Myositis Basics/Who Gets Myositis

2

Matthew J. S. Parker, Hector Chinoy, Robert G. Cooper, and Janine A. Lamb

Key Points to Remember

- The idiopathic inflammatory myopathies (IIM) are thought to result from chronic immune activation following an environmental trigger in genetically predisposed individuals.
- IIM have a bimodal distribution of age of onset, with peaks in adolescence and the sixth and seventh decades of life, and more commonly affect females.
- Inclusion body myositis and cancer-associated myositis are two IIM subtypes where older males are at higher risk, in contrast to other IIM subtypes.
- The strongest genetic risk factors for IIM lie in the major histocompatibility complex (MHC) on chromosome 6, a highly variable region which encodes many proteins that present antigens to the immune system.

M. J. S. Parker (✉)
Rheumatology Department, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Salford, UK

The National Institute for Health Research Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK

Sydney Medical School, University of Sydney, Sydney, Australia
e-mail: Matthew.Parker@sydney.edu.au

H. Chinoy
Rheumatology Department, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Salford, UK

The National Institute for Health Research Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK
e-mail: Hector.Chinoy@manchester.ac.uk

R. G. Cooper
MRC-Arthritis Research UK Centre for Integrated Research into Musculoskeletal Ageing, University of Liverpool, Liverpool, UK

Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK
e-mail: Robert.Cooper@liverpool.ac.uk

J. A. Lamb
Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK
e-mail: Janine.Lamb@manchester.ac.uk

R. Aggarwal, C. V. Oddis (eds.), *Managing Myositis*, https://doi.org/10.1007/978-3-030-15820-0_2

- Genetic risk factors identified outside the MHC region implicate both the innate and adaptive immune responses in IIM.
- Some genetic risk factors are unique to specific clinical IIM subgroups, potentially suggesting that different pathophysiologies are implicated, whilst other genetic risk factors overlap between the IIM and other seropositive autoimmune rheumatic diseases.
- Several environmental risk factors, including ultraviolet radiation exposure, occupational exposures, smoking and certain medications, have been implicated in IIM aetiology, but further studies are needed to determine causality.
- A number of viral and bacterial infectious triggers have been suggested, but data is rather limited and preliminary.

Introduction

This chapter will address the prevalence and incidence of idiopathic inflammatory myopathies (IIM) and their major subtypes. We will focus on modifiable (radiation, smoking, drugs) and non-modifiable risk factors (age, gender, ethnicity) that predispose an individual to develop IIM and what is currently known about environmental and genetic associations and interactions.

Prevalence and Incidence of Myositis and Its Subtypes

The rarity of IIM and the recent advances in our understanding of their many clinical subtypes and multisystem nature, where affected patients may present to many differing medical specialties, have made the undertaking of epidemiological studies and interpretation of previous studies a considerable challenge. As testament to this, the most widely used diagnostic criteria for IIM, those of Bohan and Peter [1], were developed and validated prior to the description of recently described clinical subtypes and before access became available to myositis-specific antibodies or magnetic resonance imaging. In the rare IIM disease spectrum, undertaking epidemiological studies has the potential to shed light on important factors involved in the disease process.

A systematic review of previous epidemiology studies indicates an annual IIM incidence of around 8 per million, ranging from 1.16 to 19 per million in different geographical areas of the world. The combined prevalence of IIM overall is around 14 per 100,000, ranging from 2.4 to 33.8 per million [2]. When taken collectively, there is no apparent geographical or spatial variation, although associations have been found for particular clinical subsets discussed below. Two studies subsequent to this review from Quebec and the USA cited similar incidence and prevalence rates [3, 4].

There has been a trend for increasing incidence and prevalence figures for IIM over time, which may be due to wider recognition, more accurate disease recording or a true increase in disease burden. The most common IIM subtypes in adults are dermatomyositis (DM), anti-synthetase syndrome and polymyositis (PM), but much of the epidemiological data collected is specific to particular

Table 2.1 Incidence and prevalence estimates of IIM and their subtypes

	Incidence estimates	Prevalence estimates
Overall IIM	8 (1–19) per million	14 (2–33) per 100,000
DM	No subtype-specific data Comprises ~20% of IIM (modulated by latitude)	No subtype-specific data Comprises ~20% of IIM (modulated by latitude)
PM	No subtype-specific data	No subtype-specific data
IBM	2–6 per million	5 per million (9–71 per million in adults >50 years old)
JDM	2–4 per million	2.5 per 100,000
IMNM	No subtype-specific data Comprises ~20% of IIM	No subtype-specific data Comprises ~20% of IIM
CAM	20–30% of DM and 10–20% PM have a malignancy	20–30% of DM and 10–20% PM have a malignancy

IIM idiopathic inflammatory myopathy, *DM* dermatomyositis, *PM* polymyositis, *IBM* inclusion body myositis, *JDM* juvenile DM, *IMNM* immune-mediated necrotising myopathy, *CAM* cancer-associated myositis

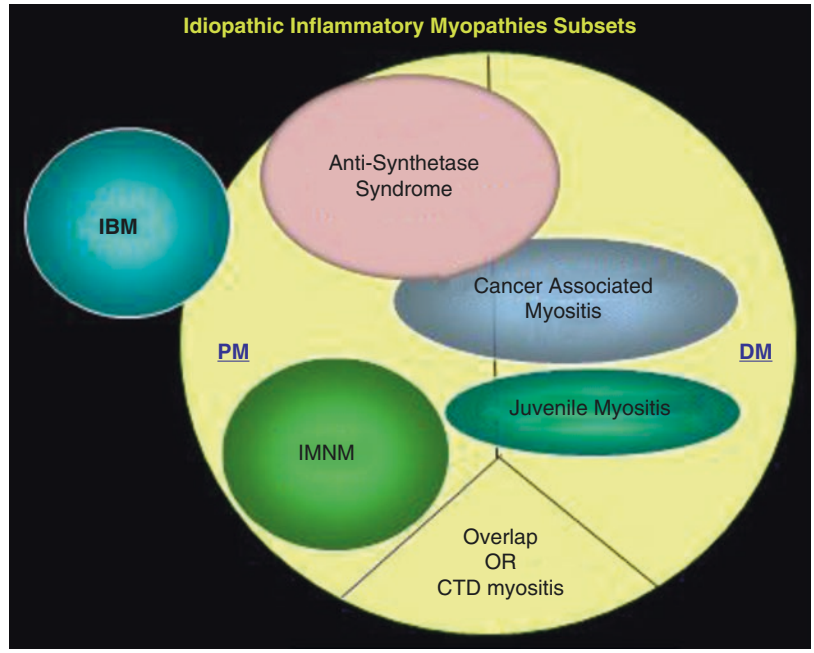

Fig. 2.1 IIM subsets, area of each subset approximates to its relative frequency compared to overall IIM prevalence

subtypes which will be briefly discussed further and is summarised in Table 2.1. Figure 2.1 shows a conceptual representation of how the subtypes overlap and relate to each other.

Inclusion Body Myositis Inclusion body myositis (IBM) represents a small IIM subset, and various diagnostic criteria (including the Griggs, Mastaglia and ENMC criteria) have been employed in different studies, which has had an impact on the interpretation of results obtained [5–7]. The estimates of prevalence and incidence vary considerably. The prevalence of IBM is around 5 per million of the general population, but this rises substantially when studying an older population (50 years and older) to between 9 and 71 per million [8–12]. The incidence of IBM has been less frequently investigated, but a recent Norwegian study calculated an annual incidence of 2–6 per million [13].

Cancer-Associated Myositis An association between IIM and cancer has long been recognised, and contemporary epidemiological research has helped further investigate this relationship. Approximately 20–30% DM patients and 10–20% of PM patients have an underlying cancer [14, 15]. A recent estimate of the standardised incidence rates for malignancy were 2.0 in DM, 1.3 in PM and 1.0 in IBM, somewhat lower than earlier estimates [16]. The cancer risk is highest in older males with dermatomyositis with most cancer diagnoses being made within 1 year on either side of the diagnosis of an incident IIM. Particular autoantibodies (anti-TIF1γ, anti-NXP2, anti-SAE) are associated with adult DM and cancer [17, 18]. These antibodies do not associate with cancers in juvenile DM.

Juvenile Dermatomyositis Although different studies have used different age ranges of disease onset to define their cases, the annual incidence of juvenile DM appears similar to that of adults, at between two and four per million [19–22]. One study estimated the prevalence from their data at 2.5 per 100,000 persons [19].

Immune-Mediated Necrotising Myopathy Overall it has been estimated that immune-mediated necrotising myopathy (IMNM) makes up around 20% of all IIM and the incidence and prevalence can be roughly extrapolated from this figure in reference to the epidemiology figures for IIM collectively,

reported above [23]. One study in particular has shown a statistically significant increase in IMNM incidence over time, which may in part be due to a general increase in relevant environmental exposures such as statin therapy [24].

Age, Gender, Racial/Ethnic and Geographical Differences

The age at IIM disease onset has a bimodal distribution, with peaks in both childhood and in adulthood. However, IIM can affect all age groups. The peak for adults is in the 55–64 age group, with roughly two-thirds of patients being female. Therefore, the gender demographics of the IIM are broadly similar to those of many other autoimmune diseases, including rheumatoid arthritis. An exception is IBM, where affected patients are characteristically older (disease onset typically in the seventh decade and with a delay in diagnosis of around 5 years) and with a male gender preponderance [25].

Although individual studies may support an impression of racial and ethnic differences in the epidemiology of certain IIM subtypes, for example, the high incidence of anti-MDA5 positive clinically amyopathic DM in Japan, it is difficult to directly compare studies undertaken in different regions employing varied methodologies [26]. IIM are internationally prevalent, but different geographical areas have slightly different distributions of autoantibody subsets which could relate to referral bias in the comparison of different studies. There is little evidence to support the notion of spatial clustering as a consequence of rural or urban habitation, or of seasonal clustering when cases are analysed as a whole (with the possible exception of juvenile DM, discussed below).

There is little data on the epidemiology comparing differing ethnicities within the same geographical areas. A population subset of a single study from the US found 43% of their myositis incident cases were African American compared to 38% Caucasian and 5% Hispanic [4]. However, these data likely mostly reflect the characteristics of the general Medicaid program population rather than a particular risk in African Americans. Further investigation may shed more light on this issue.

Points to Remember
Age: Bimodal, 2–16 years and 30–70 years
Gender: Female>male (2:1), except IBM where male > female
Ethnicity/race: None confirmed

Risk of Myositis in Family Members of IIM Patients

There are rare reports of familial co-occurrence in IIM [27, 28]. However, due to the low incidence of the disease, the number of published multi-case family studies is extremely limited, with the exception of familial IBM. Increased rates of other autoimmune diseases, such as autoimmune thyroid disease, rheumatoid arthritis and type 1 diabetes, have been reported in the first-degree relatives of IIM sufferers, with an overall prevalence of 21.9% compared to 4.9% in non-autoimmune families [29]. Similarly, type 1 diabetes and systemic lupus erythematosus are more common than would be expected in the family members of patients with juvenile DM [30]. This aggregation of autoimmune disease within IIM families may suggest that shared environmental and/or genetic factors contribute to disease risk. The familial recurrence rate, and the rate of disease concordance in monozygotic compared to dizygotic twins, can be used to estimate the *genetic heritability*, the proportion of phenotypic variation that is attributable to genetic factors. In other autoimmune diseases, genetic factors have been shown to play a large role in disease susceptibility; for example, in type 1 diabetes and rheumatoid arthritis, the genetic heritability is approximately 88% [31] and 66% [32], respectively. However, due to the rarity of IIM, few

Points to Remember
First-degree relatives of IIM patients have an increased risk of autoimmune disease in general but not specifically for developing myositis.

family or twin studies have been carried out, therefore disease heritability remains unknown.

The Role of Environmental and Genetic Factors in the Development of Myositis

Although the aetiology and pathogenesis of IIM is poorly understood, autoimmune diseases are known to be complex disorders that result from chronic immune activation following specific environmental exposures in genetically predisposed individuals. Several environmental risk factors, including occupational exposures and infectious agents, have been implicated in IIM. The variety of these environmental insults may contribute to the clinical heterogeneity observed in IIM.

Points to Remember
All risk factors seem to increase risk for one or another subtype of IIM, but none is sufficient alone or necessary to cause the disease.

Environmental Risks: The Role of Noninfectious Risk Factors

Several environmental factors have been associated with IIM, although causality has not yet been proven. A role for ultraviolet radiation (UV) exposure has been postulated to act through immunomodulatory effects. The direct absorption of UV radiation by DNA and production of reactive oxygen species may lead to changes in the production of various immune mediators, which, in turn, suppress systemic immune responses, promoting defects in cellular immunity. Hence, the prevalence of DM, as a proportion of DM and PM, as well as the presence of the DM-specific autoantibody, anti-Mi-2, has been shown to increase from north to south with latitudinal gradient [33, 34]. Seasonal effects on incidence and prevalence also have been reported in some studies of juvenile onset DM [2]. In individuals who are current or previous smokers, the frequency of the most common adult myositis-specific autoantibody, anti-Jo-1, is increased, particularly in individuals who carry a specific genetic variant (*HLA-DRB1*03)* [35]. The latter observation suggests an interaction between genes and environment that increases susceptibility to develop one of the IIM, an effect similarly observed for smoking in rheumatoid arthritis [36, 37]. Moreover, the likelihood of developing anti-HMGCR antibody-positive immune-mediated necrotizing myopathy as a result of exposure to lipid-lowering statins is increased in adults who are positive for the genetic variant *HLA-DRB1*11* [38]. The finding that there is an increased incidence of a range of different cancers in IIM, particularly in those individuals with DM and especially those with another DM-specific autoantibody, anti-TIF1γ [39], suggests that environmental factors may act as both carcinogens and inflammatory triggers. Whilst the reason for this association between myositis and cancer is still unknown, a model has been suggested whereby a mutation in the individual's tissue triggers an autoimmune cytolytic antitumour response, which in some patients successfully eliminates the cancer but may fail in those who develop cancer-associated dermatomyositis [40]. Contrary to adults, anti-TIF1γ autoantibodies are one of the most common autoantibodies in juvenile DM, but are not associated with malignancy in juveniles, suggesting that the increased risk of cancer with anti-TIF1γ represents a complex interplay of exposure and genetics. Although there are no known dietary risk factors for IIM, naturally occurring statins are present in certain foods, for example, high concentrations of lovastatin are found in oyster mushrooms, which may act to influence risk in some individuals [41] (Table 2.2).

Environmental Risks: The Role of Infectious Agents

Although a variety of infectious agents have been linked to the development of IIM, as dem-

Table 2.2 Environmental risk factors for IIM (causality not proven)

Noninfectious risks (strong associations)
UV exposure for DM
Smoking in anti-Jo-1 + patients, especially in those with *HLA-DRB1*03*
Statin in anti-HMGCR + patients, especially in those with *HLA-DRB1*11*
Cancer in DM, especially in those with anti-TIF1γ autoantibody
Infectious risks (weak and inconsistent associations)
Epstein-Barr virus
Retroviruses such as influenza, hepatitis and HIV
Enteroviruses, such as coxsackieviruses
Bacteria such as streptococcal, *Mycobacterium tuberculosis* and *Staphylococcus aureus*

onstrated by case reports and epidemiological studies (see Gan and Miller, 2011, for review [42]), the associations are neither strong nor consistent. A potential role of microbial pathogens, including viruses, bacteria, fungi and parasites has been suggested. Associated viruses include Epstein-Barr virus; retroviruses such as influenza, hepatitis and HIV; and enteroviruses, such as coxsackieviruses, whilst bacteria include streptococcal infection, *Mycobacterium tuberculosis* and *Staphylococcus aureus.* A potential role of infectious agents in the development of IIM is supported by their use to induce myositis in experimental animal models. Recent studies of the *microbiome*, the combined genetic material of the microorganisms in a particular environment, for example, in the human gut or on the skin, allow the role of the host microenvironment in the development of autoimmunity to be investigated [43]. In addition, novel experimental approaches are being developed to screen serum from individuals with IIM and other diseases for signatures of past or current infections. However, it is not established yet whether any identified infection is primary or secondary to the development of autoimmunity, and for some individuals the lack of obvious clinical disease and consequent delays in diagnosis makes it more difficult to identify responsible temporal environmental exposures.

Genetic Risk Factors in Idiopathic Inflammatory Myopathies

Numerous studies have been carried out over the last decade to identify genetic risk factors that predispose individuals to develop IIM. To identify genes involved in disease, these association studies compare the frequency of genetic variants in individuals with disease compared to healthy individuals (case-control studies). Most of these studies have focused on the more prevalent IIM clinical subgroups, due to the rarity of even the most common subgroups, causing sample size and consequent power issues when trying to identify statistically meaningful results.

The strongest genetic associations identified in IIM are within the major histocompatibility complex (MHC) on chromosome 6; the highly variable region which contains many of the genes that encode proteins that present antigens to the immune system to trigger an immune response. Genetic variants within this region confer susceptibility to numerous autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus and Sjögren syndrome. The largest published genetic study to date in IIM included samples from 2566 affected individuals of European ancestry collected through the Myositis Genetics Consortium (MYOGEN). The results identified that multiple variants within the MHC region may contribute independently to IIM risk [44, 45]. This increased genetic risk may be due to specific amino acids on the *HLA* genes that change the structure of the peptide-binding groove, thus affecting the ability to bind autoantigenic peptides and present them to the immune system. These specific amino acid associations differentiate IBM from PM and DM [45].

Genetic risk factors outside of the MHC region also have been implicated in IIM, including a variant of the *PTPN22* gene [44]. This results in an arginine to tryptophan amino acid change at position 620, a risk factor which also has been established for several autoimmune diseases other than IIM. Associations with genes involved in the adaptive immune response, such as *STAT4* and *UBE2L3,* which are known regulators of T and B cell differentiation, respectively,

implicate other key pathogenic mechanisms in IIM [44]. A region on chromosome 3 also has been implicated in IBM, where a frameshift mutation in CCR5 is thought to be the causal variant [45]. Whilst some of these associations are unique to different clinical IIM subgroups and may suggest different pathophysiologies between the subgroups, other associations confirm extensive genetic overlap between IIM and other seropositive rheumatic autoimmune diseases, such as rheumatoid arthritis, Sjögren syndrome and systemic sclerosis [46].

Specific MHC associations also have been identified within myositis-specific autoantibody defined subgroups (Table 2.3), in agreement with the finding that many myositis-specific autoantibodies are mutually exclusive. These association signals may be stronger than for clinically defined subgroups, and the serotype/phenotype associations are described in detail in later chapters of this handbook (Role of autoantibodies in myositis). Many studies are ongoing to better understand the links between genotypes and serotypes to better predict clinical phenotypes, and therefore better predict treatment responses in IIM.

Notably, in IIM a relatively small number of genetic risk variants have been identified, in contrast to other more common autoimmune diseases, such as rheumatoid arthritis. This observation may simply reflect statistical power problems due to sample size in a disease spectrum as rare as IIM, as well as the marked heterogeneity of these complex diseases. Also, many of the genetic variants identified have a relatively small effect on disease risk individually, and only 5.5–16% of the phenotypic variance in IIM can be explained by genetic risk factors identified from the most recent genetic studies. Although most of the largest genetic studies in IIM to date have focused on populations of European ancestry, some of these associations have been replicated in other ethnic groups, such as Han Chinese and Japanese, suggesting some common aetiology between ethnicities [47, 48].

Overall, there is likely to be a complex interaction between genetic and environmental factors in IIM initiation and progression. Whilst it is not yet known how these genetic variants contribute to disease pathogenesis in IIM, integrating genetic and environmental data will potentially lead to increasingly refined models of disease pathogenesis. These will be necessary to provide earlier disease detection, improved diagnostic accuracy and prediction of disease progression, and to identify clinically meaningful patient subgroups for stratified treatment approaches. Such insights would clearly have the potential to improve therapeutic outcomes in these difficult diseases (Table 2.3).

Table 2.3 Genetic risk factors in IIM

MHC variants
Confers highest risk
Examples: *HLA-DRB1*03* in anti-Jo-1 antibody, *HLA-DRB1*11* in anti-HMGCR antibody
Non-MHC region
PTPN22 gene
STAT4 gene
UBE2L3 gene
Frameshift mutation in CCR5 (chromosome 3)

Conclusion

Substantial work already has been undertaken towards establishing the epidemiology of IIM (Table 2.1) and non-modifiable risk factors such as gender and age for IIM, and different subtypes are well known. As current research stands, relatively few environmental and genetic associations have been identified, particularly for IIM subtypes, and no common causal link has been established. Further work will lead to discovery of additional genes and the putative environmental triggers involved in initiating disease pathogenesis, and identify persons at risk of IIM to enable limitation or prevention of disease development.

References

1. Bohan A, Peter JB. Polymyositis and dermatomyositis (parts 1 and 2). N Engl J Med. 1975;292:344–7, 403–7.
2. Meyer A, Meyer N, Schaeffer M, Gottenberg J-E, Geny B, Sibilia J. Incidence and prevalence of inflammatory myopathies: a systematic review. Rheumatology (Oxford). 2015;54:50–63.

3. Bernatsky S, Joseph L, Pineau CA, Belisle P, Boivin JF, Banerjee D, Clarke AE. Estimating the prevalence of polymyositis and dermatomyositis from administrative data: age, sex and regional differences. Ann Rheum Dis. 2009;68:1192–6.
4. Smoyer-Tomic KE, Amato AA, Fernandes AW. Incidence and prevalence of idiopathic inflammatory myopathies among commercially insured, Medicare supplemental insured, and Medicaid enrolled populations: an administrative claims analysis. BMC Musculoskelet Disord. 2012;13:103.
5. Griggs R, Askanas V, DiMauro S, Engel A, Karpati G, Mendell J, Rowland L. Inclusion body myositis and myopathies. Ann Neurol. 1995;38:705–13.
6. Mastaglia FL, Phillips BA. Idiopathic inflammatory myopathies: epidemiology, classification, and diagnostic criteria. Rheum Dis Clin N Am. 2002;28:723–41.
7. Rose MR. 188th ENMC international workshop: inclusion body myositis, 2–4 December 2011, Naarden, The Netherlands. Neuromuscul Disord. 2013;23:1044–55.
8. Phillips BA, Zilko PJ, Mastaglia FL. Prevalence of sporadic inclusion body myositis in Western Australia. Muscle Nerve. 2000;23:970–2.
9. 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. 2008;15:1350–3.
10. Tan JA, Roberts-Thomson PJ, Blumbergs P, Hakendorf P, Cox SR, Limaye V. Incidence and prevalence of idiopathic inflammatory myopathies in South Australia: a 30-year epidemiologic study of histology-proven cases. Int J Rheum Dis. 2013;16:331–8.
11. Wilson FC, Ytterberg SR, St. Sauver JL, Reed AM. Epidemiology of sporadic inclusion body myositis and polymyositis in Olmsted County, Minnesota. J Rheumatol. 2008;35:445–7.
12. Suzuki N, Aoki M, Mori-Yoshimura M, Hayashi YK, Nonaka I, Nishino I. Increase in number of sporadic inclusion body myositis (sIBM) in Japan. J Neurol. 2012;259:554–6.
13. Dobloug GC, Antal EA, Sveberg L, Garen T, Bitter H, Stjärne J, Grøvle L, Gran JT, Molberg Ø. High prevalence of inclusion body myositis in Norway; a population-based clinical epidemiology study. Eur J Neurol. 2014;22:672–80.
14. Hill CL, Zhang Y, Sigurgeirsson B, Pukkala E, Mellemkjaer L, Airio A, Evans SR, Felson DT. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet. 2001;357:96–100.
15. Zantos D, Zhang Y, Felson D. The overall and temporal association of cancer with polymyositis and dermatomyositis. J Rheumatol. 1994;21:1855–9.
16. Dobloug GC, Garen T, Brunborg C, Gran JT, Molberg Ø. Survival and cancer risk in an unselected and complete Norwegian idiopathic inflammatory myopathy cohort. Semin Arthritis Rheum. 2015;45:301–8.
17. Jones J, Wortmann R. Idiopathic inflammatory myopathies-a review. Clin Rheumatol. 2015;34:839–44.
18. Muro Y, Sugiura K, Nara M, Sakamoto I, Suzuki N, Akiyama M. High incidence of cancer in anti-small ubiquitin-like modifier activating enzyme antibody-positive dermatomyositis. Rheumatology (Oxford). 2015;54:1745–7.
19. Symmons DP, Sills JA, Davis SM. The incidence of juvenile dermatomyositis: results from a nation-wide study. Br J Rheumatol. 1995;34:732–6.
20. Darin N, Tulinius M. Neuromuscular disorders in childhood: a descriptive epidemiological study from western Sweden. Neuromuscul Disord. 2000;10:1–9.
21. Mendez EP, Lipton R, Ramsey-Goldman R, Roettcher P, Bowyer S, Dyer A, Pachman LM. US incidence of juvenile dermatomyositis, 1995–1998: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases registry. Arthritis Rheum. 2003;49:300–5.
22. Denardo B, Tucker L, Miller L, Szer I, Schaller J. Demography of a regional pediatric rheumatology patient population. Affiliated Children's Arthritis Centers of New England. J Rheumatol. 1994;21:1553–61.
23. Bergua C, Chiavelli H, Simon J, Boyer O, Jouen F, Stenzel W, Martinet J. Immune-mediated necrotizing myopathy. Z Rheumatol. 2016;75:151–6.
24. Klein M, Mann H, Pleštilová L, Zámečník J, Betteridge Z, McHugh N, Vencovský J. Increasing incidence of immune-mediated necrotizing myopathy: single-centre experience. Rheumatology (Oxford). 2015;54:2010–4.
25. Molberg Ø, Dobloug C. Epidemiology of sporadic inclusion body myositis. Curr Opin Rheumatol. 2016;28:657–60.
26. Tansley SL, McHugh NJ, Wedderburn LR. Adult and juvenile dermatomyositis: are the distinct clinical features explained by our current understanding of serological subgroups and pathogenic mechanisms? Arthritis Res Ther. 2013;15:211.
27. Rider L, Gurley R, Pandey J, et al. Clinical, serologic, and immunogenetic features of familial idiopathic inflammatory myopathy. Arthritis Rheum. 1998;41:710–9.
28. Ozaki T, Yamashita H, Hosono Y, Nakashima R, Mimori T, Takahashi Y, Kaneko H, Kano T, Mimori A. Two patients in the same family with anti-ARS antibody-associated myositis. Mod Rheumatol. 2014;24:699–700.
29. Gi LR, Lin J, Plotz PH, Bale SJ, Wilder R, Mbauya A, Miller FW. Familial autoimmunity in pedigrees of idiopathic inflammatory myopathy patients suggests common genetic risk factors for many autoimmune diseases. Rheumatism. 1998;41:400–5.
30. Niewold TB, Wu SC, Smith M, Morgan GA, Pachman LM. Familial aggregation of autoimmune disease in juvenile dermatomyositis. Pediatrics. 2011;127:e1239–46.
31. Hyttinen V, Kaprio J, Kinnunen L, Koskenvuo M, Tuomilehto J. Genetic liability of Type 1 diabetes and

the onset age among 22,650 young Finnish twin pairs. Diabetes. 2003;52:1052–5.
32. Van Der Woude D, Houwing-Duistermaat JJ, Toes REM, Huizinga TWJ, Thomson W, Worthington J, Van Der Helm-Van Mil AHM, De Vries RRP. Quantitative heritability of anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis. Arthritis Rheum. 2009;60:916–23.
33. Okada S, Weatherhead E, Targoff IN, Wesley R, Miller FW. Global surface ultraviolet radiation intensity may modulate the clinical and immunologic expression of autoimmune muscle disease. Arthritis Rheum. 2003;48:2285–93.
34. Love LA, Weinberg CR, McConnaughey DR, Oddis CV, Medsger TA, Reveille JD, Arnett FC, Targoff IN, Miller FW. Ultraviolet radiation intensity predicts the relative distribution of dermatomyositis and anti-Mi-2 autoantibodies in women. Arthritis Rheum. 2009;60:2499–504.
35. Chinoy H, Adimulam S, Marriage F, et al. Interaction of HLA-DRB1*03 and smoking for the development of anti-Jo-1 antibodies in adult idiopathic inflammatory myopathies: a European-wide case study. Ann Rheum Dis. 2012;71:961–5.
36. Padyukov L, Suva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum. 2004;50:3085–92.
37. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006;54:38–46.
38. Mammen AL, Gaudet D, Brisson D, Christopher-Stine L, Lloyd TE, Leffell MS, Zachary AA. Increased frequency of DRB1*11:01 in anti-hydroxymethylglutaryl- coenzyme a reductase-associated autoimmune myopathy. Arthritis Care Res. 2012;64:1233–7.
39. Chinoy H, Fertig N, Oddis CV, Ollier WER, Cooper RG. The diagnostic utility of myositis autoantibody testing for predicting the risk of cancer-associated myositis. Ann Rheum Dis. 2007;66:1345–9.
40. Shah AA, Casciola-Rosen L, Rosen A. Review: cancer-induced autoimmunity in the rheumatic diseases. Arthritis Rheumatol. 2015;67:317–26.
41. Atli B, Yamac M, Yildiz Z. Optimization of submerged fermentation conditions for lovastatin production by the culinary-medicinal oyster mushroom, Pleurotus ostreatus (higher Basidomycetes). Int J Med Mushrooms. 2013;15:487–95.
42. Gan L, Miller FW. State of the art: what we know about infectious agents and myositis. Curr Opin Rheumatol. 2011;23:585–94.
43. Shamriz O, Mizrahi H, Werbner M, Shoenfeld Y, Avni O, Koren O. Microbiota at the crossroads of autoimmunity. Autoimmun Rev. 2016;15:859–69.
44. Rothwell S, Cooper RG, Lundberg IE, 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.
45. Rothwell S, Cooper RG, Lundberg IE, 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.
46. Kirino Y, Remmers EF. Genetic architectures of seropositive and seronegative rheumatic diseases. Nat Rev Rheumatol. 2015;11:401–14.
47. Sugiura T, Kawaguchi Y, Goto K, Hayashi Y, Tsuburaya R, Furuya T, Gono T, Nishino I, Yamanaka H. Positive association between STAT4 polymorphisms and polymyositis/dermatomyositis in a Japanese population. Ann Rheum Dis. 2012;71:1646–50.
48. Chen S, Wu W, Li J, et al. Single nucleotide polymorphisms in the FAM167A-BLK gene are associated with polymyositis/dermatomyositis in the Han Chinese population. Immunol Res. 2015;62:153–62.