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Local immunoglobulin expression in myositis is associated with interferon gamma signaling and correlates with disease activity.

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Keywords: antibody, RNA-sequencing, autoantibodies, dermatomyositis, immune-mediated necrotizing myositis

ABSTRACT

Objectives: Autoantibodies may play a role in the pathogenesis of myositis and are locally produced within muscle tissue. This study aimed to characterize the local expression of immunoglobulin genes across different subgroups of myositis, identify pathways associated with this expression, and evaluate correlations with disease activity.

Methods: Bulk RNA sequencing was performed on muscle biopsies from 289 individuals, including patients with various forms of myositis and healthy controls. Expression levels of immunoglobulin gene regions were compared across clinical and autoantibody-defined subgroups. Pathway enrichment analysis and unsupervised clustering were conducted, and correlations between immunoglobulin gene expression and disease activity were assessed.

Results: Local immunoglobulin gene expression was highest in inclusion body myositis (IBM) and antisynthetase syndrome (ASyS), followed by dermatomyositis, and lowest in immune-mediated necrotizing myopathy. Among isotypes, IgG, IgA, and IgM predominated, while IgD and IgE expression was minimal. Certain immunoglobulin VJ segments were more frequently used across all patients, with no significant differences in specific region usage between patient groups. Immunoglobulin gene expression strongly correlated with disease activity, particularly in patients with anti-Mi2, anti-MDA5, anti-Jo1 autoantibodies, and IBM. Pathway analysis revealed a robust association between immunoglobulin expression and interferon-gamma (IFN- γ) signaling. Unsupervised clustering based solely on immunoglobulin gene expression clearly separated healthy controls from patients with ASyS and IBM.

Conclusions: Immunoglobulin is locally expressed in the muscle of patients with myositis, particularly IBM and ASyS. This expression correlates with disease activity, involves preferential usage of specific isotypes and gene segments, and is closely linked to IFN- γ -associated immune pathways.

INTRODUCTION

Inflammatory myopathies are a heterogeneous group of autoimmune disorders characterized by chronic muscle inflammation and varying degrees of extramuscular involvement, most commonly affecting the skin, lungs, and joints (1). The major subtypes include dermatomyositis (DM), antisynthetase syndrome (ASyS), inclusion body myositis (IBM), and immune-mediated necrotizing myopathy (IMNM) (1). A defining feature of these conditions is the presence of myositis-specific autoantibodies, which delineate clinically and mechanistically distinct subgroups and are associated with differences in pathogenesis, histopathology, disease trajectory, and treatment response (1, 2).

Accumulating evidence suggests that antibodies may be generated locally within inflamed muscle tissue, potentially explaining the selective involvement of muscle tissue and certain muscle groups in these diseases. Histopathological analyses of muscle biopsies from patients with myositis have identified antigen-experienced B cells and plasma cells infiltrating the tissue. In particular, biopsies from individuals IBM show abundant CD138⁺ plasma cells, and transcriptomic studies reveal that immunoglobulin (Ig) genes are among the most upregulated in affected muscle samples (3-5). Laser-capture microdissection followed by Ig transcript sequencing has demonstrated clonally related B cells and plasma cells dispersed across myositis lesions, further supporting the concept of local B-cell maturation and differentiation into antibody-secreting cells (6). In DM and overlap myositis, muscle biopsies can exhibit lymphoid follicles and B-cell aggregates resembling germinal centers, which may serve as niches for in situ antibody production (7, 8). Similarly, in ASyS, muscle biopsies frequently display perimysial clusters of CD20⁺ B cells and CD138⁺ plasma cells (9). Collectively, these

findings suggest that inflamed muscle in myositis provides a permissive microenvironment for B-cell activation, maturation, and local immunoglobulin synthesis (3, 4, 6).

To date, no large-scale transcriptomic study has systematically quantified immunoglobulin gene expression across the full spectrum of myositis subtypes or explored its relationship with clinical disease activity and associated inflammatory pathways. In this study, we address this knowledge gap by analyzing RNA-sequencing data from muscle biopsies of patients with DM, ASyS, IMNM, and IBM. We comprehensively profile the expression of immunoglobulin heavy- and light-chain regions in each subtype, assess their association with clinical markers of disease severity, and examine their relationship with key inflammatory signatures.

METHODS

Patients

Muscle biopsies from myopathy patients were collected from Institutional Review Board (IRB)-approved longitudinal cohorts at the National Institutes of Health (Bethesda, MD), Johns Hopkins Myositis Center (Baltimore, MD), Vall d'Hebron Hospital (Barcelona), Clinic Hospital (Barcelona), and Charité-Universitätsmedizin (Berlin). Patients were classified as IBM if they met Lloyd's criteria (10). Autoantibodies were detected by ELISA, immunoprecipitation of *in vitro* transcription and translation-generated proteins (IVTT-IP), EUROLINE myositis profile line blotting, or immunoprecipitation from ³⁵S-methionine-labeled cell lysates. Patients testing positive for a myositis-specific autoantibody were classified based on their myositis-specific autoantibody according to the NIH criteria (11): those positive for anti-Mi2, anti-NXP2, anti-MDA5, or anti-TIF1γ were classified as DM; those positive for anti-Jo1, were classified as ASyS; and those with autoantibodies against SRP or HMGCR were classified as IMNM. Patients with less prevalent autoantibodies were excluded from the analysis.

RNA sequencing

Bulk RNAseq was performed on frozen muscle biopsy specimens as previously described (4, 12-16). Briefly, muscle biopsies underwent immediate flash freezing and were stored at -80°C across all contributing centers. Samples were then transported in dry ice to the NIH and processed uniformly to prepare the library and conduct the analysis. RNA was extracted with TRIzol. Libraries were either prepared with the

NeoPrep system according to the TruSeq Stranded mRNA Library Prep protocol (Illumina, San Diego, CA) or with the NEBNext Poly(A) mRNA Magnetic Isolation Module and Ultra[™] II Directional RNA Library Prep Kit for Illumina (New England BioLabs, ref. #E7490, and #E7760).

Statistical and bioinformatic analysis

For RNAseq analysis, sequencing reads were demultiplexed using bcl2fastq/2.20.0 and preprocessed using fastp/0.21.0. The abundance of each gene was determined using Salmon/1.5.2. Counts were normalized using the Trimmed Means of M values (TMM) from edgeR/3.34.1 for graphical analysis. Differential expression was performed using limma/3.48.3. Pathway enrichment was assessed using ReactomePA (v1.48.0) to perform gene set enrichment analysis (GSEA) against the Reactome database, and results were visualized with enrichplot (v1.24.4). Gene lists were curated from the HUGO Gene Nomenclature Committee (HGNC). Relative expression was expressed as the log2 fold-change (logFC). Where applicable, P-values were adjusted for multiple comparisons using the Benjamini–Hochberg procedure, with a false discovery rate threshold of $q < 0.05$ considered statistically significant.

RESULTS

Muscle biopsies from 289 individuals were analyzed, comprising 252 patients with inflammatory myopathies and 37 healthy controls. Patients were categorized into clinically and serologically defined subgroups: DM (n=82, including anti-Mi2 [n=22], anti-NXP2 [n=21], anti-TIF1 γ [n=28], and anti-MDA5 [n=11]), ASyS with anti-Jo1 antibodies (n=37), IMNM (n=80, including anti-HMGCR [n=60] and anti-SRP [n=20]), and IBM (n=53) (Supplementary Table 1).

Elevated Local Immunoglobulin Expression in IBM and Antisynthetase Syndrome

IgG, IgM, and IgA were the predominant isotypes detected, while overexpression of IgD and IgE was negligible across all groups. Expression levels of IgG, IgM, and IgA were strongly correlated with one another, while their associations with IgD and IgE were comparatively weak (Figure 2).

Muscle biopsies from patients with IBM and anti-Jo1 ASyS exhibited significantly higher expression of immunoglobulin genes compared to other subgroups (Table 1, Figure 1). In IBM, multiple immunoglobulin heavy-chain constant regions were markedly upregulated, particularly those encoding IgG isotypes. For example, the constant region of IgG3 showed a log fold change (logFC) of 4.2 ($q = 3.99 \times 10^{-2}$), while that of IgG1 had a logFC of 3.7 ($q = 4.42 \times 10^{-21}$) compared to other muscle biopsies. Alternatively, anti-Jo1 samples demonstrated relatively elevated expression of IgM and IgA constant regions (IGHM logFC = 3.1, $q = 4.43 \times 10^{-2}$; IGHA1 logFC = 2.0, $q = 3.59 \times 10^{-}$). DM biopsies showed intermediate immunoglobulin expression, while IMNM had the lowest levels (Table 1, Figure 1).

Local Immunoglobulin Expression Correlates with Disease Activity

Immunoglobulin gene expression was significantly positively correlated with multiple transcriptomic markers of disease activity, including type I interferon-inducible genes (ISG15, MX1), type II interferon-inducible genes (GBP2, IFI30), T-cell markers (CD3E, CD4, CD8), macrophage markers (CD14, CD68), and muscle regeneration markers (MYH3, MYH8, NCAM1, PAX7). In contrast, immunoglobulin expression was inversely associated with mitochondrial genes (MT-CO1, MT-CO2) and genes encoding mature muscle structural proteins (ACTA1, MYH1, MYH2). Across all patients, higher levels of intramuscular immunoglobulin transcripts were associated with increased disease activity (Figure 3).

The strength of these associations varied across clinical and serological subgroups. Anti-Mi2 dermatomyositis showed the strongest correlation between local immunoglobulin expression and disease activity, followed by anti-MDA5, anti-Jo1, and IBM, which demonstrated moderate associations. Anti-TIF1 γ and anti-HMGCR subgroups exhibited weaker but consistent correlations, while anti-NXP2 and anti-SRP patients showed minimal association (Supplementary Figure 1). These findings suggest that the contribution of local immunoglobulin expression to disease activity may differ across myositis subtypes.

Expression of Light Chain and Non-Constant Regions of the Heavy Chain

Analysis of the diversity (D) region of the heavy chain and the joining (J) region of the light chains was not feasible due to insufficient read coverage. In contrast, expression of the constant regions of the light chains, as well as the measurable variable (V) and joining (J) regions of both heavy and light chains, revealed a consistent pattern of

preferential overexpression in IBM and ASyS (Supplementary Figures 2–6; Supplementary Tables 2–6). This trend was uniform across all analyzed regions, without evidence of preferential segment usage in specific myositis subgroups.

Expression of different immunoglobulin segments—whether constant or variable—was highly correlated and strongly associated with transcriptomic markers of disease activity (Supplementary Figures 7–8). This included the abovementioned constant regions of different immunoglobulin isotypes and extended to other regions of both heavy and light chains.

Regarding the light chain constant regions, IGKC and IGLC2 were the most abundantly expressed, followed by IGLC3 and IGLC1, while IGLC6 and IGLC7 showed low expression (Supplementary Figure 2; Supplementary Table 2). Among the variable regions, IGHV1-18 was the most highly expressed heavy chain variable segment across all study groups (Supplementary Figure 3; Supplementary Table 3). The heavy chain joining region exhibited low expression overall (Supplementary Figure 4; Supplementary Table 4). For the light chains, IGKV4-1 was the most highly expressed kappa chain variable segment (Supplementary Figure 5; Supplementary Table 5), while several lambda chain variable segments—including IGLV1-40 and IGLV2-23— showed abundant expression (Supplementary Figure 6; Supplementary Table 6).

Type II Interferon Signaling Drives Local Immunoglobulin Expression

Gene set enrichment analysis of genes correlated with IGHG1 expression revealed a robust association between local immunoglobulin expression and the IFN- γ pathway (Figure 4). Consistent with this, immunoglobulin transcripts correlated tightly with IFN- γ –

inducible genes (e.g. GBP2, Figure 5). These results suggest that local immunoglobulin production may be driven by IFN- γ in myositis muscle.

Immunoglobulin Gene Expression Distinguishes Select Myositis Subgroups

We investigated whether immunoglobulin gene expression alone could stratify patients into clinically meaningful subgroups. Dermatomyositis and IMNM did not form distinct clusters. In contrast, samples from patients with ASyS and IBM were clearly separated from healthy muscle biopsies (Figure 6).

DISCUSSION

Our data reveal a pronounced intramuscular humoral immune signature in myositis, especially in IBM and ASyS. Consistent with earlier transcriptomic studies in IBM, we found that immunoglobulin gene transcripts are overexpressed genes in affected muscle (3-6). In IBM and ASyS, transcripts of heavy chains for IgG, IgA and IgM were markedly elevated, reflecting infiltration by class-switched B cells or plasma cells. This local immunoglobulin expression closely tracked clinical severity, suggesting it could serve as a biomarker of disease activity. Indeed, unsupervised clustering by Ig-gene expression cleanly separated IBM and ASyS muscles from controls, underscoring its potential utility in stratifying myositis subtypes.

A striking feature was the strong association of the local Ig transcript signature with a type II interferon (IFN- γ) gene program. Recent analyses have shown that IBM and ASyS muscle are characterized by a predominance of IFN- γ -induced transcripts (12, 15). At the cellular level, IFN- γ is primarily produced by infiltrating cytotoxic T cells in IBM/ASyS, which in turn acts on muscle fibers and resident immune cells. Of note, IFN- γ is a key factor to induce the migration of B cells from the lymph nodes to the tissues as tissue-resident B cells (17) that will survive in the tissues if they receive survival signals by continuous antigenic stimulation. This could explain why, in myositis, B-cells are preferentially attracted to tissues where there is expression of their cognate autoantigens. Also, IFN- γ signaling directly promotes plasma cell differentiation in muscle and other tissues (18, 19). Such a mechanism would explain the high levels of intramuscular Ig transcription seen in IBM and ASyS.

The identification of a robust IFN- γ -associated Ig signature in IBM and ASyS has several clinical ramifications. First, it offers a biomarker for disease stratification and activity assessment. Muscle biopsies showing elevated immunoglobulin transcripts might help distinguish IBM/ASyS from other inflammatory myopathies. Serial measurement of this signature could also monitor response to therapy: for example, declining local Ig gene expression might indicate therapeutic suppression of B-cell activity.

Second, our findings reinforce the rationale for therapies targeting autoantibodies and B cells in myositis. Intravenous immunoglobulin, which saturates the neonatal Fc receptor (FcRn) and reduces immunoglobulin half-life, has consistently shown efficacy across multiple forms of myositis (20, 21). This same mechanism is being leveraged by synthetic FcRn inhibitors, such as efgartigimod, which have demonstrated benefit in other autoantibody-mediated diseases (22) and may similarly prove effective in myositis (23, 24).

In parallel, therapies that deplete B cells (e.g., rituximab) or target B cells and plasma cells more broadly have shown benefit in various myositis subtypes. Although the largest clinical trial of rituximab in myositis did not meet its primary endpoint (25), subsequent case series (26), post-hoc analysis (27), and extensive clinical experience support its effectiveness in reducing autoantibody titers and improving outcomes in refractory patients. Our findings may help account for the limited efficacy of rituximab reported in some studies given that the drug may not effectively target tissue-resident B cells as it does circulating ones.

A more recent and promising strategy is autologous CD19-directed CAR-T cell therapy, which has induced rapid and sustained remissions in patients with refractory disease. For instance, in three ASyS patients, CAR-T cell therapy led to rapid clinical improvement, seroconversion to autoantibody negativity, normalization of creatine kinase levels, and durable recovery of muscle strength (28). Notably, the only patient who did not seroconvert relapsed after 9 months but achieved drug-free remission following anti-BCMA therapy (29). These striking results underscore the central pathogenic role of B cells in ASyS and support the idea that eliminating autoantibody-producing cells may reset the autoimmune response. Our data further support this therapeutic direction by highlighting substantial local B-cell activity in the muscle tissue of myositis patients.

The present study has limitations. Because we used bulk RNA sequencing on heterogeneous muscle biopsies, we cannot definitively assign Ig transcripts to specific cell types (e.g. resident plasma cells vs. infiltrating B cells). Nor can we reconstruct full B-cell receptor sequences, as our data lack complete V(D)J coverage. Also, immunoglobulin gene segments that differ substantially from the reference genome may not have been fully captured or analyzed; however, any resulting bias would likely affect all groups equally. Although this study does not provide functional validation of the pathogenic role of locally expressed autoantibodies, such evidence has been demonstrated previously for several myositis-associated autoantibodies (2). Likewise, the results are restricted to the transcriptomic measurement and did not explore the abundance at the protein level.

Future studies should address these gaps. Single-cell RNA sequencing (with VDJ repertoire analysis) of muscle-infiltrating immune cells could pinpoint the exact B-cell

subsets producing the immunoglobulin transcripts and reveal clonal expansions. Spatial transcriptomics or multiplex immunofluorescence could map the cellular interactions among IFN- γ -producing T cells, and plasma cells. *In vitro* co-culture of human myotubes with immune cells under IFN- γ stimulation could test causality of B-cell recruitment and differentiation. Most importantly, future interventional studies should investigate whether inhibiting IFN- γ signaling can reduce intramuscular antibody production and improve clinical outcomes, particularly in myositis subtypes lacking effective treatments, such as IBM.

In summary, our findings demonstrate that myositis—particularly IBM and ASyS—is characterized by prominent local immunoglobulin gene expression that is driven by an IFN- γ -rich inflammatory environment and associated with disease activity. This links cellular and humoral arms of the immune response in myositis and provides a molecular basis for tailored biomarker and therapeutic strategies.

Table 1. Expression of immunoglobulin heavy chain constant region genes across disease groups, shown as comparisons versus all other muscle biopsies (vs. ALL) and versus normal muscle biopsies (vs. NT). DM: dermatomyositis; IMNM: immune-mediated necrotizing myopathy; IBM: inclusion body myositis; NT: normal muscle biopsy.

DM vs. ALL			Mi2 vs. ALL			NXP2 vs. ALL			MDA5 vs. ALL			TIF1γvs. ALL		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGHM	-0.4	0.450	IGHD	-0.9	0.304	IGHG3	-1.4	0.385	IGHA2	1.5	0.596	IGHD	0.4	0.652
IGHG3	-0.4	0.459	IGHG2	-0.7	0.559	IGHM	-1.2	0.436	IGHG4	1.6	0.615	IGHG2	0.4	0.714
IGHE	0.2	0.534	IGHA1	-0.5	0.596	IGHA1	-0.8	0.522	IGHA1	1.3	0.652	IGHA1	0.4	0.727
IGHG1	-0.2	0.722	IGHG3	-0.6	0.598	IGHG1	-0.9	0.550	IGHG3	1.3	0.687	IGHE	0.2	0.745
IGHA2	0.2	0.742	IGHG1	-0.5	0.692	IGHG2	-0.9	0.574	IGHD	1.1	0.700	IGHA2	0.3	0.809
IGHG2	-0.2	0.761	IGHG4	-0.5	0.706	IGHD	-0.6	0.644	IGHG1	1.2	0.706	IGHG1	0.2	0.906
IGHD	-0.1	0.766	IGHA2	-0.2	0.837	IGHG4	-0.4	0.817	IGHG2	1.0	0.719	IGHG3	0.1	0.930
IGHA1	-0.1	0.848	IGHM	0.0	0.993	IGHA2	-0.3	0.821	IGHE	0.2	0.888	IGHG4	-0.1	0.957
IGHG4	-0.1	0.922	IGHE	0.0	0.999	IGHE	0.1	0.869	IGHM	-0.1	0.984	IGHM	0.0	0.978

JO1 vs. ALL			IMNM vs. ALL			HMGR vs. ALL			SRP vs. ALL			IBM vs. ALL		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGHM	3.1	4.43e-09	IGHM	-2.1	0.001	IGHA2	-2.2	0.002	IGHM	-1.0	0.996	IGHG3	4.2	3.99e-25
IGHA1	2.0	3.59e-04	IGHA1	-1.6	0.002	IGHA1	-1.9	0.004	IGHE	-0.3	0.996	IGHG1	3.7	4.42e-21
IGHA2	2.0	0.001	IGHA2	-1.7	0.004	IGHM	-2.1	0.006	IGHA2	0.4	0.996	IGHM	3.6	2.03e-19
IGHG1	2.1	0.001	IGHG1	-1.8	0.005	IGHG1	-2.0	0.009	IGHG1	-0.4	0.996	IGHA1	2.9	1.09e-14
IGHG4	2.1	0.004	IGHG3	-1.8	0.006	IGHG3	-2.1	0.010	IGHD	-0.3	0.996	IGHG2	3.0	2.85e-13
IGHG3	2.0	0.008	IGHD	-1.1	0.038	IGHG2	-1.6	0.043	IGHG3	-0.3	0.996	IGHA2	2.8	5.15e-12
IGHG2	1.7	0.022	IGHG4	-1.4	0.042	IGHG4	-1.7	0.050	IGHA1	-0.3	0.996	IGHG4	2.9	4.43e-11
IGHD	1.3	0.092	IGHG2	-1.2	0.056	IGHD	-1.2	0.052	IGHG2	0.2	0.996	IGHD	1.9	2.29e-06
IGHE	-0.1	0.987	IGHE	-0.4	0.165	IGHE	-0.4	0.318	IGHG4	-0.1	0.996	IGHE	0.5	0.123

DM vs. NT			Mi2 vs. NT			NXP2 vs. NT			MDA5 vs. NT			TIF1γvs. NT		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGHM	3.0	3.05e-05	IGHM	3.3	2.32e-05	IGHM	2.2	2.07e-04	IGHG3	4.6	8.84e-05	IGHM	3.2	9.68e-05
IGHA2	3.1	1.63e-04	IGHG1	2.9	5.70e-04	IGHG4	2.9	2.81e-04	IGHA2	4.3	1.05e-04	IGHG1	3.5	1.15e-04
IGHG3	3.1	1.82e-04	IGHA2	2.7	0.001	IGHG1	2.5	6.63e-04	IGHG1	4.4	1.08e-04	IGHG3	3.5	1.80e-04
IGHG1	3.3	1.96e-04	IGHG3	2.8	0.002	IGHA2	2.6	0.001	IGHA1	3.8	4.72e-04	IGHA1	2.9	6.20e-04
IGHG4	3.2	0.001	IGHA1	2.1	0.009	IGHA1	1.8	0.003	IGHG4	4.7	6.72e-04	IGHG2	3.5	7.32e-04
IGHG2	3.0	0.001	IGHG4	2.8	0.021	IGHG2	2.3	0.004	IGHG2	4.1	8.31e-04	IGHA2	3.2	0.001
IGHA1	2.5	0.002	IGHG2	2.5	0.026	IGHG3	2.1	0.016	IGHM	3.2	0.002	IGHG4	3.2	0.002
IGHD	1.4	0.027	IGHD	0.7	0.399	IGHD	1.0	0.190	IGHD	2.5	0.012	IGHD	1.9	0.004
IGHE	0.3	0.363	IGHE	0.1	0.889	IGHE	0.3	0.625	IGHE	0.3	0.636	IGHE	0.4	0.309

JO1 vs. NT			IMNM vs. NT			HMGR vs. NT			SRP vs. NT			IBM vs. NT		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGHA1	4.3	3.92e-08	IGHG1	2.1	0.002	IGHG1	1.8	0.010	IGHA2	3.3	4.92e-06	IGHG2	5.7	4.16e-10
IGHG1	5.2	2.20e-07	IGHG3	2.0	0.011	IGHG4	1.9	0.025	IGHG1	2.9	1.04e-05	IGHA1	5.0	2.71e-09
IGHM	5.9	5.07e-07	IGHG4	2.2	0.011	IGHM	1.6	0.036	IGHG2	3.3	1.25e-05	IGHA2	5.3	1.47e-08
IGHA2	4.7	6.28e-07	IGHM	1.8	0.014	IGHG3	1.7	0.037	IGHA1	2.3	1.41e-05	IGHG1	6.5	2.91e-08
IGHG3	5.0	4.35e-06	IGHG2	2.2	0.016	IGHG2	1.9	0.052	IGHG3	3.0	1.18e-04	IGHG4	5.8	1.36e-07
IGHG2	4.6	7.62e-06	IGHA1	1.4	0.027	IGHA1	1.1	0.100	IGHM	2.3	1.96e-04	IGHM	6.3	2.24e-07
IGHG4	5.1	8.86e-06	IGHA2	1.7	0.043	IGHA2	1.2	0.160	IGHG4	3.2	0.001	IGHD	3.1	2.96e-07
IGHD	2.6	5.76e-04	IGHD	0.7	0.199	IGHD	0.6	0.336	IGHD	1.2	0.064	IGHG3	6.9	5.15e-07
IGHE	0.1	0.904	IGHE	-0.2	0.603	IGHE	-0.2	0.636	IGHE	0.0	0.924	IGHE	0.6	0.072

Figure 2. Spearman correlation matrix of immunoglobulin heavy chain genes.

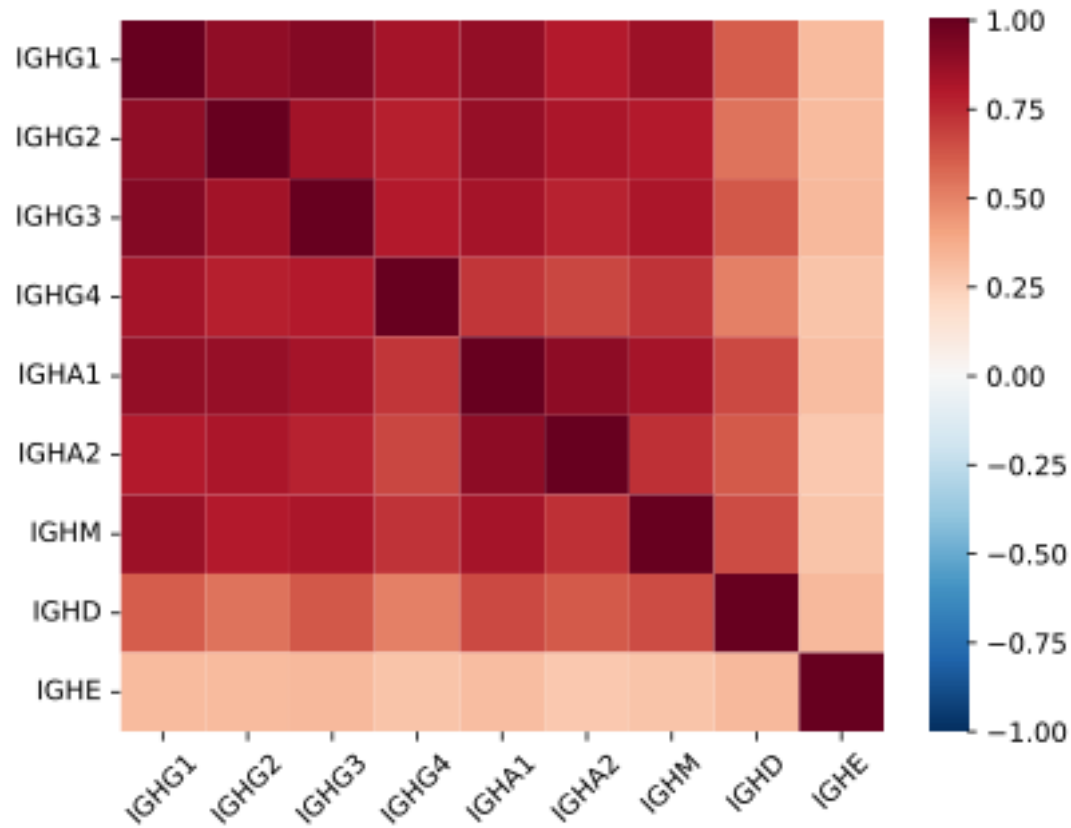


Figure 3. Spearman correlation between immunoglobulin heavy chain gene expression and transcriptomic markers of disease activity across all study samples. Shown are correlations with type I interferon-inducible genes (ISG15, MX1), type II interferon-inducible genes (GBP2, IFI30), T-cell markers (CD3E, CD4, CD8), macrophage markers (CD14, CD68), muscle differentiation markers (MYH3, MYH8, NCAM1, PAX7), mitochondrial genes (MT-CO1, MT-CO2), and structural mature muscle proteins (ACTA1, MYH1, MYH2).

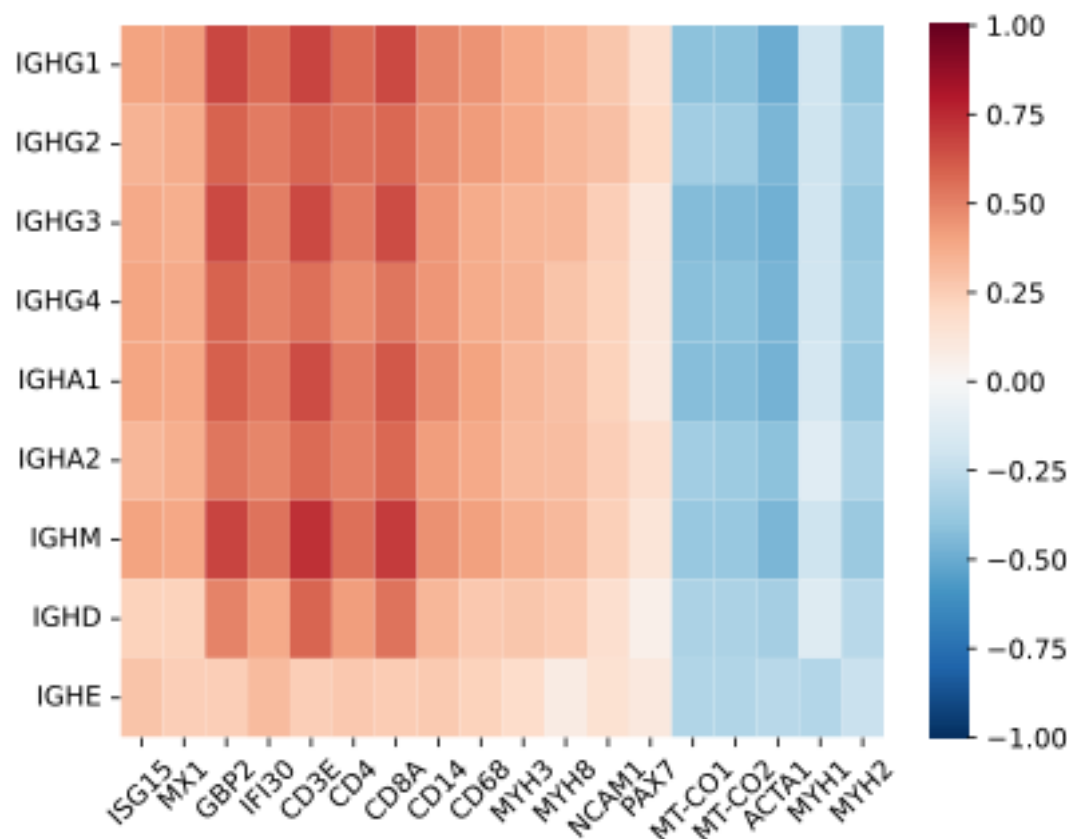


Figure 4. Gene Set Enrichment Analysis (GSEA) of Reactome pathways based on IGHG1 co-expression. This dot plot displays the top 35 Reactome pathways enriched in the Spearman correlation analysis between IGHG1 expression and genome-wide gene expression. The x-axis shows the Normalized Enrichment Score (NES), where positive values indicate pathways positively associated with IGHG1 co-expression and negative values indicate downregulated pathways.



Figure 5. Spearman correlation of the expression of immunoglobulin heavy chain genes with the interferon gamma inducible gene GBP2. Each point represents an individual sample. Expression is presented as trimmed mean of M values (TMM). Normal muscle biopsy: NT; inclusion body myositis: IBM.

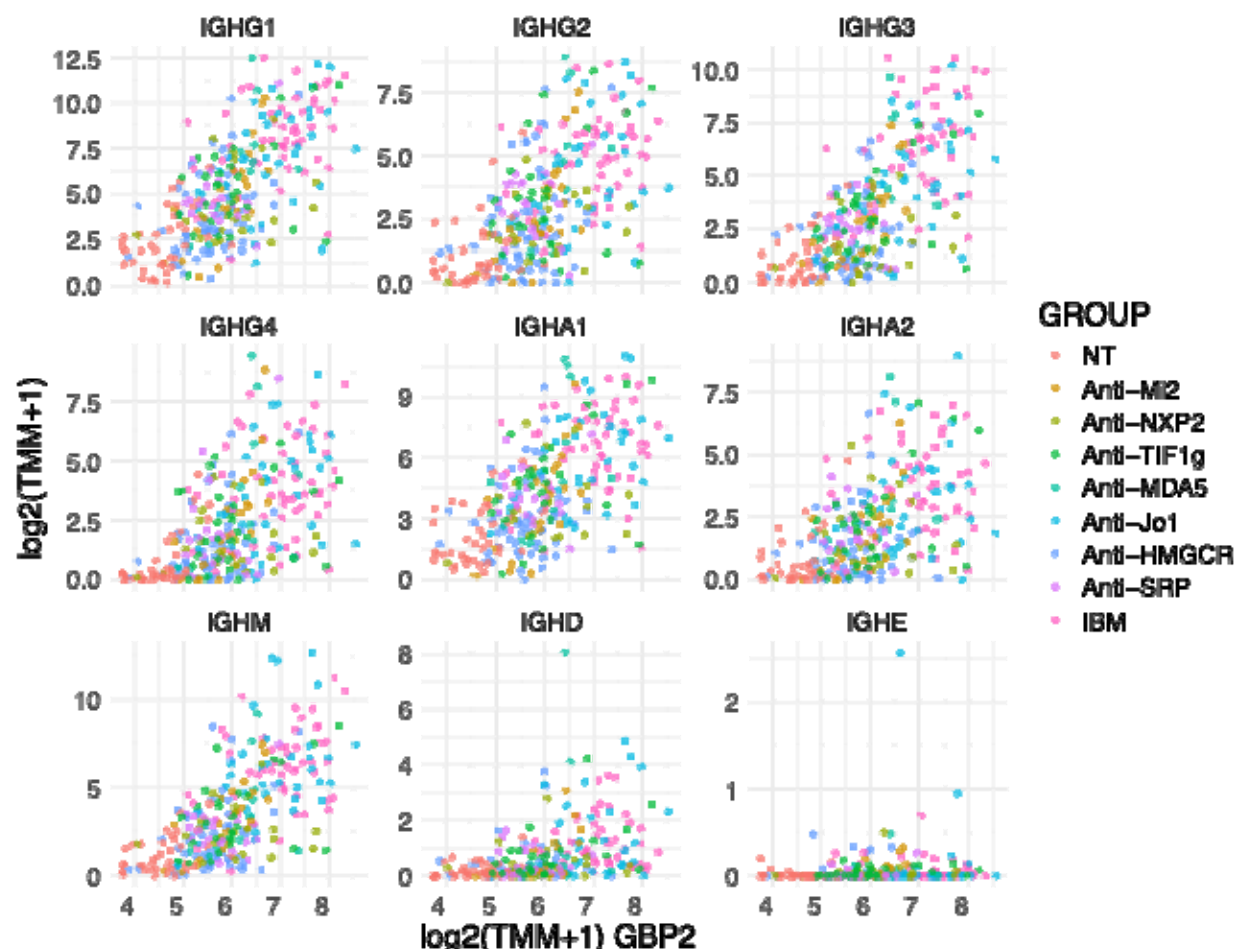
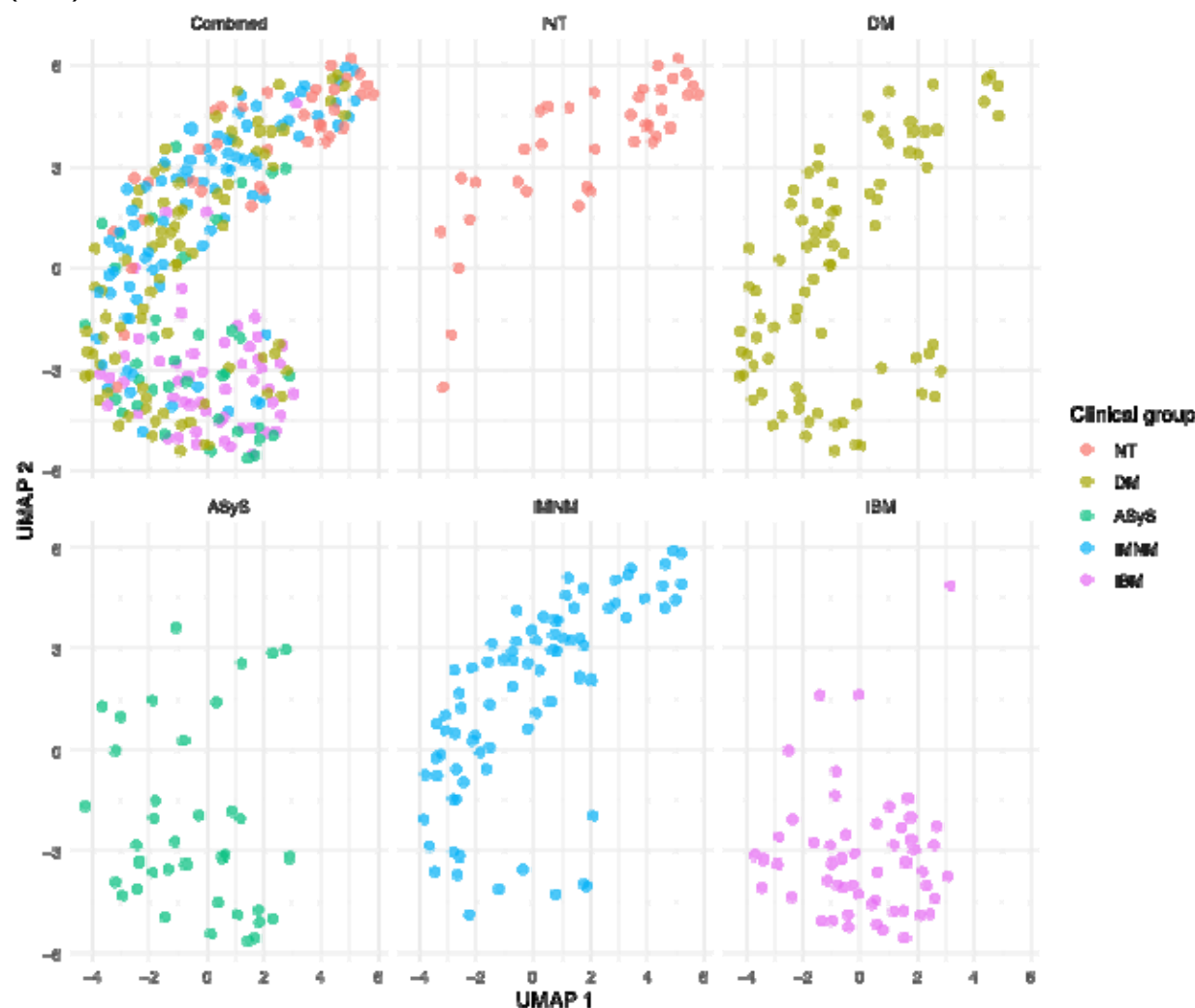


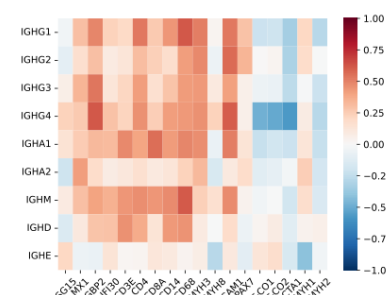
Figure 6. UMAP visualization of clinical groups based on immunoglobulin gene expression. Uniform Manifold Approximation and Projection (UMAP) was used to cluster samples by their immunoglobulin gene expression profiles. Sample groups include normal muscle biopsy (NT), dermatomyositis (DM), antisynthetase syndrome (ASyS), immune-mediated necrotizing myopathy (IMNM), and inclusion body myositis (IBM).



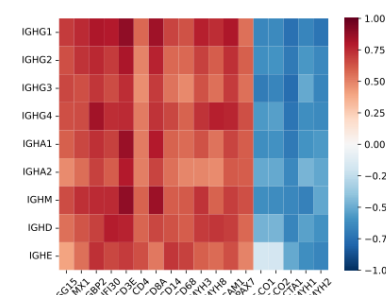
Supplementary Figure 1. Spearman correlations between immunoglobulin heavy chain gene expression and markers of disease activity across study groups.

Shown are correlations with type I interferon-inducible genes (ISG15, MX1), type II interferon-inducible genes (GBP2, IFI30), T-cell markers (CD3E, CD4, CD8), macrophage markers (CD14, CD68), muscle differentiation markers (MYH3, MYH8, NCAM1, PAX7), mitochondrial genes (MT-CO1, MT-CO2), and structural mature muscle proteins (ACTA1, MYH1, MYH2).

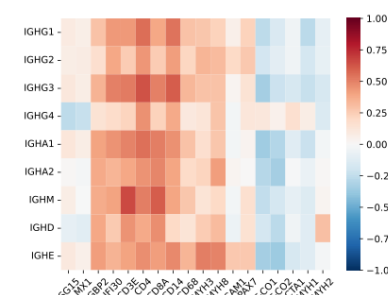
Normal muscle biopsy



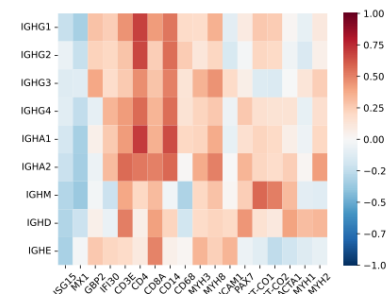
Anti-Mi2



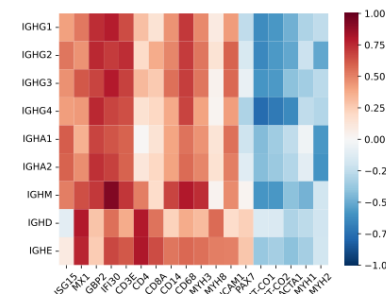
Anti-TIF1



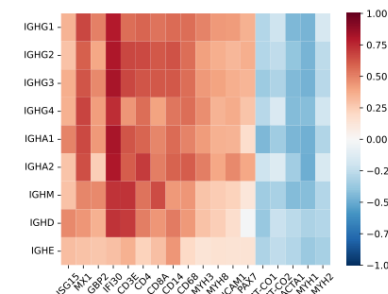
Anti-NXP2



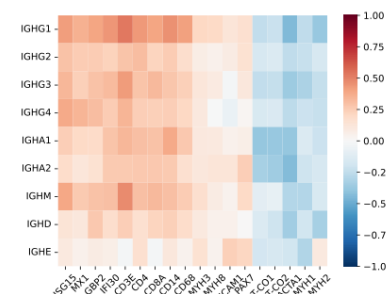
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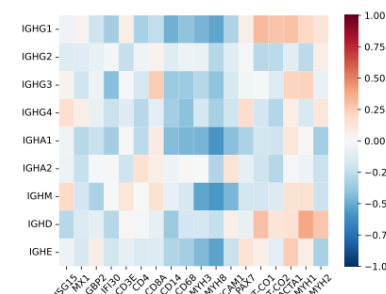
Anti-Jo1



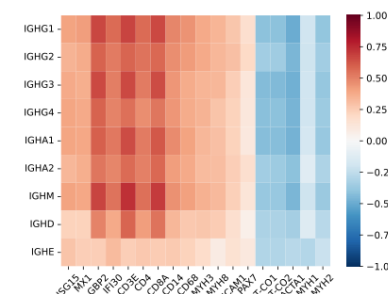
Anti-HMGCR



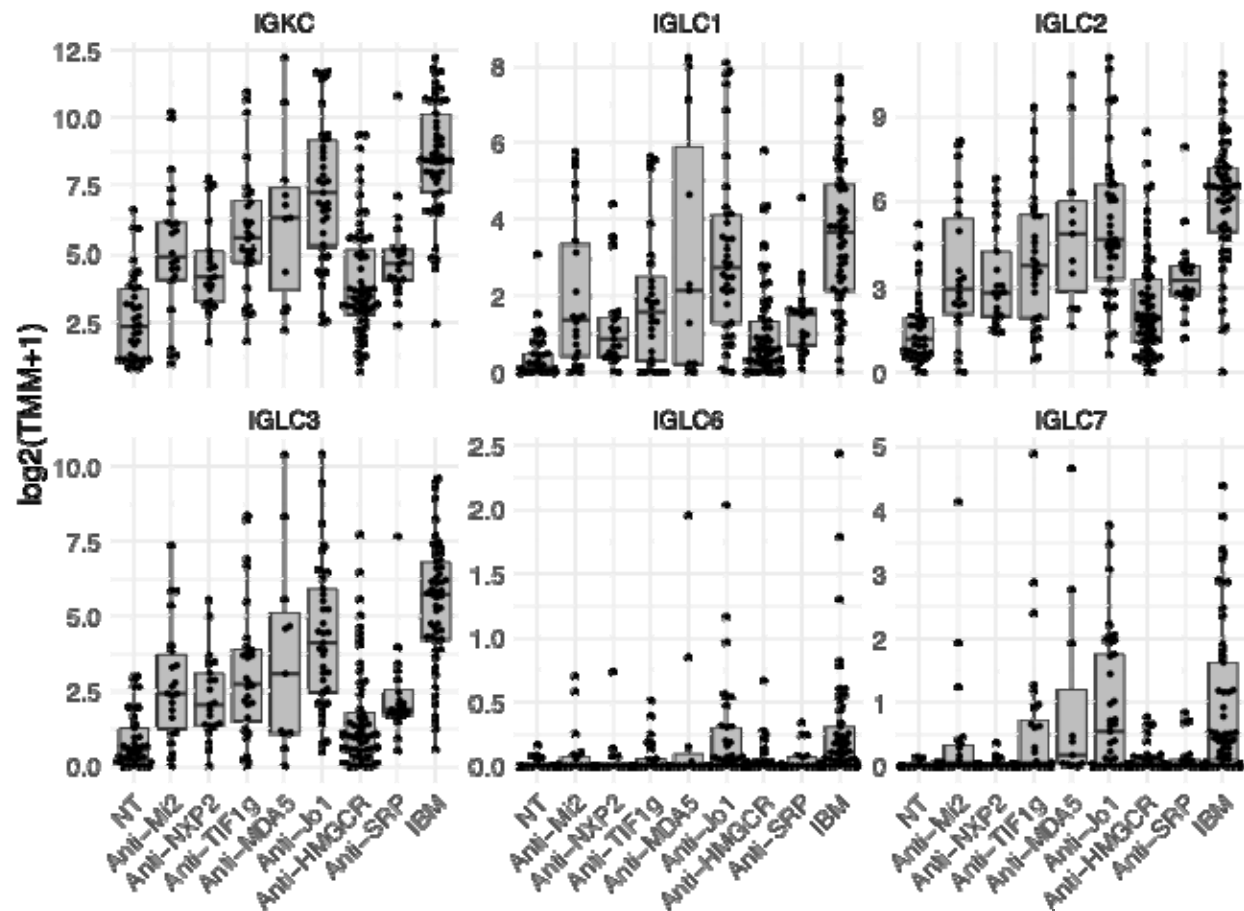
Anti-SRP



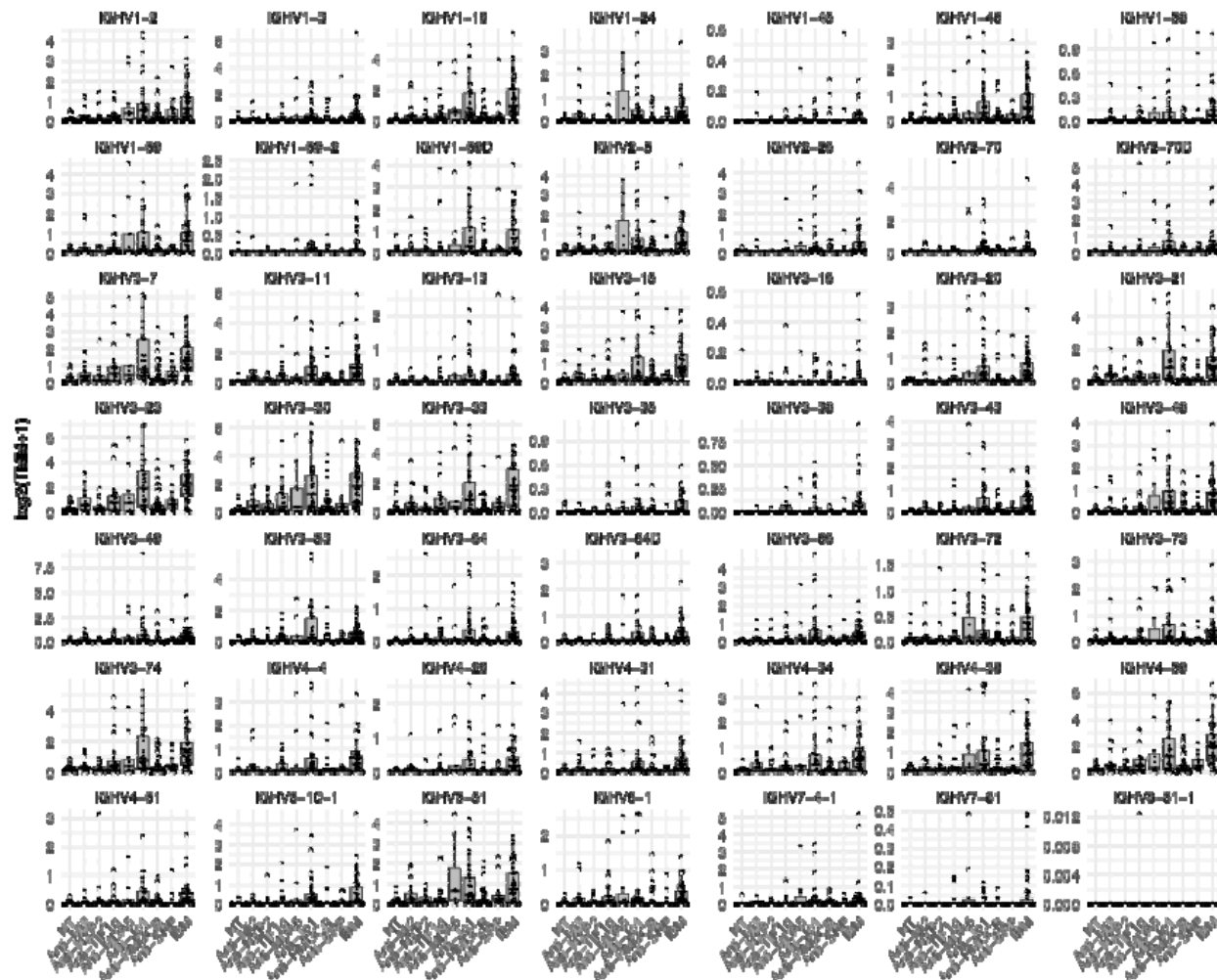
Inclusion body myositis



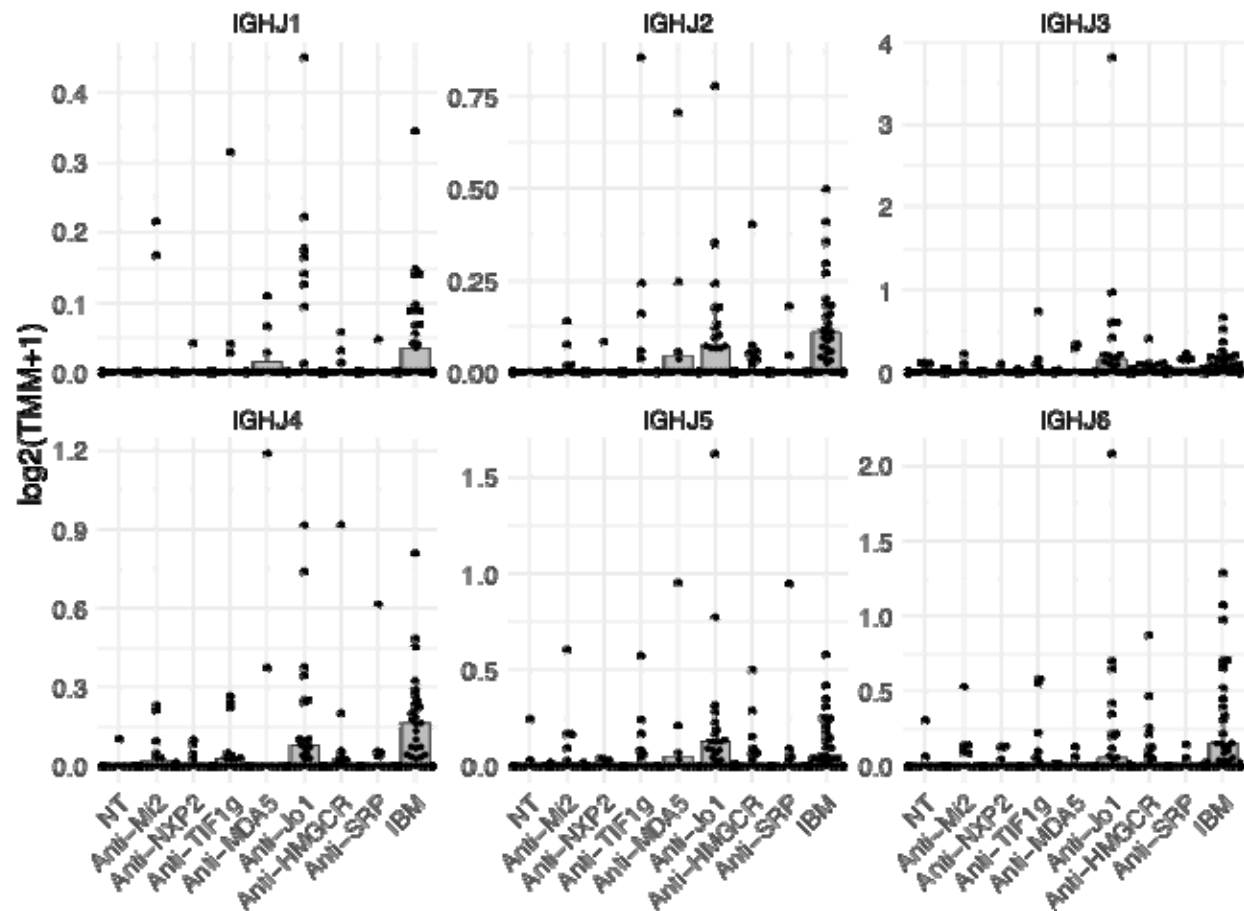
Supplementary Figure 2. Expression of immunoglobulin kappa and lambda light chain constant region genes across disease groups. Each point represents an individual sample. Expression is presented as trimmed mean of M values (TMM). Normal muscle biopsy: NT; inclusion body myositis: IBM.



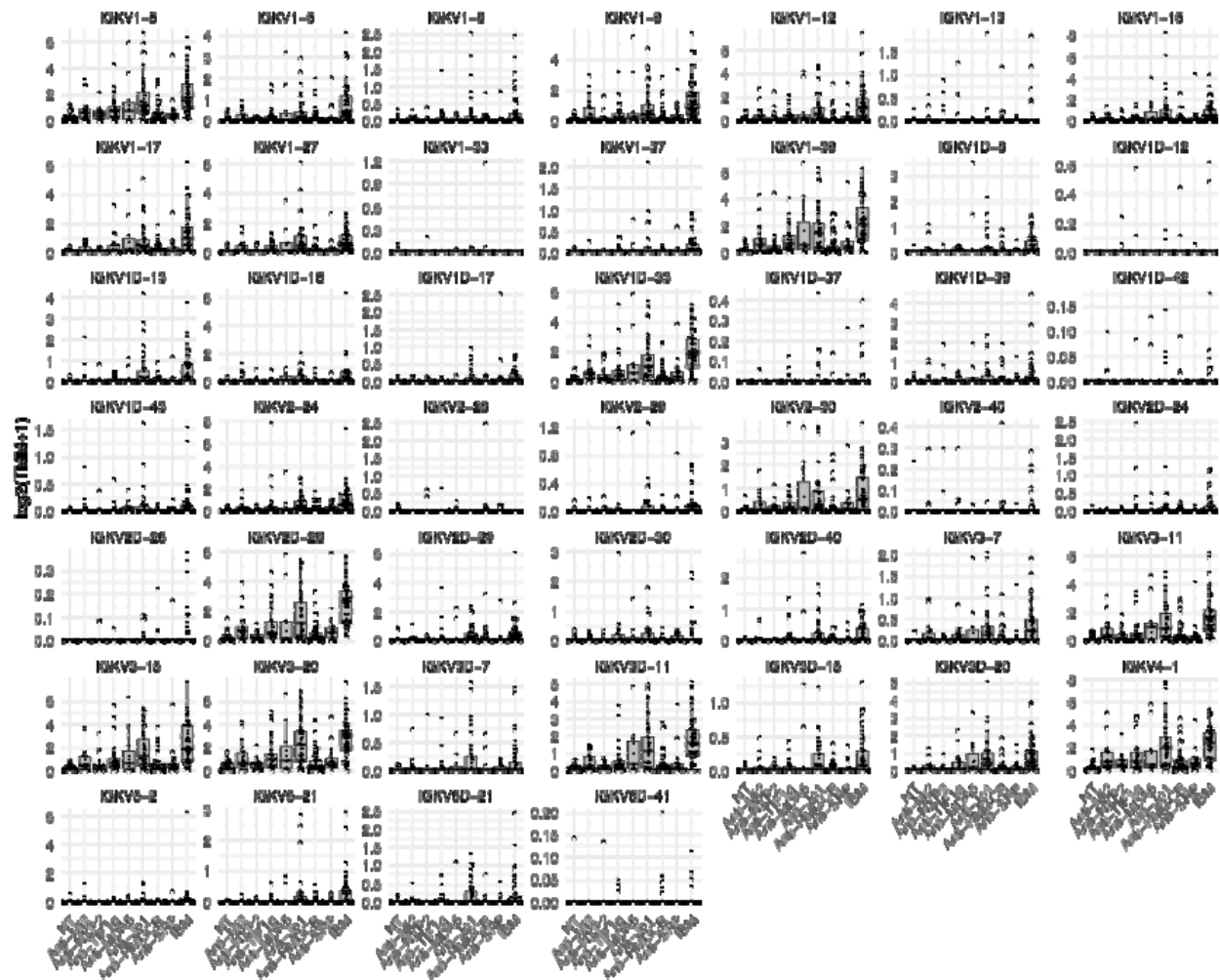
Supplementary Figure 3. Expression of immunoglobulin heavy chain variable region genes across disease groups. Each point represents an individual sample. Expression is presented as trimmed mean of M values (TMM). Normal muscle biopsy: NT; inclusion body myositis: IBM.



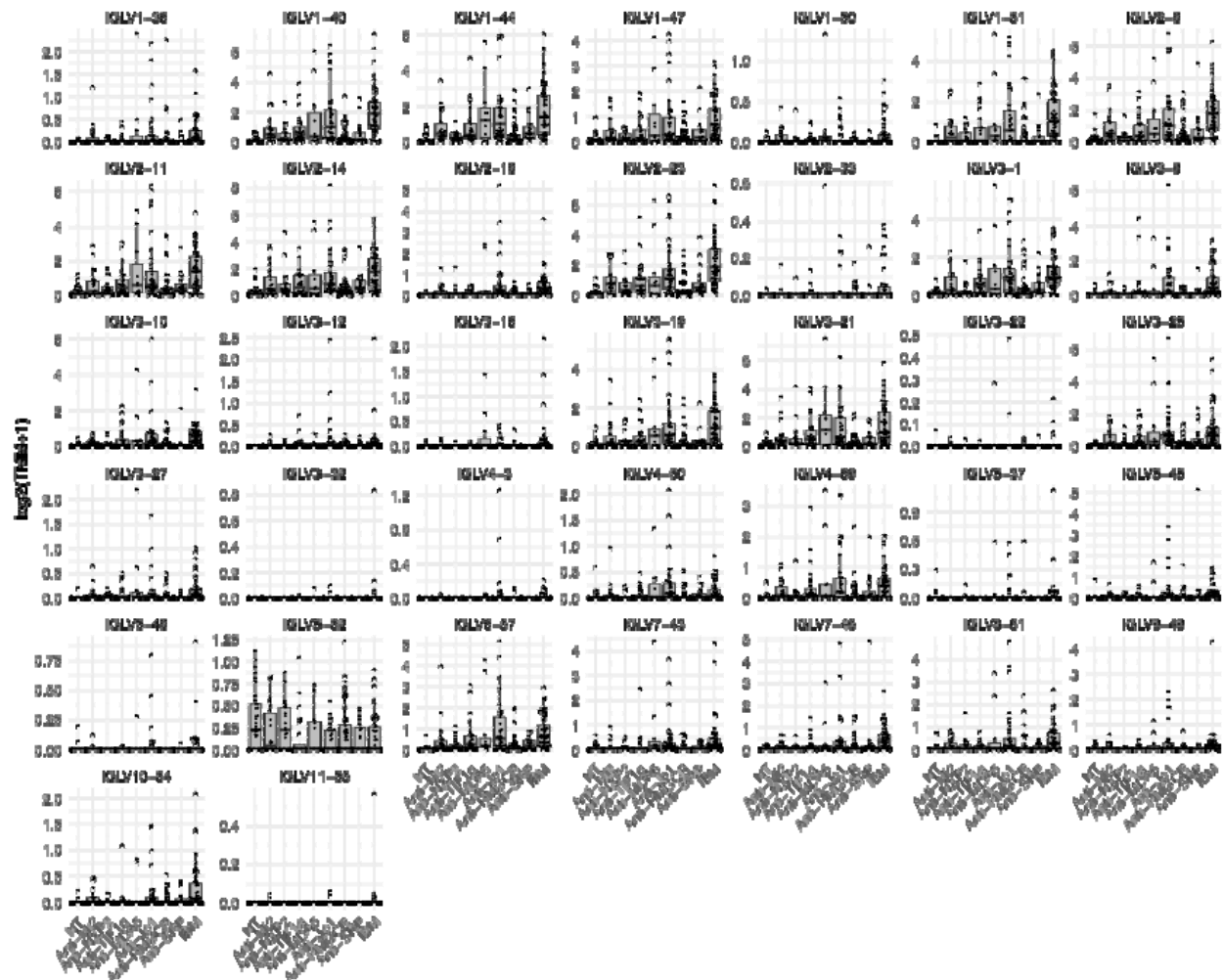
Supplementary Figure 4. Expression of immunoglobulin heavy chain joining region genes across disease groups. Each point represents an individual sample. Expression is presented as trimmed mean of M values (TMM). Normal muscle biopsy: NT; inclusion body myositis: IBM.



Supplementary Figure 5. Expression of immunoglobulin kappa light chain variable region genes across disease groups. Each point represents an individual sample. Expression is presented as trimmed mean of M values (TMM). Normal muscle biopsy: NT; inclusion body myositis: IBM.



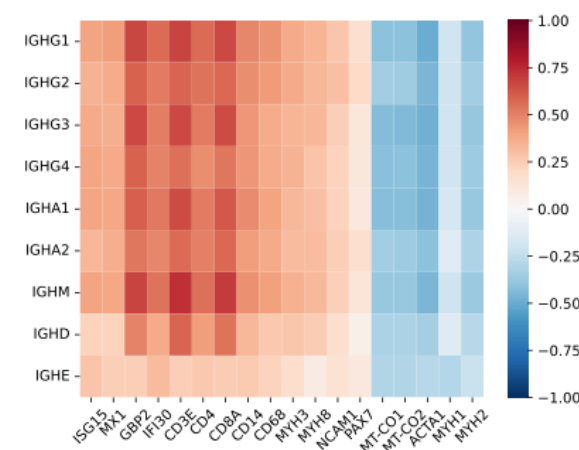
Supplementary Figure 6. Expression of immunoglobulin lambda light chain variable region genes across disease groups. Each point represents an individual sample. Expression is presented as trimmed mean of M values (TMM). Normal muscle biopsy: NT; inclusion body myositis: IBM.



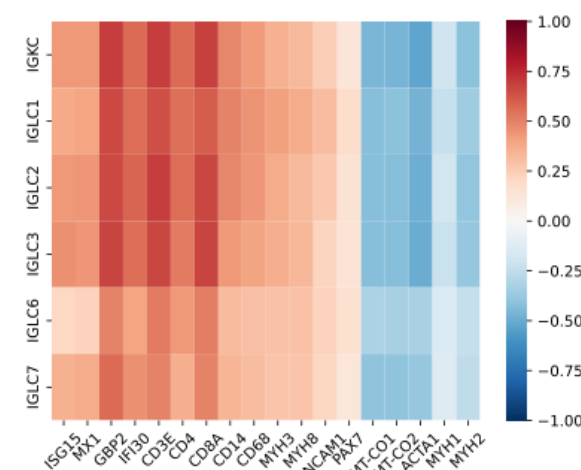


Supplementary Figure 8. Spearman correlation between immunoglobulin gene expression and markers of disease activity. Shown are correlations with type I interferon-inducible genes (ISG15, MX1), type II interferon-inducible genes (GBP2, IFI30), T-cell markers (CD3E, CD4, CD8), macrophage markers (CD14, CD68), muscle differentiation markers (MYH3, MYH8, NCAM1, PAX7), mitochondrial genes (MT-CO1, MT-CO2), and structural mature muscle proteins (ACTA1, MYH1, MYH2).

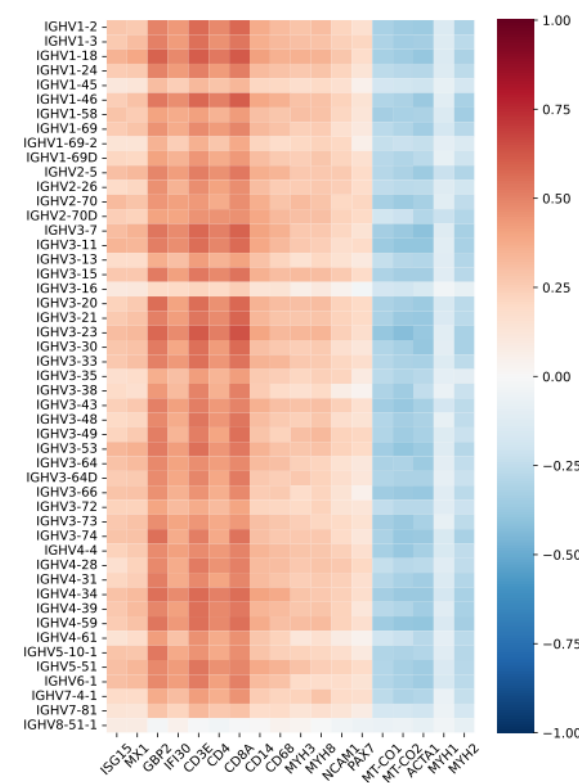
Heavy chain constant region



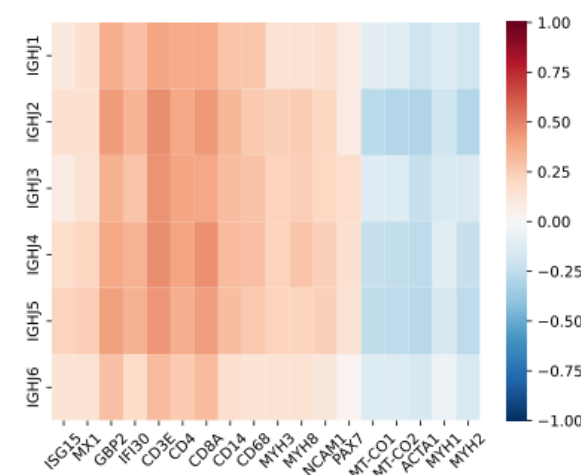
Kappa/lambda constant regions



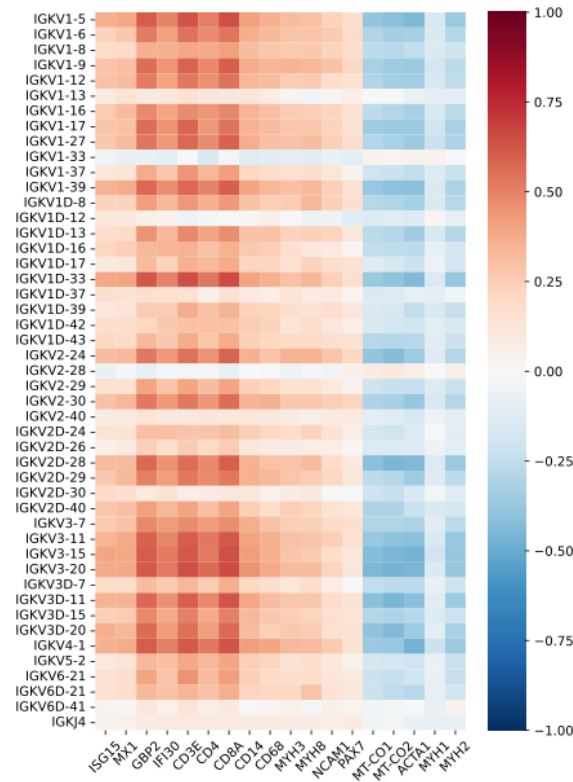
Heavy chain variable region



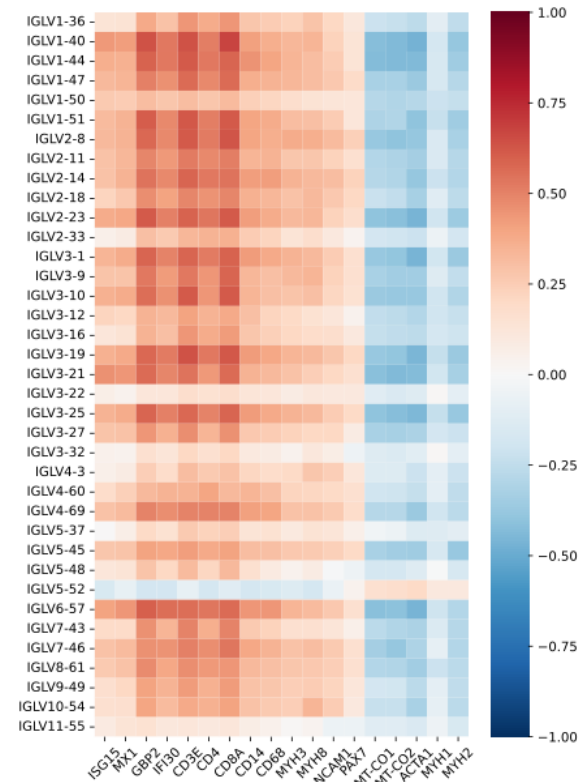
Heavy chain joining region



Kappa chain variable region



Lambda chain variable region



Supplementary Table 1. Distribution of groups included in the study.

Group	N = 289 ¹
NT	37 (13%)
Anti-Mi2	22 (7.6%)
Anti-NXP2	21 (7.3%)
Anti-TIF1 γ	28 (9.7%)
Anti-MDA5	11 (3.8%)
Anti-Jo1	37 (13%)
Anti-HMGCR	60 (21%)
Anti-SRP	20 (6.9%)
IBM	53 (18%)

¹n (%)

Supplementary Table 2. Expression of immunoglobulin kappa/lambda constant region genes across disease groups, shown as comparisons versus all other muscle biopsies (vs. ALL) and versus normal muscle biopsies (vs. NT). DM: dermatomyositis; IMNM: immune-mediated necrotizing myopathy; IBM: inclusion body myositis; NT: normal muscle biopsy.

DM vs. ALL			Mi2 vs. ALL			NXP2 vs. ALL			MDA5 vs. ALL			TIF1yvs. ALL		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGLC6	-0.7	0.024	IGLC6	-0.7	0.265	IGLC7	-1.3	0.208	IGLC2	1.5	0.587	IGLC6	-0.6	0.372
IGKC	-0.2	0.693	IGKC	-0.4	0.691	IGLC6	-0.8	0.291	IGLC7	1.2	0.701	IGLC7	0.4	0.714
IGLC7	-0.2	0.767	IGLC1	0.4	0.767	IGKC	-1.0	0.481	IGLC3	1.0	0.722	IGKC	0.3	0.762
IGLC2	0.1	0.832	IGLC2	-0.3	0.775	IGLC1	-0.8	0.658	IGKC	0.8	0.739	IGLC2	0.3	0.797
IGLC3	0.1	0.840	IGLC7	-0.3	0.804	IGLC3	-0.5	0.740	IGLC1	0.7	0.812	IGLC3	0.3	0.835
IGLC1	-0.1	0.899	IGLC3	0.0	0.995	IGLC2	-0.4	0.762	IGLC6	0.2	0.939	IGLC1	-0.2	0.892

JO1 vs. ALL			IMNM vs. ALL			HMGCR vs. ALL			SRP vs. ALL			IBM vs. ALL		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGKC	2.1	3.45e-04	IGLC7	-1.8	1.46e-04	IGLC7	-1.8	5.74e-04	IGLC7	-0.9	0.996	IGKC	3.8	1.26e-24
IGLC3	2.2	8.79e-04	IGKC	-1.9	0.001	IGLC3	-2.4	0.003	IGKC	-0.7	0.996	IGLC3	3.8	1.10e-20
IGLC7	2.1	0.001	IGLC3	-2.2	0.001	IGKC	-2.0	0.004	IGLC6	-0.3	0.996	IGLC1	3.7	5.40e-16
IGLC2	2.0	0.003	IGLC2	-1.8	0.003	IGLC2	-2.0	0.005	IGLC3	-0.4	0.996	IGLC2	3.1	7.35e-15
IGLC1	2.2	0.004	IGLC6	-0.8	0.012	IGLC6	-0.9	0.012	IGLC2	-0.3	0.996	IGLC7	2.6	6.01e-09
IGLC6	1.0	0.130	IGLC1	-1.8	0.017	IGLC1	-2.2	0.017	IGLC1	0.0	0.999	IGLC6	1.7	3.94e-07

DM vs. NT			Mi2 vs. NT			NXP2 vs. NT			MDA5 vs. NT			TIF1yvs. NT		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGKC	3.1	6.28e-05	IGLC3	3.6	7.39e-05	IGLC3	3.1	1.79e-05	IGLC2	4.5	2.31e-05	IGKC	3.5	9.68e-06
IGLC3	3.7	7.30e-05	IGKC	2.8	2.46e-04	IGLC2	2.7	9.99e-05	IGKC	3.9	1.64e-04	IGLC2	3.3	2.84e-04
IGLC2	3.2	2.25e-04	IGLC1	3.9	2.49e-04	IGKC	2.3	1.75e-04	IGLC3	4.5	8.89e-04	IGLC7	2.2	5.43e-04
IGLC7	1.7	3.31e-04	IGLC2	2.8	0.003	IGLC1	2.8	0.001	IGLC7	2.9	0.001	IGLC3	3.8	6.17e-04
IGLC1	3.5	6.19e-04	IGLC7	1.5	0.007	IGLC7	0.6	0.154	IGLC1	4.2	0.004	IGLC1	3.4	0.003
IGLC6	0.2	0.671	IGLC6	-0.1	0.906	IGLC6	-0.1	0.900	IGLC6	0.7	0.321	IGLC6	0.1	0.737

JO1 vs. NT			IMNM vs. NT			HMGCR vs. NT			SRP vs. NT			IBM vs. NT		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGLC7	3.7	2.53e-09	IGKC	1.8	0.002	IGKC	1.6	0.010	IGLC1	3.5	2.12e-06	IGLC7	4.0	1.92e-11
IGKC	5.1	2.49e-08	IGLC1	2.2	0.009	IGLC1	1.8	0.039	IGLC2	2.8	6.68e-06	IGLC1	6.6	1.17e-09
IGLC3	5.5	3.81e-07	IGLC2	1.8	0.010	IGLC2	1.5	0.044	IGLC3	3.2	1.07e-05	IGKC	6.4	1.45e-09
IGLC2	4.8	5.07e-07	IGLC3	2.0	0.011	IGLC3	1.7	0.045	IGKC	2.6	2.23e-05	IGLC6	2.1	1.77e-08
IGLC1	5.5	2.68e-05	IGLC7	0.6	0.109	IGLC7	0.4	0.261	IGLC7	1.0	0.051	IGLC3	6.8	1.92e-08
IGLC6	1.4	2.54e-04	IGLC6	0.0	0.910	IGLC6	-0.1	0.813	IGLC6	0.5	0.196	IGLC2	5.8	5.41e-07

Supplementary Table 3. Expression of top 10 immunoglobulin heavy chain variable region genes across disease groups, shown as comparisons versus all other muscle biopsies (vs. ALL) and versus normal muscle biopsies (vs. NT). DM: dermatomyositis; IMNM: immune-mediated necrotizing myopathy; IBM: inclusion body myositis; NT: normal muscle biopsy.

DM vs. ALL			Mi2 vs. ALL			NXP2 vs. ALL			MDA5 vs. ALL			TIF1γvs. ALL		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGHV1-69-2	-0.8	0.003	IGHV3-38	-1.1	0.009	IGHV4-28	-1.3	0.030	IGHV5-51	1.8	0.448	IGHV1-69-2	-0.9	0.087
IGHV3-38	-0.6	0.006	IGHV7-81	-0.8	0.018	IGHV1-24	-1.4	0.034	IGHV1-2	1.3	0.649	IGHV1-45	-0.5	0.177
IGHV3-16	-0.5	0.007	IGHV4-61	-1.2	0.032	IGHV4-4	-1.5	0.034	IGHV1-24	1.1	0.694	IGHV3-16	-0.5	0.250
IGHV1-45	-0.4	0.012	IGHV1-69-2	-1.0	0.035	IGHV3-20	-1.5	0.035	IGHV1-69	1.2	0.700	IGHV1-24	-0.8	0.259
IGHV2-26	-0.8	0.013	IGHV3-35	-0.8	0.039	IGHV2-26	-1.2	0.072	IGHV2-5	1.1	0.701	IGHV7-4-1	-0.7	0.309
IGHV7-81	-0.4	0.018	IGHV2-26	-1.2	0.057	IGHV1-69	-1.5	0.084	IGHV6-1	0.9	0.716	IGHV1-69D	-0.9	0.313
IGHV3-48	-0.9	0.025	IGHV1-45	-0.6	0.079	IGHV3-48	-1.3	0.129	IGHV3-33	1.1	0.717	IGHV4-28	-0.6	0.372
IGHV3-35	-0.5	0.027	IGHV3-16	-0.6	0.081	IGHV1-58	-0.8	0.130	IGHV4-34	0.9	0.719	IGHV3-13	-0.5	0.383
IGHV3-64D	-0.7	0.032	IGHV3-64D	-0.9	0.111	IGHV3-64D	-1.0	0.153	IGHV3-13	0.8	0.719	IGHV2-5	-0.7	0.422
IGHV3-43	-0.8	0.032	IGHV3-13	-0.8	0.123	IGHV4-59	-1.7	0.168	IGHV3-49	0.9	0.721	IGHV4-61	-0.5	0.516

JO1 vs. ALL			IMNM vs. ALL			HMGR vs. ALL			SRP vs. ALL			IBM vs. ALL		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGHV3-23	2.8	9.65e-07	IGHV3-73	-1.2	3.31e-04	IGHV3-53	-1.5	5.68e-04	IGHV3-35	-0.6	0.928	IGHV4-59	3.6	5.44e-19
IGHV3-7	2.6	1.69e-06	IGHV3-53	-1.4	4.95e-04	IGHV3-74	-1.9	0.001	IGHV3-64	-0.8	0.972	IGHV1-18	3.3	5.57e-16
IGHV3-21	2.5	3.00e-05	IGHV3-74	-1.7	0.001	IGHV3-7	-2.0	0.001	IGHV1-69-2	-0.6	0.990	IGHV3-30	3.5	1.12e-15
IGHV3-48	2.3	6.20e-05	IGHV3-21	-1.7	0.001	IGHV4-4	-1.4	0.002	IGHV6-1	-0.8	0.994	IGHV1-46	2.7	6.46e-13
IGHV3-20	2.1	9.71e-05	IGHV5-10-1	-1.1	0.003	IGHV3-66	-1.3	0.002	IGHV3-73	-0.8	0.996	IGHV3-23	3.1	1.01e-12
IGHV3-74	2.2	1.74e-04	IGHV3-7	-1.6	0.003	IGHV3-73	-1.2	0.003	IGHV4-61	-0.7	0.996	IGHV3-74	2.7	1.32e-11
IGHV2-70	1.8	4.67e-04	IGHV3-11	-1.4	0.004	IGHV4-59	-2.0	0.003	IGHV3-11	-0.9	0.996	IGHV3-15	2.7	1.96e-11
IGHV3-53	2.1	4.84e-04	IGHV3-66	-1.1	0.004	IGHV5-10-1	-1.2	0.003	IGHV7-81	-0.3	0.996	IGHV3-33	2.9	3.27e-11
IGHV3-66	1.9	8.59e-04	IGHV1-18	-1.5	0.004	IGHV5-51	-1.7	0.003	IGHV2-5	-0.8	0.996	IGHV4-39	2.6	4.82e-11
IGHV3-49	2.0	0.001	IGHV3-20	-1.2	0.004	IGHV3-49	-1.4	0.004	IGHV3-64D	-0.5	0.996	IGHV3-7	2.7	1.41e-10

DM vs. NT			Mi2 vs. NT			NXP2 vs. NT			MDA5 vs. NT			TIF1γvs. NT		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGHV1-18	1.9	6.02e-05	IGHV7-81	-0.8	1.10e-05	IGHV1-18	1.3	0.017	IGHV5-51	3.4	5.79e-04	IGHV3-53	1.9	2.18e-04
IGHV3-7	2.1	1.94e-04	IGHV3-38	-0.8	3.64e-05	IGHV3-64	1.1	0.036	IGHV1-2	2.9	5.89e-04	IGHV1-18	2.1	2.99e-04
IGHV3-11	1.5	5.00e-04	IGHV3-7	1.9	0.002	IGHV3-7	1.4	0.049	IGHV1-18	2.9	0.002	IGHV3-7	2.5	4.92e-04
IGHV3-53	1.3	0.001	IGHV1-18	1.7	0.003	IGHV4-39	1.1	0.072	IGHV3-11	2.4	0.002	IGHV4-59	2.1	0.002
IGHV2-5	1.3	0.003	IGHV4-34	1.5	0.004	IGHV3-11	1.0	0.075	IGHV3-7	2.9	0.003	IGHV3-11	1.7	0.002
IGHV4-34	1.3	0.004	IGHV3-23	2.1	0.005	IGHV7-81	-0.5	0.102	IGHV3-33	3.0	0.004	IGHV3-23	2.6	0.002
IGHV3-23	2.0	0.004	IGHV1-69-2	-0.9	0.006	IGHV5-51	1.3	0.106	IGHV4-59	2.8	0.004	IGHV3-30	2.2	0.004
IGHV4-59	1.8	0.004	IGHV4-59	1.9	0.007	IGHV2-5	1.0	0.111	IGHV4-34	2.2	0.004	IGHV1-69	1.4	0.007
IGHV5-51	1.6	0.005	IGHV3-74	1.4	0.007	IGHV3-23	1.1	0.120	IGHV2-5	2.6	0.006	IGHV3-74	2.1	0.008
IGHV3-30	1.9	0.007	IGHV3-35	-0.6	0.008	IGHV4-34	0.9	0.127	IGHV3-30	2.6	0.011	IGHV1-69-2	-0.8	0.011

JO1 vs. NT			IMNM vs. NT			HMGR vs. NT			SRP vs. NT			IBM vs. NT		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGHV3-7	4.7	1.81e-10	IGHV1-18	1.2	0.008	IGHV1-18	1.0	0.037	IGHV4-59	2.4	2.37e-04	IGHV1-18	5.1	1.92e-13
IGHV1-18	4.0	1.21e-09	IGHV3-7	1.2	0.029	IGHV3-23	1.0	0.127	IGHV3-7	2.3	3.55e-04	IGHV1-46	3.8	4.21e-13
IGHV3-20	3.0	1.22e-09	IGHV3-23	1.3	0.044	IGHV3-11	0.7	0.140	IGHV3-23	2.3	0.002	IGHV3-7	4.7	1.66e-12
IGHV3-48	3.4	1.77e-09	IGHV1-2	0.9	0.062	IGHV3-30	1.0	0.142	IGHV1-18	1.7	0.007	IGHV3-43	3.0	1.94e-12
IGHV3-21	3.9	6.18e-08	IGHV3-48	0.8	0.084	IGHV3-7	0.8	0.156	IGHV1-2	1.7	0.008	IGHV3-53	3.2	2.83e-12
IGHV2-5	3.1	6.49e-08	IGHV3-30	1.1	0.096	IGHV2-5	0.6	0.199	IGHV5-51	1.7	0.009	IGHV4-34	3.5	4.27e-12
IGHV1-46	2.8	1.87e-07	IGHV3-11	0.7	0.099	IGHV3-38	-0.3	0.216	IGHV2-70D	1.2	0.009	IGHV2-5	3.5	2.41e-11
IGHV3-11	3.2	1.91e-07	IGHV1-46	0.7	0.103	IGHV7-81	-0.3	0.221	IGHV3-74	1.5	0.017	IGHV3-30	5.3	4.45e-11
IGHV3-43	2.6	2.02e-07	IGHV4-59	1.0	0.105	IGHV1-2	0.6	0.223	IGHV3-43	1.1	0.030	IGHV3-11	4.0	8.47e-11
IGHV3-49	3.0	2.90e-07	IGHV7-81	-0.3	0.114	IGHV3-48	0.6	0.237	IGHV2-70	0.8	0.031	IGHV3-48	3.4	9.50e-11

Supplementary Table 4. Expression of immunoglobulin heavy chain joining region genes across disease groups, shown as comparisons versus all other muscle biopsies (vs. ALL) and versus normal muscle biopsies (vs. NT). DM: dermatomyositis; IMNM: immune-mediated necrotizing myopathy; IBM: inclusion body myositis; NT: normal muscle biopsy.

DM vs. ALL			Mi2 vs. ALL			NXP2 vs. ALL			MDA5 vs. ALL			TIF1γvs. ALL		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGHJ3	-0.8	0.001	IGHJ2	-0.8	0.034	IGHJ2	-0.7	0.165	IGHJ6	-0.4	0.767	IGHJ3	-0.6	0.204
IGHJ2	-0.6	0.010	IGHJ3	-0.8	0.067	IGHJ3	-0.7	0.191	IGHJ2	0.4	0.795	IGHJ1	-0.4	0.298
IGHJ1	-0.4	0.014	IGHJ1	-0.6	0.117	IGHJ5	-0.6	0.248	IGHJ5	0.3	0.856	IGHJ2	-0.4	0.455
IGHJ6	-0.6	0.024	IGHJ4	-0.6	0.204	IGHJ6	-0.5	0.439	IGHJ1	0.1	0.959	IGHJ5	-0.4	0.476
IGHJ5	-0.4	0.075	IGHJ6	-0.6	0.244	IGHJ1	-0.4	0.449	IGHJ3	-0.1	0.961	IGHJ6	-0.4	0.578
IGHJ4	-0.4	0.087	IGHJ5	-0.4	0.395	IGHJ4	-0.4	0.586	IGHJ4	0.1	0.976	IGHJ4	-0.3	0.626

JO1 vs. ALL			IMNM vs. ALL			HMGCR vs. ALL			SRP vs. ALL			IBM vs. ALL		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGHJ5	1.0	0.053	IGHJ4	-0.5	0.040	IGHJ4	-0.6	0.050	IGHJ6	-0.6	0.991	IGHJ2	1.0	1.16e-04
IGHJ3	0.9	0.057	IGHJ2	-0.5	0.064	IGHJ5	-0.5	0.171	IGHJ2	-0.4	0.996	IGHJ6	1.2	3.96e-04
IGHJ2	0.7	0.202	IGHJ6	-0.5	0.108	IGHJ2	-0.4	0.178	IGHJ1	-0.3	0.996	IGHJ4	1.0	0.001
IGHJ4	0.7	0.216	IGHJ1	-0.3	0.123	IGHJ1	-0.3	0.248	IGHJ4	-0.2	0.996	IGHJ1	0.5	0.020
IGHJ1	0.5	0.238	IGHJ5	-0.4	0.158	IGHJ6	-0.4	0.368	IGHJ5	-0.1	0.996	IGHJ3	0.7	0.036
IGHJ6	0.5	0.529	IGHJ3	-0.2	0.563	IGHJ3	-0.3	0.444	IGHJ3	0.1	0.996	IGHJ5	0.6	0.064

DM vs. NT			Mi2 vs. NT			NXP2 vs. NT			MDA5 vs. NT			TIF1γvs. NT		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGHJ1	-0.3	0.145	IGHJ1	-0.5	0.029	IGHJ3	-0.5	0.213	IGHJ2	0.6	0.167	IGHJ1	-0.4	0.175
IGHJ3	-0.4	0.196	IGHJ2	-0.5	0.034	IGHJ1	-0.4	0.233	IGHJ5	0.5	0.355	IGHJ3	-0.4	0.291
IGHJ2	-0.1	0.696	IGHJ3	-0.6	0.048	IGHJ2	-0.4	0.278	IGHJ4	0.4	0.516	IGHJ4	0.2	0.638
IGHJ6	-0.1	0.697	IGHJ4	-0.2	0.443	IGHJ5	-0.4	0.347	IGHJ6	-0.2	0.714	IGHJ5	-0.1	0.889
IGHJ4	0.0	0.887	IGHJ6	-0.2	0.528	IGHJ6	-0.2	0.645	IGHJ3	0.1	0.899	IGHJ2	0.0	0.942
IGHJ5	0.0	0.901	IGHJ5	-0.2	0.609	IGHJ4	0.0	0.956	IGHJ1	0.0	0.953	IGHJ6	0.0	0.974

JO1 vs. NT			IMNM vs. NT			HMGCR vs. NT			SRP vs. NT			IBM vs. NT		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGHJ5	1.0	0.001	IGHJ1	-0.3	0.163	IGHJ1	-0.3	0.224	IGHJ3	0.5	0.207	IGHJ2	1.2	5.96e-06
IGHJ2	0.8	0.002	IGHJ6	-0.1	0.802	IGHJ4	-0.2	0.620	IGHJ1	-0.2	0.345	IGHJ4	1.2	4.87e-05
IGHJ4	0.9	0.003	IGHJ4	-0.1	0.802	IGHJ5	-0.1	0.743	IGHJ6	-0.2	0.538	IGHJ6	1.3	4.24e-04
IGHJ3	1.0	0.017	IGHJ2	-0.1	0.822	IGHJ2	-0.1	0.846	IGHJ4	0.2	0.599	IGHJ3	0.8	0.005
IGHJ6	0.7	0.052	IGHJ3	0.0	0.906	IGHJ3	-0.1	0.869	IGHJ5	0.2	0.618	IGHJ5	0.8	0.008
IGHJ1	0.4	0.127	IGHJ5	0.0	0.907	IGHJ6	0.0	0.973	IGHJ2	0.1	0.848	IGHJ1	0.5	0.049

Supplementary Table 5. Expression of top 10 immunoglobulin kappa variable region genes across disease groups, shown as comparisons versus all other muscle biopsies (vs. ALL) and versus normal muscle biopsies (vs. NT). DM: dermatomyositis; IMNM: immune-mediated necrotizing myopathy; IBM: inclusion body myositis; NT: normal muscle biopsy.

DM vs. ALL			Mi2 vs. ALL			NXP2 vs. ALL			MDA5 vs. ALL			TIF1yvs. ALL		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGKV1D-17	-0.8	8.15e-04	IGKV2-28	-0.9	0.016	IGKV6D-21	-1.0	0.072	IGKV3D-20	1.1	0.708	IGKV1D-17	-0.9	0.058
IGKV6-21	-0.9	0.002	IGKV2D-24	-1.1	0.016	IGKV2D-40	-1.1	0.077	IGKV1-39	1.2	0.715	IGKV1D-16	-0.8	0.201
IGKV2-29	-0.7	0.004	IGKV1D-12	-0.8	0.018	IGKV3-7	-1.2	0.079	IGKV1D-12	-0.4	0.717	IGKV1D-43	-0.6	0.241
IGKV1-37	-0.6	0.013	IGKV6-21	-1.2	0.023	IGKV1-27	-1.5	0.080	IGKV1D-16	0.9	0.718	IGKV5-2	-0.6	0.259
IGKV5-2	-0.6	0.019	IGKV2-29	-1.0	0.025	IGKV1D-8	-0.9	0.135	IGKV2-30	1.0	0.719	IGKV2-28	-0.4	0.280
IGKV1D-12	-0.4	0.023	IGKV1-37	-1.0	0.027	IGKV2-24	-1.3	0.188	IGKV3-11	1.0	0.721	IGKV2-29	-0.5	0.304
IGKV1D-13	-0.8	0.025	IGKV1D-17	-0.8	0.072	IGKV1-9	-1.5	0.190	IGKV1-17	1.0	0.721	IGKV6-21	-0.6	0.310
IGKV3D-15	-0.6	0.032	IGKV3D-15	-0.8	0.150	IGKV1-37	-0.7	0.199	IGKV1-13	-0.5	0.722	IGKV3D-15	-0.6	0.420
IGKV2D-29	-0.8	0.033	IGKV2D-29	-1.0	0.155	IGKV2D-28	-1.7	0.210	IGKV2-40	-0.3	0.723	IGKV1D-39	-0.5	0.440
IGKV1-17	-1.0	0.038	IGKV1D-13	-1.0	0.167	IGKV1-17	-1.3	0.218	IGKV1D-43	0.6	0.723	IGKV1D-12	-0.3	0.503

JO1 vs. ALL			IMNM vs. ALL			HMGR vs. ALL			SRP vs. ALL			IBM vs. ALL		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGKV4-1	2.5	2.92e-05	IGKV1D-33	-2.0	6.18e-04	IGKV1-12	-2.1	1.71e-04	IGKV3D-11	-1.3	0.996	IGKV2D-28	4.3	1.38e-28
IGKV3-20	2.4	1.33e-04	IGKV3D-11	-1.9	6.32e-04	IGKV1D-33	-2.2	0.001	IGKV3-7	-0.7	0.996	IGKV3-11	3.6	1.10e-19
IGKV3D-11	2.2	7.40e-04	IGKV1-12	-1.8	6.36e-04	IGKV2D-28	-2.3	0.002	IGKV1D-17	0.6	0.996	IGKV3-20	3.5	4.24e-18
IGKV1-27	2.0	0.002	IGKV3-15	-2.1	6.71e-04	IGKV2-30	-1.6	0.002	IGKV1D-13	-0.7	0.996	IGKV1D-33	3.5	4.84e-18
IGKV3-15	2.1	0.004	IGKV2D-28	-2.1	7.87e-04	IGKV3-15	-2.2	0.002	IGKV1-27	-0.8	0.996	IGKV3-15	3.5	8.57e-17
IGKV1-5	1.9	0.004	IGKV3-11	-1.9	8.77e-04	IGKV1-5	-2.0	0.002	IGKV3-11	-1.1	0.996	IGKV1-9	3.4	1.27e-16
IGKV3-11	1.9	0.006	IGKV1-5	-1.8	0.001	IGKV3D-20	-1.5	0.003	IGKV2D-29	-0.7	0.996	IGKV1-39	3.6	2.54e-16
IGKV3D-20	1.8	0.008	IGKV1-27	-1.4	0.002	IGKV1-9	-1.8	0.003	IGKV1-8	-0.5	0.996	IGKV3D-11	3.4	1.06e-15
IGKV6D-21	1.4	0.010	IGKV3D-20	-1.4	0.002	IGKV3-20	-2.2	0.004	IGKV1-17	-0.9	0.996	IGKV1-5	3.1	2.03e-14
IGKV1D-33	1.8	0.017	IGKV3-20	-1.9	0.002	IGKV1-39	-2.1	0.005	IGKV2D-24	-0.4	0.996	IGKV1-6	2.9	2.29e-14

DM vs. NT			Mi2 vs. NT			NXP2 vs. NT			MDA5 vs. NT			TIF1yvs. NT		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGKV4-1	2.7	8.76e-05	IGKV1D-12	-0.9	5.75e-07	IGKV4-1	2.1	6.18e-04	IGKV1-39	3.8	4.57e-04	IGKV2D-28	3.3	6.89e-06
IGKV1-39	2.6	9.37e-05	IGKV2-28	-1.3	2.17e-06	IGKV1-5	1.9	0.003	IGKV3D-20	2.7	6.54e-04	IGKV1-39	2.9	3.40e-05
IGKV2D-28	2.5	1.75e-04	IGKV1D-33	2.6	9.26e-06	IGKV1D-33	1.8	0.009	IGKV4-1	3.2	0.002	IGKV3-15	2.9	1.11e-04
IGKV3-15	2.5	1.95e-04	IGKV3-15	2.6	1.43e-04	IGKV2-30	1.2	0.028	IGKV3-11	3.2	0.002	IGKV4-1	3.0	3.28e-04
IGKV3-20	2.6	2.54e-04	IGKV3-20	2.8	2.13e-04	IGKV3-15	1.6	0.034	IGKV1D-12	-0.6	0.002	IGKV3-20	3.0	3.49e-04
IGKV1D-33	2.2	2.85e-04	IGKV2D-28	2.6	5.69e-04	IGKV3-20	1.6	0.040	IGKV1D-33	3.1	0.002	IGKV1-5	2.4	6.73e-04
IGKV3D-11	1.9	3.93e-04	IGKV4-1	2.7	7.97e-04	IGKV1-39	1.5	0.059	IGKV3D-11	2.9	0.002	IGKV3D-20	1.7	0.001
IGKV3D-20	1.4	4.91e-04	IGKV1-39	2.6	0.001	IGKV3D-11	1.1	0.079	IGKV2-30	2.5	0.003	IGKV3D-11	2.1	0.001
IGKV1-5	2.2	5.69e-04	IGKV2D-24	-0.7	0.002	IGKV3-11	1.2	0.087	IGKV1-17	2.6	0.003	IGKV1-27	1.6	0.004
IGKV3-11	2.0	9.52e-04	IGKV3-11	2.2	0.002	IGKV6D-21	-0.7	0.087	IGKV3-15	2.9	0.006	IGKV2-30	1.6	0.006

JO1 vs. NT			IMNM vs. NT			HMGR vs. NT			SRP vs. NT			IBM vs. NT		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGKV2-24	3.1	8.26e-09	IGKV4-1	1.7	0.011	IGKV4-1	1.5	0.030	IGKV4-1	2.3	9.98e-04	IGKV2D-28	6.3	2.86e-15
IGKV3D-20	3.2	9.68e-09	IGKV1-39	1.4	0.028	IGKV1-17	0.9	0.047	IGKV3-20	2.4	0.001	IGKV1-27	3.9	3.74e-14
IGKV2-30	3.1	1.86e-08	IGKV3-20	1.5	0.046	IGKV1-39	1.1	0.102	IGKV1-39	2.4	0.002	IGKV3-11	5.3	1.05e-12
IGKV3-11	4.0	2.69e-08	IGKV1-17	0.9	0.047	IGKV3-20	1.2	0.126	IGKV2D-28	2.2	0.009	IGKV3D-20	3.9	2.67e-12
IGKV3D-11	4.1	5.59e-08	IGKV2D-28	1.3	0.050	IGKV2D-28	1.0	0.141	IGKV1-5	1.8	0.010	IGKV1-9	4.8	1.35e-11
IGKV1-27	3.3	2.39e-07	IGKV2-24	0.8	0.065	IGKV5-2	-0.4	0.174	IGKV1D-33	1.8	0.012	IGKV2-24	4.0	3.95e-11
IGKV1-9	3.3	2.55e-07	IGKV3D-20	0.7	0.069	IGKV3-11	0.8	0.174	IGKV3-15	1.9	0.012	IGKV2-30	3.8	4.53e-11
IGKV3-15	4.4	4.58e-07	IGKV3-15	1.1	0.087	IGKV3D-11	0.8	0.184	IGKV2-30	1.5	0.020	IGKV1-17	4.4	8.92e-11
IGKV4-1	5.0	6.64e-07	IGKV1D-33	0.9	0.091	IGKV2D-30	-0.4	0.186	IGKV2-24	1.4	0.021	IGKV1D-33	5.3	1.10e-10
IGKV3-20	4.9	8.59e-07	IGKV3-11	0.9	0.100	IGKV3-15	0.9	0.203	IGKV3D-20	1.1	0.023	IGKV1-16	3.4	2.56e-10

Supplementary Table 6. Expression of top 10 immunoglobulin lambda variable region genes across disease groups, shown as comparisons versus all other muscle biopsies (vs. ALL) and versus normal muscle biopsies (vs. NT). DM: dermatomyositis; IMNM: immune-mediated necrotizing myopathy; IBM: inclusion body myositis; NT: normal muscle biopsy.

DM vs. ALL			Mi2 vs. ALL			NXP2 vs. ALL			MDA5 vs. ALL			TIF1yvs. ALL		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGLV4-3	-0.6	2.13e-04	IGLV5-37	-0.9	0.012	IGLV3-9	-1.5	0.068	IGLV3-21	2.0	0.406	IGLV5-37	-0.8	0.056
IGLV5-37	-0.6	9.71e-04	IGLV3-32	-0.7	0.017	IGLV5-52	1.2	0.116	IGLV7-43	1.3	0.614	IGLV4-3	-0.6	0.075
IGLV3-32	-0.5	9.71e-04	IGLV4-3	-0.7	0.025	IGLV3-1	-1.3	0.254	IGLV2-11	1.5	0.632	IGLV10-54	-0.9	0.107
IGLV5-48	-0.6	0.001	IGLV2-33	-0.8	0.040	IGLV4-69	-1.0	0.279	IGLV1-51	1.6	0.667	IGLV3-22	-0.5	0.127
IGLV2-33	-0.6	0.003	IGLV3-22	-0.6	0.048	IGLV3-25	-1.2	0.295	IGLV3-16	0.9	0.670	IGLV5-48	-0.6	0.131
IGLV3-22	-0.4	0.005	IGLV7-43	-1.1	0.073	IGLV2-8	-1.3	0.336	IGLV6-57	1.1	0.692	IGLV5-52	-1.0	0.147
IGLV10-54	-0.7	0.015	IGLV5-48	-0.6	0.073	IGLV1-44	-1.2	0.356	IGLV1-47	1.1	0.701	IGLV3-32	-0.4	0.156
IGLV3-16	-0.4	0.050	IGLV3-16	-0.7	0.089	IGLV10-54	-0.6	0.377	IGLV3-27	0.8	0.705	IGLV8-61	-1.0	0.182
IGLV7-43	-0.6	0.072	IGLV3-12	-0.7	0.110	IGLV5-48	-0.4	0.384	IGLV3-10	1.1	0.706	IGLV3-16	-0.6	0.194
IGLV4-60	-0.5	0.081	IGLV4-60	-0.7	0.224	IGLV4-60	-0.6	0.390	IGLV1-44	1.1	0.708	IGLV7-43	-0.8	0.220

JO1 vs. ALL			IMNM vs. ALL			HMGR vs. ALL			SRP vs. ALL			IBM vs. ALL		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGLV3-25	2.3	6.68e-05	IGLV3-21	-2.2	6.82e-05	IGLV3-21	-2.3	1.82e-04	IGLV3-10	-1.2	0.811	IGLV2-23	3.7	1.68e-19
IGLV1-44	2.0	0.001	IGLV1-40	-2.2	9.20e-05	IGLV3-19	-2.1	2.80e-04	IGLV1-51	-1.3	0.993	IGLV2-8	3.4	2.74e-17
IGLV1-40	2.1	0.002	IGLV3-10	-1.5	9.75e-05	IGLV3-25	-1.9	3.33e-04	IGLV3-16	-0.5	0.996	IGLV1-40	3.4	7.54e-16
IGLV3-19	2.0	0.002	IGLV3-19	-1.9	1.33e-04	IGLV1-40	-2.4	3.89e-04	IGLV1-50	-0.4	0.996	IGLV1-51	3.6	4.03e-15
IGLV3-1	2.0	0.002	IGLV3-25	-1.6	7.48e-04	IGLV2-11	-2.1	8.41e-04	IGLV3-27	-0.5	0.996	IGLV1-44	2.9	1.30e-12
IGLV6-57	1.8	0.003	IGLV6-57	-1.5	0.001	IGLV2-23	-2.3	0.001	IGLV5-37	-0.3	0.996	IGLV2-14	2.9	1.54e-11
IGLV2-8	2.0	0.003	IGLV1-51	-1.8	0.001	IGLV6-57	-1.7	0.001	IGLV1-40	-1.0	0.996	IGLV3-1	2.8	1.84e-11
IGLV2-11	1.9	0.006	IGLV2-23	-1.9	0.002	IGLV1-44	-2.1	0.001	IGLV9-49	-0.4	0.996	IGLV3-19	2.8	3.55e-11
IGLV2-23	1.9	0.007	IGLV2-11	-1.7	0.002	IGLV2-8	-2.0	0.003	IGLV8-61	-0.6	0.996	IGLV3-9	2.6	3.42e-10
IGLV4-60	1.4	0.009	IGLV2-8	-1.8	0.002	IGLV3-9	-1.4	0.003	IGLV3-19	-0.8	0.996	IGLV6-57	2.4	4.10e-10

DM vs. NT			Mi2 vs. NT			NXP2 vs. NT			MDA5 vs. NT			TIF1yvs. NT		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGLV6-57	2.4	1.45e-07	IGLV1-40	3.4	3.46e-07	IGLV6-57	1.8	1.11e-04	IGLV6-57	3.3	1.01e-04	IGLV6-57	2.7	1.60e-06
IGLV1-40	2.9	6.71e-07	IGLV3-32	-0.9	5.75e-07	IGLV2-23	2.4	4.58e-04	IGLV3-21	4.0	5.12e-04	IGLV1-40	3.0	3.34e-06
IGLV2-23	2.8	1.96e-05	IGLV5-37	-1.1	4.85e-06	IGLV3-21	2.0	0.003	IGLV2-11	3.5	5.67e-04	IGLV1-44	2.8	3.35e-05
IGLV1-44	2.6	2.15e-05	IGLV4-3	-0.8	8.83e-06	IGLV1-40	2.0	0.004	IGLV1-51	3.4	9.35e-04	IGLV3-25	2.2	6.12e-05
IGLV3-21	2.5	9.46e-05	IGLV3-22	-0.8	1.44e-05	IGLV2-14	2.2	0.009	IGLV1-40	3.6	0.001	IGLV2-23	2.9	1.71e-04
IGLV3-25	1.8	2.09e-04	IGLV2-23	3.0	6.75e-05	IGLV2-11	1.8	0.009	IGLV1-44	3.6	0.002	IGLV5-37	-0.9	2.88e-04
IGLV2-11	2.0	8.14e-04	IGLV1-44	2.6	1.83e-04	IGLV1-44	1.5	0.020	IGLV1-47	2.8	0.002	IGLV4-69	1.9	3.24e-04
IGLV3-32	-0.6	8.14e-04	IGLV2-8	2.6	4.53e-04	IGLV3-19	1.5	0.033	IGLV2-8	2.9	0.003	IGLV3-1	2.3	3.27e-04
IGLV4-3	-0.6	8.66e-04	IGLV6-57	2.0	4.81e-04	IGLV1-47	1.1	0.064	IGLV3-10	2.2	0.007	IGLV3-21	2.6	3.28e-04
IGLV3-1	1.9	9.59e-04	IGLV3-25	2.0	6.43e-04	IGLV5-48	-0.6	0.081	IGLV3-1	2.7	0.007	IGLV4-3	-0.7	3.28e-04

JO1 vs. NT			IMNM vs. NT			HMGR vs. NT			SRP vs. NT			IBM vs. NT		
Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val	Gene	LogFC	q-val
IGLV3-25	3.9	4.73e-11	IGLV6-57	1.2	0.002	IGLV6-57	1.0	0.019	IGLV1-44	2.7	3.09e-05	IGLV6-57	4.4	4.38e-18
IGLV6-57	3.9	2.48e-10	IGLV2-23	1.5	0.008	IGLV5-52	-1.3	0.028	IGLV2-23	2.7	5.64e-05	IGLV1-51	5.1	1.89e-13
IGLV1-40	4.6	1.21e-08	IGLV5-52	-1.4	0.012	IGLV5-48	-0.5	0.040	IGLV2-14	2.4	7.48e-04	IGLV3-1	4.5	2.47e-13
IGLV2-23	4.6	1.61e-08	IGLV1-44	1.4	0.014	IGLV2-23	1.1	0.066	IGLV6-57	1.8	8.63e-04	IGLV3-10	3.3	4.45e-13
IGLV3-1	3.8	5.05e-08	IGLV5-48	-0.5	0.024	IGLV1-44	1.0	0.107	IGLV3-1	2.0	0.001	IGLV2-23	6.0	8.21e-13
IGLV1-44	4.3	5.55e-08	IGLV1-40	1.1	0.031	IGLV1-40	0.9	0.112	IGLV2-11	2.0	0.002	IGLV2-8	5.2	2.32e-12
IGLV2-14	4.0	4.61e-07	IGLV2-14	1.2	0.055	IGLV3-32	-0.4	0.112	IGLV1-40	1.8	0.008	IGLV1-44	5.1	2.54e-11
IGLV2-8	4.1	4.62e-07	IGLV5-37	-0.5	0.056	IGLV3-22	-0.4	0.112	IGLV2-8	1.9	0.008	IGLV1-40	5.6	3.14e-11
IGLV1-51	3.6	8.26e-07	IGLV1-47	0.9	0.057	IGLV1-47	0.8	0.121	IGLV3-25	1.6	0.016	IGLV2-18	2.8	5.25e-11
IGLV2-11	3.8	1.16e-06	IGLV3-32	-0.4	0.059	IGLV5-37	-0.4	0.134	IGLV3-21	1.4	0.039	IGLV3-25	4.1	6.21e-11

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