et al. Dense genotyping of immune-related loci in idiopathic inflammatory myopathies confirms HLA alleles as the strongest genetic risk factor and suggests different genetic background for major clinical subgroups. *Ann. Rheum. Dis* 2016;75:1558–66. [PubMed: 26362759] This report describes the largest genetic study of ideopathic inflammatory myopathies: Polymyositis, IBM, and adult and juvenile Dermatomyositis.
26. Scott AP, Laing NG, Mastaglia F, Dalakas M, Needham M, Allcock RJN. Investigation of NOTCH4 coding region polymorphisms in sporadic inclusion body myositis. *J. Neuroimmunol* 2012;250:66–70. [PubMed: 22732452]
27. Watts GDJ, Wymer J, Kovach MJ, Mehta SG, Mumm S, Darvish D, et al. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. *Nat. Genet* 2004;36:377–81. [PubMed: 15034582]
28. Meyer H, Weihl CC. The VCP/p97 system at a glance: connecting cellular function to disease pathogenesis. *J. Cell Sci* 2014;127:3877–83. [PubMed: 25146396]
29. Johnson JO, Mandrioli J, Benatar M, Abramzon Y, Van Deerlin VM, Trojanowski JQ, et al. Exome Sequencing Reveals VCP Mutations as a Cause of Familial ALS. *Neuron* 2010;68:857–64. [PubMed: 21145000]
30. Koppers M, van Blitterswijk MM, Vlam L, Rowicka PA, van Vught PWJ, Groen EIJ, et al. VCP mutations in familial and sporadic amyotrophic lateral sclerosis. *Neurobiol. Aging* 2012;33:837.e7–837.e13.
31. Majounie E, Traynor BJ, Chiò A, Restagno G, Mandrioli J, Benatar M, et al. Mutational analysis of the VCP gene in Parkinson's disease. *Neurobiol. Aging* 2012;33:209.e1–209.e2.
32. Spina S, Van Laar AD, Murrell JR, Hamilton RL, Kofler JK, Epperson F, et al. Phenotypic variability in three families with valosin-containing protein mutation. *Eur J Neurol* 2013;20:251–8. [PubMed: 22900631]
33. Gonzalez MA, Feely SM, Spezziani F, Strickland AV, Danzi M, Bacon C, et al. A novel mutation in VCP causes Charcot-Marie-Tooth Type 2 disease. *Brain* 2014;137:2897–902. [PubMed: 25125609]
34. Benatar M, Wu J, Fernandez C, Weihl CC, Katzen H, Steele J, et al. Motor neuron involvement in multisystem proteinopathy: Implications for ALS. *Neurology* 2013;80:1874–80. [PubMed: 23635965]
- 35. Weihl CC, Baloh RH, Lee Y, Chou TF, Pittman SK, Lopate G, et al. Targeted sequencing and identification of genetic variants in sporadic inclusion body myositis. *Neuromuscul. Disord* 2015;25:289–96. [PubMed: 25617006] This study utilized a candidate gene sequencing approach to identify novel variants in IBM patients. Several genes were found to contain variants, including VCP, BAG3, FLNC, and HNRNPA2B1

36. Ruparel AA, Oorschot V, Ramm G, Bryson-Richardson RJ. FLNC myofibrillar myopathy results from impaired autophagy and protein insufficiency. *Hum. Mol. Genet* 2016;25:2131–42. [PubMed: 26969713]
37. Behl C BAG3 and friends: Co-chaperones in selective autophagy during aging and disease. *Autophagy* 2011;7:795–8. [PubMed: 21681022]
38. Baixauli F, López-Otín C, Mittelbrunn M. Exosomes and autophagy: Coordinated mechanisms for the maintenance of cellular fitness. *Front. Immunol* 2014;5:1–6. [PubMed: 24474949]
39. Nogalska A, Terracciano C, D'Agostino C, King Engel W, Askanas V. p62/SQSTM1 is overexpressed and prominently accumulated in inclusions of sporadic inclusion-body myositis muscle fibers, and can help differentiating it from polymyositis and dermatomyositis. *Acta Neuropathol* 2009;118:407–13. [PubMed: 19557423]
40. Dubourg O, Wanschitz J, Maisonneuve T, Béhin A, Allenbach Y, Herson S, et al. Diagnostic value of markers of muscle degeneration in sporadic inclusion body myositis. *Acta Myol* 2011;30:103–8. [PubMed: 22106712]
41. Ikenaga C, Kubota A, Kadoya M, Taira K, Uchio N, Hida A, et al. Clinicopathologic features of myositis patients with CD8-MHC-I complex pathology. *Neurology* 2017;89:1060–8. [PubMed: 28794251]
42. Kimonis VE, Fulchiero E, Vesa J, Watts G. VCP disease associated with myopathy, Paget disease of bone and frontotemporal dementia: Review of a unique disorder. *Biochim. Biophys. Acta - Mol. Basis Dis* 2008;1782:744–8.
43. Rohrer JD, Warren JD, Reiman D, Uphill J, Beck J, Collinge J, et al. A novel exon 2 I27V VCP variant is associated with dissimilar clinical syndromes. *J. Neurol* 2011;258:1494–6. [PubMed: 21387114]
44. Ju JS, Fuentealba RA, Miller SE, Jackson E, Piwnicka-Worms D, Baloh RH, et al. Valosin-containing protein (VCP) is required for autophagy and is disrupted in VCP disease. *J. Cell Biol* 2009;187:875–88. [PubMed: 20008565]
- 45. Gang Q, Bettencourt C, Machado PM, Brady S, Holton JL, Pittman AM, et al. Rare variants in SQSTM1 and VCP genes and risk of sporadic inclusion body myositis. *Neurobiol. Aging* 2016;47:218.e1–218.e9. This study identified SQSTM1/p62 and VCP variants in sporadic IBM patients.
46. Cai H, Yabe I, Sato K, Kano T, Nakamura M, Hozen H, et al. Clinical, pathological, and genetic mutation analysis of sporadic inclusion body myositis in Japanese people. *J. Neurol* 2012;259:1913–22. [PubMed: 22349865]
- 47. Güttches AK, Brady S, Krause K, Maerkens A, Uszkoreit J, Eisenacher M, et al. Proteomics of rimmed vacuoles define new risk allele in inclusion body myositis. *Ann. Neurol* 2017;81:227–39. [PubMed: 28009083] Güttches et. al. used a proteomic approach to identify novel rimmed vacuole containing proteins in IBM; they then used whole exome sequencing to find rare variants in these proteins associated with IBM. Of note, variants within FYCO1, an LC3 interacting protein, were found to be overrepresented in IBM patients.
48. Pankiv S, Alemu EA, Brech A, Bruun JA, Lamark T, Øvervatn A, et al. FYCO1 is a Rab7 effector that binds to LC3 and PI3P to mediate microtubule plus end - Directed vesicle transport. *J. Cell Biol* 2010;188:253–69. [PubMed: 20100911]
49. Ahmed M, Machado PM, Miller A, Spicer C, Herbelin L, He J, et al. Targeting protein homeostasis in sporadic inclusion body myositis. *Sci. Transl. Med* 2016;8:28–31.
50. Lindgren U, Roos S, Hedberg Oldfors C, Moslemi AR, Lindberg C, Oldfors A. Mitochondrial pathology in inclusion body myositis. *Neuromuscul. Disord* 2015;25:281–8. [PubMed: 25638290]
51. Oldfors A, Larsson NG, Lindberg C, Holme E. Mitochondrial DNA deletions in inclusion body myositis. *Brain* 1993;116:325–36. [PubMed: 8384916]
52. Oldfors A, Moslemi AR, Jonasson L, Ohlsson M, Kollberg G, Lindberg C. Mitochondrial abnormalities in inclusion-body myositis. *Neurology* 2006;66:S49–55. [PubMed: 16432145]
53. Rygiel KA, Miller J, Grady JP, Rocha MC, Taylor RW, Turnbull DM. Mitochondrial and inflammatory changes in sporadic inclusion body myositis. *Neuropathol. Appl. Neurobiol* 2015;41:288–303. [PubMed: 24750247]

54. Roses AD, Lutz MW, Crenshaw DG, Grossman I, Saunders AM, Gottschalk WK. TOMM40 and APOE: Requirements for replication studies of association with age of disease onset and enrichment of a clinical trial. *Alzheimer's Dement* 2013;9:132–6. [PubMed: 23333464]
55. Mastaglia FL, Rojana-udomsart A, James I, Needham M, Day TJ, Kiers L, et al. Polymorphism in the TOMM40 gene modifies the risk of developing sporadic inclusion body myositis and the age of onset of symptoms. *Neuromuscul. Disord* 2013;23:969–74. [PubMed: 24103330]
56. Gang Q, Bettencourt C, Machado PM, Fox Z, Brady S, Healy E, et al. The effects of an intronic polymorphism in TOMM40 and APOE genotypes in sporadic inclusion body myositis. *Neurobiol. Aging* 2015;36:1766.e1–1766.e3.
57. Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *N. Engl. J. Med* 2017;377:1713–22. [PubMed: 29091557]
58. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N. Engl. J. Med* 2017;377:1723–32. [PubMed: 29091570]
59. Bengtsson NE, Hall JK, Odom GL, Phelps MP, Andrus CR, Hawkins RD, et al. Corrigendum: Muscle-specific CRISPR/Cas9 dystrophin gene editing ameliorates pathophysiology in a mouse model for Duchenne muscular dystrophy. *Nat. Commun. Nature Publishing Group*; 2017;8:16007.
60. Elkina Y, von Haehling S, Anker SD, Springer J. The role of myostatin in muscle wasting: An overview. *J. Cachexia. Sarcopenia Muscle* 2011;2:143–51. [PubMed: 21966641]
61. Kota J, Handy CR, Haidet AM, Montgomery CL, Eagle A, Rodino-Klapac LR, et al. Follistatin gene delivery enhances muscle growth and strength in nonhuman primates. *Sci. Transl. Med* 2009;1:1–8.
62. Amato AA, Sivakumar K, Goyal N, David WS, Salajegheh M, Praestgaard J, et al. Treatment of sporadic inclusion body myositis with bimagrumab. *Neurology* 2014;83:2239–46. [PubMed: 25381300]
63. Mendell JR, Sahenk Z, Malik V, Gomez AM, Flanigan KM, Lowes LP, et al. A Phase 1/2a Follistatin Gene Therapy Trial for Becker Muscular Dystrophy. *Mol. Ther* 2015;23:192–201. [PubMed: 25322757]
64. Mendell JR, Sahenk Z, Al-Zaidy S, Rodino-Klapac LR, Lowes LP, Alfano LN, et al. Follistatin Gene Therapy for Sporadic Inclusion Body Myositis Improves Functional Outcomes. *Mol. Ther* 2017;25:870–9. [PubMed: 28279643]
65. Hansen J, Brandt C, Nielsen AR, Hojman P, Whitham M, Febbraio MA, et al. Exercise induces a marked increase in plasma follistatin: Evidence that follistatin is a contraction-induced hepatokine. *Endocrinology* 2011;152:164–71. [PubMed: 21068158]
66. Greenberg SA. Unfounded Claims of Improved Functional Outcomes Attributed to Follistatin Gene Therapy in Inclusion Body Myositis. *Mol. Ther* 2017;25:2235–7. [PubMed: 28927986]
67. Johnson LG, Collier KE, Edwards DJ, Philippe DL, Eastwood PR, Walters SE, et al. Improvement in Aerobic Capacity After an Exercise Program in Sporadic Inclusion Body Myositis. *J. Clin. Neuromuscul. Dis* 2009;10:178–84. [PubMed: 19494728]
68. Spector SA, Lemmer JT, Koffman BM, Fleisher TA, Feuerstein IM, Hurley BF, et al. Safety and efficacy of strength training in patients with sporadic inclusion body myositis. *Muscle Nerve* 1997;20:1242–8. [PubMed: 9324080]
69. Arnardottir S, Alexanderson H, Lundberg IE, Borg K. Sporadic inclusion body myositis: pilot study on the effects of a home exercise program on muscle function, histopathology, and inflammatory reaction. *J Rehabil Med* 2002;35:31–5.
70. Alexanderson H, Lundberg IE. Exercise as a therapeutic modality in patients with idiopathic inflammatory myopathies. *Curr. Opin. Rheumatol* 2012;24:201–7. [PubMed: 22189517]
71. Love LA, Leff RL, Fraser DD, Targoff IN, Dalakas M, Plotz PH, Miller FW. A New Approach to the Classification of Idiopathic Inflammatory Myopathy: Myositis-Specific Autoantibodies Define Useful Homogeneous Patient Groups. *Medicine* 1991;70:360–74. [PubMed: 1659647]
72. Lampe J, Gossrau G, Kempe A, Füssell M, Schwurack K, Schroder R, Krause S, Kohnen R, Walter M, Reichmann H, Lochmüller. Analysis of HLA class I and II alleles in sporadic inclusion-body myositis. *J Neurol* 2003;250:1313–17. [PubMed: 14648147]

73. Price P, Santoso L, Mastaglia F, Garlepp M, Kok CC, Allcock R, Laing N. Two major histocompatibility complex haplotypes influence susceptibility to sporadic inclusion body myositis: Critical evaluation of an association with HLA-DR3. *Tissue Antigens* 2003;64:575–80.
74. O'Hanlon TP, Carrick DM, Arnett FC, Reveille JD, Carrington M, Gao X, Oddis CV, Morel PA, Malley JE, Malley K, Dreyfuss J, Shamim EA, Rider LG, Chanock SJ, Foster CB, Bunch T, Plotz PH, Love LA, Miller FW. Immunogenetic Risk and Protective factors for the Idiopathic Inflammatory Myopathies: Distinct HLA-A, -B, -Cw, -DRB1 and -DQA1 Allelic Profiles and Motifs Define Clinicopathologic Groups in Caucasians. *Medicine* 2005;84:338–49. [PubMed: 16267409]
75. Scott AP, Allcock RJN, Mastaglia F, Nishino I, Nonaka I, Laing N. Sporadic inclusion body myositis in Japanese is associated with the MHC ancestral haplotype 52.1. *Neuromuscul. Disord* 2006;16: 311–15. [PubMed: 16564169]
76. Mastaglia FL, Needham M, Scott A, James I, Zilko P, Day T, Kiers L, Corbett A, Witt CS, Allcock R, Laing N, Garlepp M, Christiansen FT. Sporadic inclusion body myositis: HLA-DRB1 allele interactions influence disease risk and clinical phenotype. *Neuromuscul. Disord* 2009;19:763–65. [PubMed: 19720533]

Degenerative

Autoimmune

Figure: Models of IBM pathogenesis.

In the degenerative model, disrupted proteostasis (A) leads to muscle degeneration and atrophy, and inflammation (B) is secondary to abnormal antigen presentation by muscle cells. In the autoimmune model, refractory autoimmune cells (C) secrete factors that cause protein aggregation (D), and these processes cause muscle degeneration and atrophy.

Table 1:
HLA and Non-HLA Gene Associations with IBM.

The HLA locus has been repeatedly shown to contain the strongest risk alleles for the development of IBM, in particular the DR3 serotype. The HLA locus contains genes that encode MHC class I (HLA-A, B, and C) and MHC class II (e.g. DOB, DQ, and DR). In some studies, only the serotype is reported (e.g. B8, DR3, DR53), whereas sequencing studies may identify a specific allele (e.g. DRB1*03:01 refers to specific 03 allele of beta chain of DR class II molecule associated with DR3 serotype). More recently, areas outside of HLA loci have been suggested to be associated with IBM.

HLA Association	# patients, ethnicity	Odds Ratio (95% CI)	Reported p value	Reference
A3 (A*03)	47 German	Not reported	0.0002	72
B52 (B*5201)	31 Japan	5.67 (3.24–9.91)	< 0.001	75
B52 (5201), DR15 (1502)	31 Japan	6.468 (3.63–11.52)	< 0.001	75
B8	47 German	Not reported	0.002	72
B8	52 Netherlands	7.5 (4.2–13.6)	< 0.00001	20
B8	80 Australia	3.94 (2.22–7.18)	< 0.01	16, 22, 73, 76
B8 + DR3 (8.1AH)	80 Australia	6.1 (3.3–11.7)	< 0.01	76
C4A*Q0	13 Australia	Not reported	< 0.005	16
Cw*14	48 Caucasian, US	29.3 (2.68–1449.2)	0.017	74
DOB	30 Finnish	3.22 (1.7829–5.8025)	0.0002	18
DQA1*0201	48 Caucasian, US	0.1 (0.03–0.48)	0.0013	74
DQA1*03	48 Caucasian, US	0.1 (0.03–0.43)	0.0002	74
DQA1*0501	48 Caucasian, US	2.4 (1.23–5.01)	0.0065	74
DQ2 (DQB1*02)	52 Netherlands	6.1 (3.1–11.7)	0.00001	20
DQ8 (DQB1*03)	52 Netherlands	0.0 (0.0–0.6)	0.001	20
DQB1	30 Finnish	3.89 (2.1804–6.9282)	0.0001	18
DQ5 (DQB1*05)	47 German	Not reported	0.02	72
DR1 (DRB1*01:01)	105 Australia	2.02 (1.11–3.67)	0.019	17
DR1 (DRB1*01:01)	252 Caucasian	4.64 (3.33–6.49)	1.6×10^{-16}	19
DR3 (DRB1*03)	52 Netherlands	10.8 (5.6–20.9)	< 0.00001	20
DR3 (DRB1*03)	80 Australia	9.56 (5.12–18.96)	< 0.01	16, 73, 76
DR3 (DRB1*03)	47 German	Not reported	0.0000002	72
DR3 (DRB1*03:01)	105 Australia	10.19 (5.67–18.8)	2.3×10^{-18}	17
DR3 (DRB1*03:01)	252 Caucasian	7.97 (5.88–10.95)	5.8×10^{-34}	19
DR3 (DRB1*03:01)	48 Caucasian, US	5.0 (2.56–9.76)	< 0.0001	74
DR3 (03:01)/DR1(01:01) diplotype	105 Australia	8.4 (1.89–77.83)	0.0009	17
DR4 (DRB1*04)	52 Netherlands	0.2 (0.1–0.5)	0.007	20
DR4 (DRB1*04)	80 Australia	0.30 (0.13–0.62)	< 0.01	76
DR7 (DRB1*07)	80 Australia	0.21 (0.07–0.49)	< 0.01	76
DR7 (DRB1*07:01)	105 Australia	0.20 (0.08–0.44)	0.000007	17
DR13 (DRB1*13:01)	105 Australia	2.26 (1.11–4.64)	0.023	17

HLA Association	# patients, ethnicity	Odds Ratio (95% CI)	Reported p value	Reference
DR13 (DRB1*13:01)	252 Caucasian	3.19 (2.14–4.72)	3.3×10^{-8}	19
DR15 (DRB1*15:02)	31 Japan	5.32 (3.02–9.40)	< 0.001	75
DR52	52 Netherlands	4.2 (1.7–10.2)	0.01	20
DR53	52 Netherlands	0.1 (0.0–0.3)	< 0.00001	20
Non-HLA Association				
CCR3/CCR2	252 Caucasian	0.42 (0.29–0.60)	1.93×10^{-6}	19
FLJ14816/GLI2	252 Caucasian	1.60 (1.31–1.96)	5.66×10^{-6}	19
LOC100128517/LOC728961	252 Caucasian	2.23 (1.57–3.17)	7.52×10^{-6}	19
STARD3	30 Finnish	4.83 (2.2197–10.4886)	0.0002	18
SETD4	30 Finnish	3.74 (1.8120–7.7085)	0.0007	18
SGPL1	30 Finnish	5.15 (2.0335–13.0413)	0.0011	18