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INVITED REVIEW

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The Notch signaling pathway in skeletal muscle health and disease

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Abstract

The Notch signaling pathway is a key regulator of skeletal muscle development and regeneration. Over the past decade, the discoveries of three new muscle disease genes have added a new dimension to the relationship between the Notch signaling pathway and skeletal muscle: *MEGF10*, *POGLUT1*, and *JAG2*. We review the clinical syndromes associated with pathogenic variants in each of these genes, known molecular and cellular functions of their protein products with a particular focus on the Notch signaling pathway, and potential novel therapeutic targets that may emerge from further investigations of these diseases. The phenotypes associated with two of these genes, *POGLUT1* and *JAG2*, clearly fall within the realm of muscular dystrophy, whereas the third, *MEGF10*, is associated with a congenital myopathy/muscular dystrophy overlap syndrome classically known as early-onset myopathy, areflexia, respiratory distress, and dysphagia. JAG2 is a canonical Notch ligand, POGLUT1 glycosylates the extracellular domain of Notch receptors, and MEGF10 interacts with the intracellular domain of NOTCH1. Additional genes and their encoded proteins relevant to muscle function and disease with links to the Notch signaling pathway include *TRIM32*, *ATP2A1* (SERCA1), *JAG1*, *PAX7*, and *NOTCH2NLC*. There is enormous potential to identify convergent mechanisms of skeletal muscle disease and new therapeutic targets through further investigations of the Notch signaling pathway in the context of skeletal muscle development, maintenance, and disease.

Abbreviations: ABCA1, adenosine triphosphate–binding cassette transporter 1; ADAM10, A disintegrin and metalloproteinase domain–containing protein 10; ADAMTS1, A disintegrin-like and metalloproteinase with thrombospondin type 1 motif; BMD, Becker muscular dystrophy; C1q, complement component 1q; CK, creatine kinase; CMD, congenital muscular dystrophy; CSL, CBF-1/RBPJ-κ, Suppressor of Hairless, Lag-1; DLL1, delta-like canonical Notch ligand 1; DLL4, delta-like canonical Notch ligand 4; DMD, Duchenne muscular dystrophy; DOS, Delta and OS M-11-like protein; DRPR, Draper; DSL, Delta-Serrate-LAG2; EC, endothelial cell; EGF, epidermal growth factor–like domain; EMARDD, early-onset myopathy, areflexia, respiratory distress, and dysphagia; EMG, electromyography; EMI, elastin microfibril interfacer 1; FDA, US Food and Drug Administration; HEK293, human embryonic kidney; hnRNPL, heterogeneous nuclear ribonucleoprotein L; ICD, intracellular domain; IL-4, interleukin-4; ITAM, immunoreceptor tyrosine-based activator motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; JAG1, Jagged1; JAG2, Jagged2; LGMD, limb-girdle muscular dystrophy; MAML1, mastermind-like 1; MEGF10, multiple epidermal growth factor–like domains protein 10; MEGF11, multiple epidermal growth factor–like domains protein 11; MEGF12, multiple epidermal growth factor–like domains protein 12; MuSC, muscle stem cell; NCS, nerve conduction studies; NECD, Notch extracellular domain; NFATc2, nuclear factor of activated T cells c2; N1ICD, Notch1 intracellular domain; NICD, Notch intracellular domain; NIID, neuronal intranuclear inclusion disease; NPxY, Asn-Pro-x-Tyr; OMIM, online Mendelian Inheritance in Man; OPDM, oculopharyngodistal myopathy; PAX7, paired box 7; POFUT1, protein-*O*-fucosyltransferase 1; POGLUT1, protein-*O*-glucosyltransferase 1; RNAi, RNA interference; SERCA, sarco/endoplasmic reticulum Ca ATPase; SMARD1, spinal muscular atrophy with respiratory distress 1; TM, transmembrane domain; TRIM32, tripartite motif containing 32.

The objectives of this activity are to: 1) Recognize the phenotypes of muscle disease produced by pathogenic variants in 3 different muscle disease genes involved in the Notch signaling pathway; 2) Be able to order appropriate genetic testing in these patients.

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KEYWORDS
JAG2, MEGF10, muscular dystrophy, Notch signaling pathway, POGLUT1

1 | INTRODUCTION

Since the landmark discovery in 1986 of *DMD* (dystrophin),[1] the causative gene for Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD), dozens of additional genes have been associated with various phenotypic subtypes of muscular dystrophy. Common disease mechanisms across multiple subtypes have, however, been more difficult to identify, with only a few major clusters such as the dystroglycanopathies identified to date. Given the common phenotypic features within muscular dystrophy categories, such as limb-girdle muscular dystrophy (LGMD), there is a high likelihood that convergent disease mechanisms exist across more muscular dystrophy subtypes than is currently recognized.

There are therapeutic implications of identifying deeper biological ties between muscular dystrophy subtypes. In recent years, the US Food and Drug Administration (FDA) has approved several molecular and genetic therapies for neuromuscular disorders that target specific genes and even specific mutation types within those genes. These approaches are being applied to ever rarer forms of muscular dystrophies. However, proceeding through the preclinical and clinical research studies needed to attain FDA approval for a new therapy is lengthy and costly, and on the current trajectory it will be decades before molecular and genetic therapies are available for all known subtypes of muscular dystrophy.

The identification and characterization of disease mechanisms that are shared by multiple muscular dystrophy subtypes could pave the way for new pathway-based treatments that have therapeutic effects for multiple disease subtypes.[2] This has the potential to accelerate the timeline for broader therapeutic coverage of patients with muscular dystrophy, with a greater impact on the entire muscular dystrophy population.

One disease mechanism that bears further analysis is the Notch signaling pathway, which is known to maintain muscle stem cell (MuSC, also known as satellite cell) quiescence. Recently, three different muscle disease genes that are known to interact with the Notch signaling pathway have been identified: *MEGF10*, *POGLUT1*, and most recently *JAG2*. In this review we examine the clinical, genetic, biochemical, and cellular knowledge of these genes and their protein products, as well as their interactions with each other and with the Notch signaling pathway.

1.1 | The Notch signaling pathway in muscle development

The Notch signaling pathway has been a high-profile subject of investigation since its discovery in the early 20th century, with intensified interest after the *Drosophila* Notch gene was first reported in 1983.[3] This pathway is well-conserved across species and is regulated by a set of ligands and receptors that promote cell-to-cell communications. Among other activities, it plays a key role in determining specification and differentiation of cell fates during various aspects of invertebrate and vertebrate development and regeneration, including myogenesis.[4–7]

In mammals, Notch1, Notch2, Notch3, and Notch4 are the core receptors in the Notch signaling pathway (Table 1). Each of these receptors consists of a Notch extracellular domain (NECD), a transmembrane domain (TM), and a Notch intracellular domain (NICD).[27] Both *trans* (intercellular) and *cis* (intracellular) interactions of ligands with the Notch receptors have been discovered[28–30] (Figure 1). In mammals, the canonical Notch ligands include Delta-like1, Delta-like3, Delta-like4, Jagged1, and Jagged2[31] (Table 1). These proteins are encoded by the genes *DLL1*, *DLL3*, *DLL4*, *JAG1*, and *JAG2*, respectively. In *Drosophila* there are two canonical Notch ligands: Delta and Serrate (orthologous to the mammalian Delta-like and Jagged proteins, respectively).[32] The typical *trans* interaction begins with binding of the extracellular domain of the ligand from the signaling cell to the NECD of the signal receiving cell, initiating two cleavage events in the Notch receptor of the receiving cell (Figure 1A). In the first cleavage event, members of the ADAM family of metalloproteinases separate the ligand-bound NECD from the TM-NICD.[27] The NECD undergoes endocytosis by the signaling cell, whereas the TM domain and NICD are separated from each other by γ-secretase in the second cleavage event.[33] The NICD then enters the nucleus and binds to the DNA transcription factor CBF-1/RBPJ-κ, Suppressor of Hairless, Lag-1 (also known as CSL), converting it from a transcription-repressing state to an activating state by displacing co-repressors and recruiting Mastermind-like protein (MAML1) and other coactivators, initiating the transcription of downstream Notch signaling pathway genes.[34,35] Notch ligands also have an inhibitory effect on Notch within the same cells (*cis*-inhibition) of *Drosophila*.[36–38] The extracellular Delta-Serrate-LAG2 (DSL) domain of human Jagged1 contributes to both trans-activation and cis-inhibition.[39] Most of the canonical Notch signaling pathway components have known functions in skeletal muscle development or function, yet aside from *JAG2*, the other canonical Notch signaling pathway genes are associated with diseases that do not primarily manifest in skeletal muscle (Table 1).

The Notch1 intracellular domain (N1ICD) is an active regulator of cell fate choice for MuSCs, promoting their self-renewal via Pax7 upregulation while inhibiting MuSC proliferation.[40] The N1ICD also has the capability of dedifferentiating myocytes into Pax7+ quiescent MuSCs, suggesting that the Notch signaling pathway has potential as a therapeutic target for muscle diseases.[41] The mechanisms of Notch signaling pathway regulation of MuSCs remains incompletely understood, but one key component is A disintegrin-like and metalloproteinase with thrombospondin type 1 motif (ADAMTS1), which is secreted by macrophages, targets NOTCH1, stimulates MuSC activation, and promotes muscle regeneration.[42] Notch signaling and p53 activity diminish with aging, and stabilizing this Notch-p53 axis improves the regenerative capacity of aged MuSCs.[43]

TABLE 1 Expression and function of canonical Notch signaling pathway components in skeletal muscle

Notch component	RNA expression	Protein expression	Muscle function	Disease association
NOTCH1	5.0 nTPM	Medium	Regulates MuSC fates[8]	Adams-Oliver syndrome 5,[9] aortic valve disease 1[10]
NOTCH2	6.5 nTPM	Not detected	MuSC self-renewal[11]	Alagille syndrome 2,[12] Hajdu-Cheney syndrome[13]
NOTCH3	30.0 nTPM	Low	Inhibits Notch1 in MuSCs[14]	CADASIL[15]
NOTCH4	5.7 nTPM	No data	Unknown	None known
DLL1	5.4 nTPM	No data	Inhibits myoblast differentiation[16]	Neurodevelopmental disorder[17]
DLL3	No data	No data	Unknown	Spondylocostal dysostosis[18]
DLL4	10.1 nTPM	Low	Regulates skeletal muscle mass[19]	Adams-Oliver syndrome 6[20]
JAG1	9.8 nTPM	Medium	Rescues DMD in dogs[21]	Alagille syndrome 1,[22] Charcot-Marie-Tooth disease 2HH,[23] tetralogy of Fallot[24]
JAG2	9.7 nTPM	Medium	Canonical Notch ligand	JAG2-related muscular dystrophy[25]

Note: RNA and protein expression data from the Human Protein Atlas.[26] Protein expression levels were measured in myocytes.
Abbreviations: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; DLL, delta-like canonical Notch ligand; DMD, Duchenne muscular dystrophy; MuSC, muscle stem cell; nTPM, normalized transcripts per million.

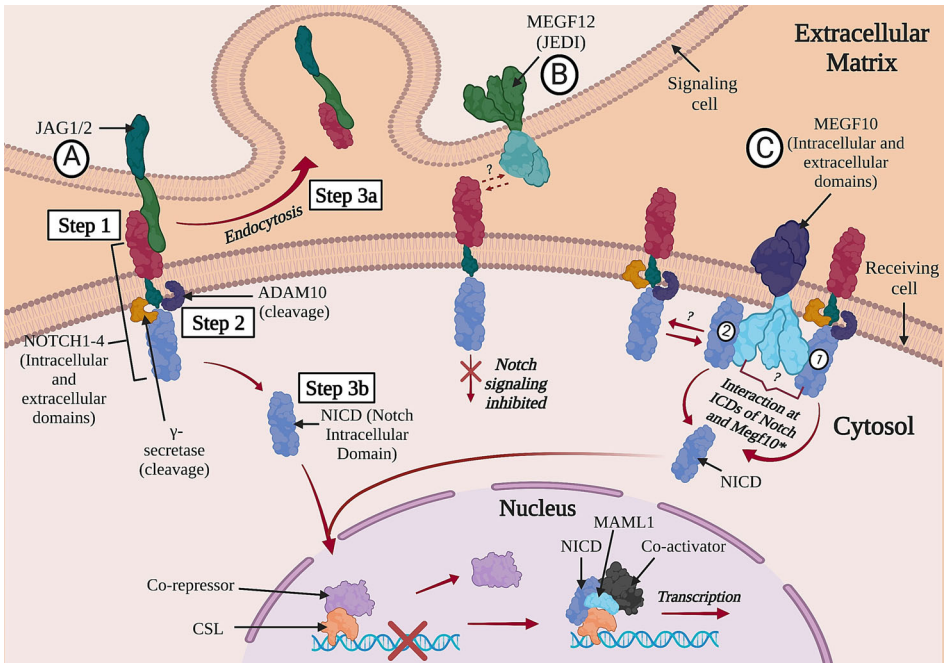

FIGURE 1 Diagram of the Notch signaling pathway showing putative interactions between Notch receptors and several key molecules of interest: JAG1/JAG2 (A); MEGF12, also known as JEDI (B); and MEGF10 (C). Several key steps in the interaction between a Notch receptor and a ligand are numbered in the diagram.
Abbreviations: ADAM10, A Disintegrin and metalloproteinase domain–containing protein 10; CSL, CBF-1/RBPJ-κ, Suppressor of Hairless, LAG-1; JAG1/2, Jagged1/2; MAML1, mastermind-like1; MEGF10/12, multiple epidermal growth factor–like domains protein 10/12; NECD, notch extracellular domain; NICD, Notch intracellular domain; TM, transmembrane domain.

The Notch signaling pathway regulates other components of developing and mature skeletal muscle. For example, delta-like canonical Notch ligand 1 (DLL1) activation restrains fibroadipogenic progenitor (FAP) differentiation, yet dystrophin-deficient FAPs are unresponsive to this regulatory mechanism.[44] There is emerging evidence that Delta-like canonical Notch ligand 4 (DLL4) derived from muscle endothelial cells (ECs) induces quiescence in MuSCs.[45] With regard to potential immune system interactions, protein *O*-fucosyltransferase 1 (POFUT1) modulates myogenesis via Notch signaling[46] and myoblast fusion via nuclear factor of activated T cells c2/interleukin-4 (NFATc2/IL-4) signaling.[47] POFUT1 deficiency in skeletal myofibers is also associated with reduced Notch signaling and degeneration of motor nerve innervation at the neuromuscular junction.[48]

A growing list of noncanonical or less-characterized Notch ligands that fine-tune Notch signaling is becoming recognized. Among these is MEGF12 (also known as JEDI or PEAR1), a transmembrane protein that has an inhibitory role in the Notch signaling pathway.[49] Although the specific mechanism of this interaction is yet to be understood, it is hypothesized that MEGF12 competes with other Notch ligands, such as Jagged1/2, to exert its inhibitory effect by repressing Notch activation[49] (Figure 1B). Notably, MEGF12 is a paralog of the muscle disease gene MEGF10 (Figure 1C), which is discussed in greater depth in the following sections.

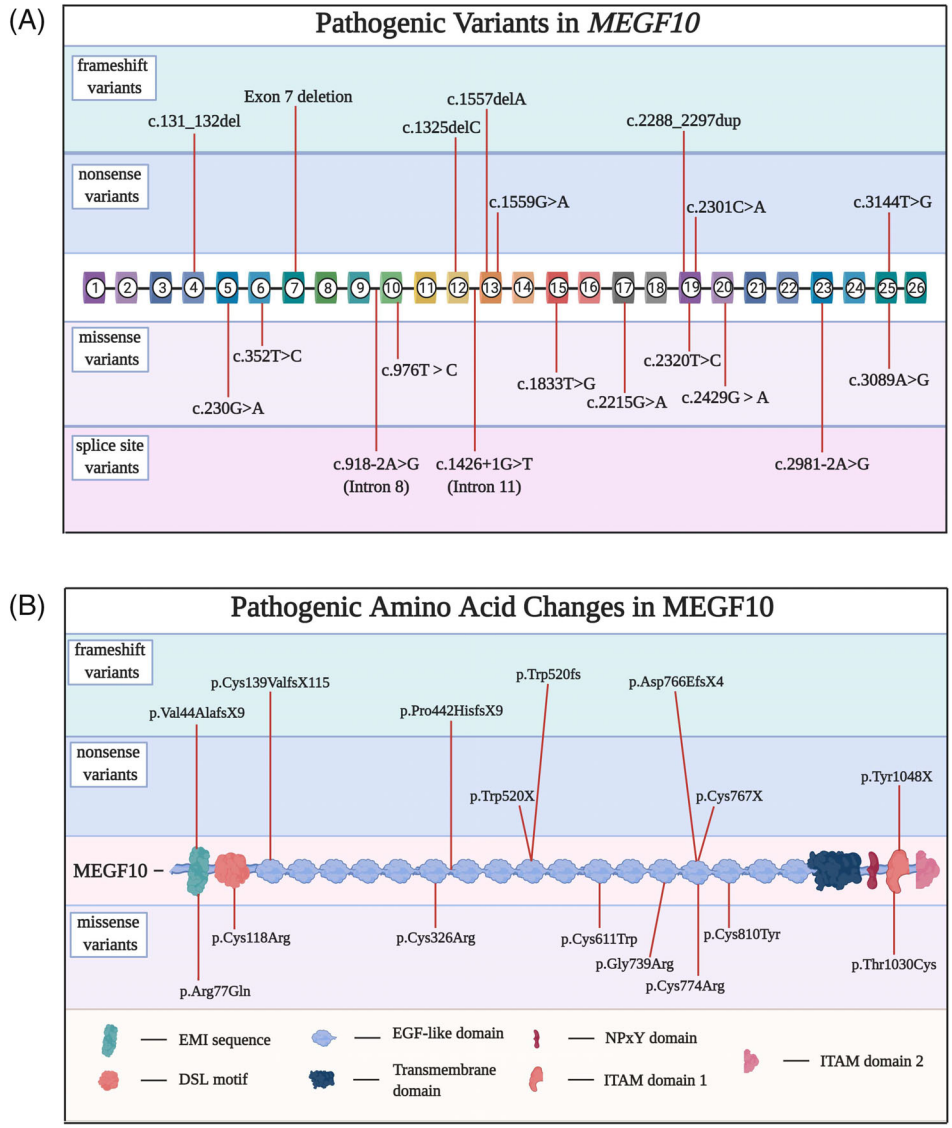

FIGURE 2 A, Diagram of pathogenic variants in *MEGF10* mutations categorized by variant type: nonsense, frameshift, missense, and splice site. Variants' positions were determined using the reference human *MEGF10* transcript variant 1 (NM_032446.3). B, Diagram of amino acids in the human MEGF10 protein affected by pathogenic variants.

1.2 | MEGF10 myopathy

Individuals with clinical features similar to spinal muscular atrophy with respiratory distress type 1 (SMARD1) but with muscle histological features indicating a primary myopathy, were described in 2007.[50] The affected individuals in the initial case series had infantile-onset weakness with early respiratory failure, normal echocardiograms, normal to mildly elevated serum creatine kinase (CK) levels, normal velocities on nerve conduction studies (NCS), and myopathic findings on electromyography (EMG).[50] Some affected individuals achieve independent ambulation, typically with some limitations. The disease was named early-onset myopathy, areflexia, respiratory distress, and dysphagia (EMARDD, OMIM 614399). Several years later, biallelic pathogenic variants in the gene *MEGF10* were discovered in a set of individuals affected by EMARDD,[51] followed by additional reports substantiating the initial findings and expanding the phenotype to include some features of muscular dystrophy, cleft palate in some affected individuals, and in some individuals a milder clinical course.[52–58] Histological features on muscle biopsies range from mild fiber size variability to dystrophic findings to minicores.[50,52] These diseases are now collectively referred to as MEGF10 myopathy to reflect the phenotypic diversity. A range of pathogenic variants has been described for *MEGF10* (Figure 2A,B),[51–59] with a high degree of conservation of affected amino acid residues (Figure S1). MEGF10 myopathy could be classified as an ultrarare disease; aside from the first article linking the disease to pathogenic variants in MEGF10, most subsequent reports in the literature describe one or two kindreds.

1.3 | MEGF10 and its orthologs and paralogs

The human gene *MEGF10* is located on chromosome 5q23.2[60]; the longest known transcript contains 25 exons with a repetitive element at the 3′ end. The gene is highly expressed in the fetal and adult brain, adult spinal cord, and regenerating skeletal muscle.[61,62] The protein product MEGF10 is a single transmembrane 1147 amino acid protein

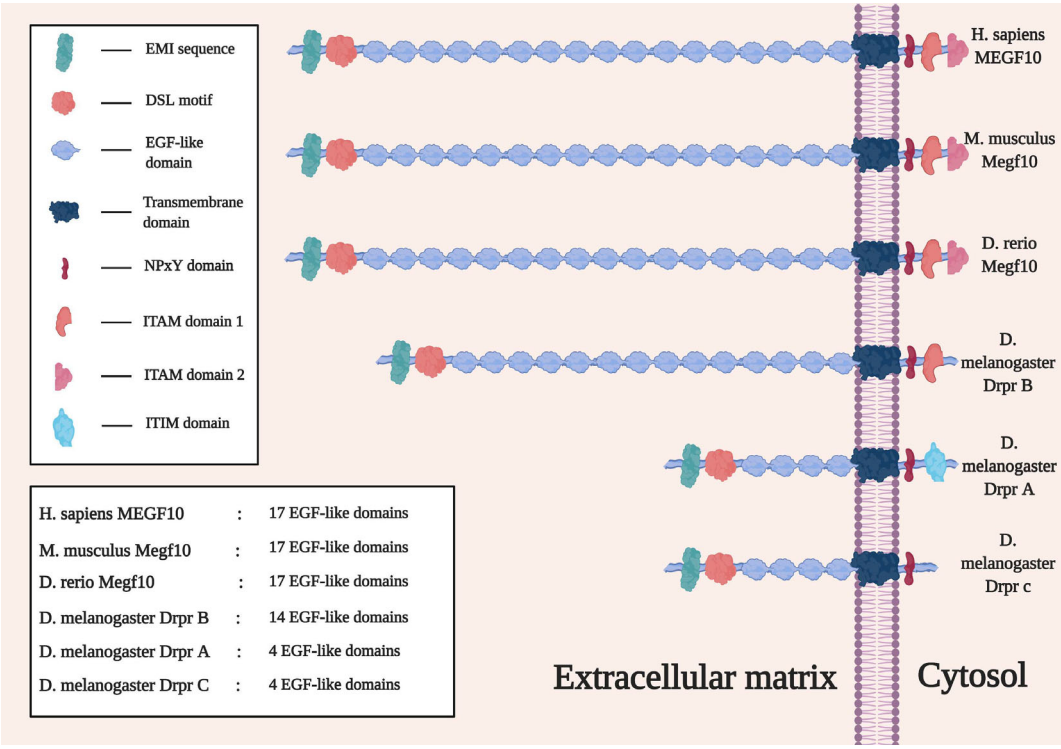

FIGURE 3 Isoforms of the Megf10 protein in human, mouse, zebrafish, and fruit fly. Each isoform has an EMI domain, a Delta and OS M-11-like (DSL) motif, epidermal growth factor–like domains, a transmembrane domain, and an Asn-Pro-x-Tyr (NPxY) domain. Immunoreceptor tyrosine-based activator motif (ITAM) domain 2 is only conserved in human, mouse, and zebrafish. ITAM domain 1 is very well conserved across species. Drpr A has an immunoreceptor tyrosine-based inhibitory motif (ITIM) domain, which is not present in the other isoforms or species.

with an N-terminal extracellular signal sequence, an elastin microfibril interfacer 1 (EMI) domain, a DSL motif, 17 epidermal growth factor–like domain (EGF)-like domains, a transmembrane domain, and a C-terminal intracellular domain (ICD) with 13 tyrosine residues.[60,61,63] Homologous genes are descended from a common ancestral gene; orthologs are homologous genes found in different organisms, and paralogs are homologous genes that are found in the same genomes of the same organisms. The mouse and zebrafish orthologs also have an EMI domain, a DSL motif, 17 EGF-like domains and a transmembrane domain. Several isoforms of the orthologous *Drosophila* protein Drpr have been identified, and three of them, named Drpr A, B, and C, are well-characterized (these were previously known as Drpr II, I, and III, respectively).[64,65] Each has an EMI domain, a DSL motif, and a transmembrane domain as well. However, the Drpr proteins differ from their human, mouse, and zebrafish counterparts regarding the number of EGF-like domains; Drpr B has 14 of these domains, whereas Drpr A and C each has 4. Drpr A has an immunoreceptor tyrosine-based inhibitory motif (ITIM) domain that is not seen in the other isoforms (Figure 3). There is generally good conservation of key domains among these orthologs and isoforms (Figure 3 and Table S1).

There are two mammalian paralogs of *MEGF10*: *MEGF11* and *MEGF12*.[49,60] Despite expression of *MEGF10* in the brain and retina, patients with EMARDD do not have structural or functional brain abnormalities, or visual defects.[51,52] However, deficiencies in *Drpr*, the *Drosophila* homolog of *MEGF10*, *MEGF11*, and *MEGF12*, lead to muscle and brain defects in fruit flies.[66] These observations suggest that functional redundancy by MEGF11 and/or MEGF12 may compensate for MEGF10 deficiency in mammalian brains. *MEGF12*, which encodes a transmembrane protein, contains 14 EGF-like repeats and a DSL domain. MEGF10 and MEGF11 are known to have a small but significant protein structure homology with MEGF12 at their extracellular domains.[60]

1.4 | Animal models of MEGF10 deficiency (*Mus musculus*, *Danio rerio*, and *Drosophila melangogaster*)

Expression of Megf10 at neuromuscular junctions in *Mus musculus* suggested a role of Megf10 in neuromuscular transmission, a process that allows for communication between the central nervous system and skeletal muscle.[51] Repetitive nerve stimulation studies in the first reported cases of EMARDD were normal and trials of cholinesterase inhibitors were not therapeutic, suggesting that there is not a dramatic physiological defect in the neuromuscular junction in the setting of human MEGF10 myopathy.[50]

A Cre-mediated Megf10 knockout (*Megf10*$^{-/-}$) mouse model was originally created for the study of retinal neurons.[67] Our laboratory reported a neuromuscular phenotype in skeletal muscle tissue and MuSCs from these *Megf10*$^{-/-}$ mice.[68] *Megf10*$^{-/-}$ mice showed reduced motor activity, and their skeletal muscles displayed mild

endomysial fibrosis and intracellular infiltration upon intraperitoneal injections of Evans blue dye.[68] Intramuscular barium chloride injections led to impaired muscle regeneration in *Megf10*$^{-/-}$ mice compared with wild-type mice, providing more evidence of Megf10 involvement in myofiber regeneration.[68,69]

Morpholino knockdown of *megf10* in *Danio rerio* (zebrafish) resulted in muscle phenotype abnormalities similar to those reported in humans with mutations in *MEGF10*.[52] Zebrafish with *megf10* knockdown had curved tails, difficulty swimming, and disorganized muscle morphology. Subsequently, a zebrafish line with a germline nonsense mutation demonstrated muscle defects and delayed somite formations.[54] Zebrafish models are thus useful for elucidating disease mechanisms for MEGF10 myopathy.

Drosophila melanogaster, commonly known as the fruit fly, is a useful system for modeling multiple human diseases, including neurological and neuromuscular diseases. *Drosophila* can recapitulate structural and functional features of human neuromuscular diseases. Key cellular and molecular processes are shared between *Drosophila* and humans, including the neuromuscular unit.[70,71] Two *Drosophila* genetic models of Drpr (ortholog of MEGF10) deficiency in skeletal muscle have been studied. One is an amorphic allele containing a deletion in the promoter and first exon of the *drpr* gene, and the other is a knockdown of *drpr* mediated by RNA interference (RNAi) in muscle.[66,72] In both genetically modified *Drosophila* models, the fruit flies showed abnormal position of legs, decreased locomotor activity, and pathological alterations in the thoracic striated muscle. In contrast, overexpression of Drpr in fly muscle resulted in pre-adult lethality (toxic) when targeted at specific stages of myogenesis.[65] Escaper flies that survived presented evident muscle abnormalities. The gain-of-function of Drpr in Serrate-positive wing cells caused extra branching at the wing margin, which phenocopies wing vein defects observed with Notch loss of function.[73] Further investigations of the spatiotemporal expression of MEGF10 and its orthologs will be crucial to understanding its function and provide insight into potential therapies.

1.5 | Megf10 in the central nervous system

In the eye, MEGF10 contributes to the formation of retinal mosaics.[67] Elsewhere in the central nervous system, MEGF10 binds to dead neurons, contributing to the engulfment activities of glial cells[74] and phagocytic activities of neurons,[75] indicating a key role in neuronal apoptosis. Parallel functions have been identified for the *Drosophila* ortholog Drpr.[76–78] The ATP binding cassette transporter ABCA1 contributes to the engulfment activity of MEGF10.[79] MEGF10 is a receptor for C1Q, a signaling molecule that marks apoptotic cells.[80] This binding interaction is impaired when pathogenic variants in *MEGF10* are expressed on human embryonic kidney-293 (HEK-293) cells.[80] A discovery with neurodevelopmental implications focuses on contributions of MEGF10 to the engulfment and phagocytosis of neuronal synapses, suggesting a role for MEGF10 in the synaptic pruning process.[81] At the other end of the lifespan, MEGF10 has been found to mediate uptake of amyloid-β into neuroblastoma cells, suggesting that a deficiency of MEGF10 may contribute to the accumulation of senile plaques containing amyloid-β in Alzheimer disease.[82]

1.6 | MEGF10 in skeletal muscle development and regeneration

During muscle development, Notch signaling regulates myoblast proliferation, migration, and differentiation[4–6] and cell adhesion activities.[7] Activation of the Notch signaling pathway helps maintain MuSCs in the quiescent state,[83,84] and contributes to their self-renewal[40] and to their homing to target myofibers.[85] In particular, it is likely that MEGF10 contributes to the regulation of some of these processes in myoblasts and MuSCs.

Megf10 expression is higher during myoblast proliferation than differentiation[68,86] and Megf10 deficiency impairs myoblast proliferation.[68] In *Drosophila*, muscle and motor phenotypes were observed with knockdown of *drpr* (the fly homolog of *Megf10*) in adult muscle precursors.[66] Overexpression of Drpr, however, was deleterious at the differentiation and specification stages.[65] *Drosophila* thus provides an additional tool to further probe the role of Megf10 in regulating myoblast proliferation and myoblast differentiation.

Murine MuSCs that express Pax7 also express Megf10,[62] and expression of both Megf10 and myogenin spikes after cardiotoxin-induced skeletal muscle injury in mice.[87] Myogenin is a transcription factor that binds sequences upstream of the *Megf10* gene and activates its expression,[87] suggesting that it helps trigger a Megf10-mediated response of MuSCs to muscle injury. In the setting of muscle injury induced by intramuscular barium chloride injections, Megf10 deficiency is associated with reduced regenerative potential.[69]

In addition, MEGF10 promotes the adhesion of HEK-293 cell membranes to substrates,[63] and Megf10 deficiency reduces murine myoblast adhesion capabilities.[68] It is not clear how adhesion may contribute to muscle development or repair, but myoblast[68] and MuSC[69] migration are both impaired in the setting of Megf10 deficiency, suggesting that movement and positioning of these muscle cells during these processes rely in part on Megf10 function.

1.7 | Interactions of MEGF10/Megf10/Drpr with the Notch signaling pathway

Reports from several groups,[49,62,85] including ours,[68] demonstrate that MEGF10 and Drpr interact with the highly conserved Notch signaling pathway. The canonical DSL and Delta and OS M-11-like protein (DOS) domains, which are established Notch ligand motifs, are both found in the extracellular N termini of MEGF10, MEGF11, MEGF12, and Drpr, suggesting that these proteins may act as Notch ligands.[49] Our work has shown that MEGF10 and Notch interact at their intracellular domains, that pathogenic mutations impair these interactions, and that part of the MEGF10 interacting domain lies in the stretch from M1003 to E1140[68] (Figure 1C). Thus, MEGF10 does not appear to be a canonical Notch ligand. MEGF10 and MEGF12 are tyrosine phosphorylated and regulate phagocytosis of apoptotic neurons via the Src family kinase-Syk pathway.[88,89] Our studies suggest that tyrosine phosphorylation of Megf10 regulates the binding of Megf10 with Notch1.[68] Further investigations are needed to elucidate the nature of the Megf10-Notch interaction in greater depth.

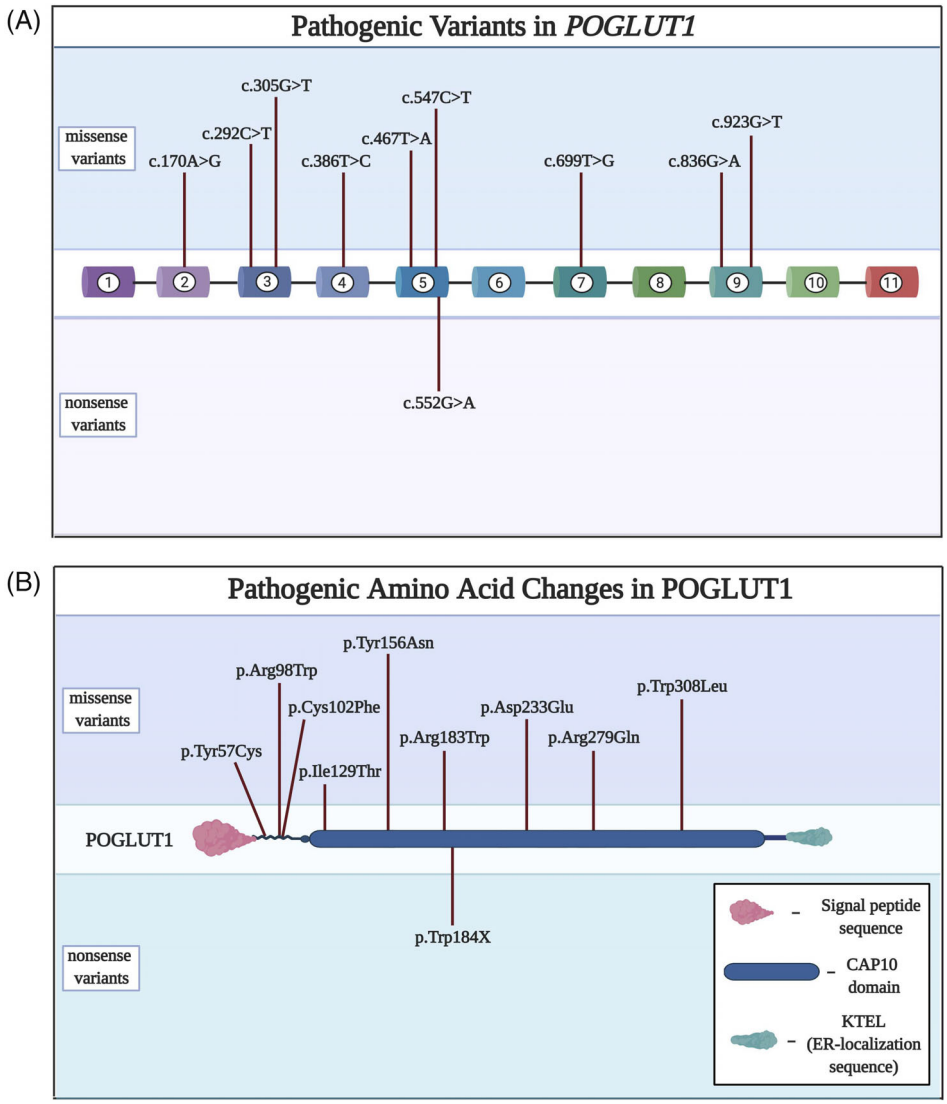

FIGURE 4 A, Pathogenic variants in POGLUT1 are predominantly missense changes distributed widely throughout the gene. B, Amino acid changes corresponding to the nucleotide changes in A. The predominance of missense variants indicates that the protein is sensitive to an array of conformational changes.

1.8 | POGLUT1-related muscular dystrophy

The first human disease associated with pathogenic variants in *POGLUT1* was Dowling-Degos disease, an autosomal dominant dermatologic condition characterized by progressive reticulate hyperpigmentation.[90] Subsequently, biallelic pathogenic variants in *POGLUT1* were associated with muscular dystrophy.[91–94] The first reported family was a large consanguineous kindred with multiple individuals affected by a progressive limb-girdle muscular dystrophy (LGMD) phenotype that included scapular winging and loss of ambulation, with evidence for reduced PAX7+ cells in muscle samples from affected individuals.[91] A more recent cohort of nine unrelated families with muscular dystrophy showed biallelic pathogenic variants in *POGLUT1* (Figure 4A,B) affecting conserved amino acids (Figure S2), firmly establishing the disease association.[93] This cohort included affected individuals with congenital muscular dystrophy (CMD) as well as those with LGMD phenotypes. Serum CK levels ranged from normal to a high of 10 times the upper limit of normal. A distinct radiological finding of "inside-to-outside" fatty degeneration was found on magnetic resonance images of skeletal muscle in both reports. Based on the sparse reports from the literature to date, POGLUT1-related muscular dystrophy could be classified as an ultrarare disease. The original designation for POGLUT1-related muscular dystrophy was LGMD type 2Z (LGMD2Z). However, the designation "Z" meant that this classification system had been exhausted; thus, as part of a reclassification effort, the disease phenotype is now recognized as LGMDR21.[95]

The gene *POGLUT1*, previously known as *hCLP46*, contains 11 exons and encodes a protein with 392 amino acids[96] that has orthologs across multiple species (Figure 5 and Table S2).[97] POGLUT1's ortholog in *Drosophila*, Rumi, is a protein *O*-glycosyltransferase that glycosylates serine residues in the extracellular domain of Notch[98] and regulates Notch signaling.[99] Studies in mammalian cell culture systems, including C2C12 myoblasts, identified corresponding regulatory activities of POGLUT1 on the Notch signaling pathway.[100,101] However, POGLUT1 has two known enzymatic functions, serving as a glucosyltransferase and xylosyltransferase, with variable effects on cellular proliferation under different circumstances.[97] Deficiency of POGLUT1 and its orthologs also has divergent effects on Notch receptor expression in different contexts, leading to

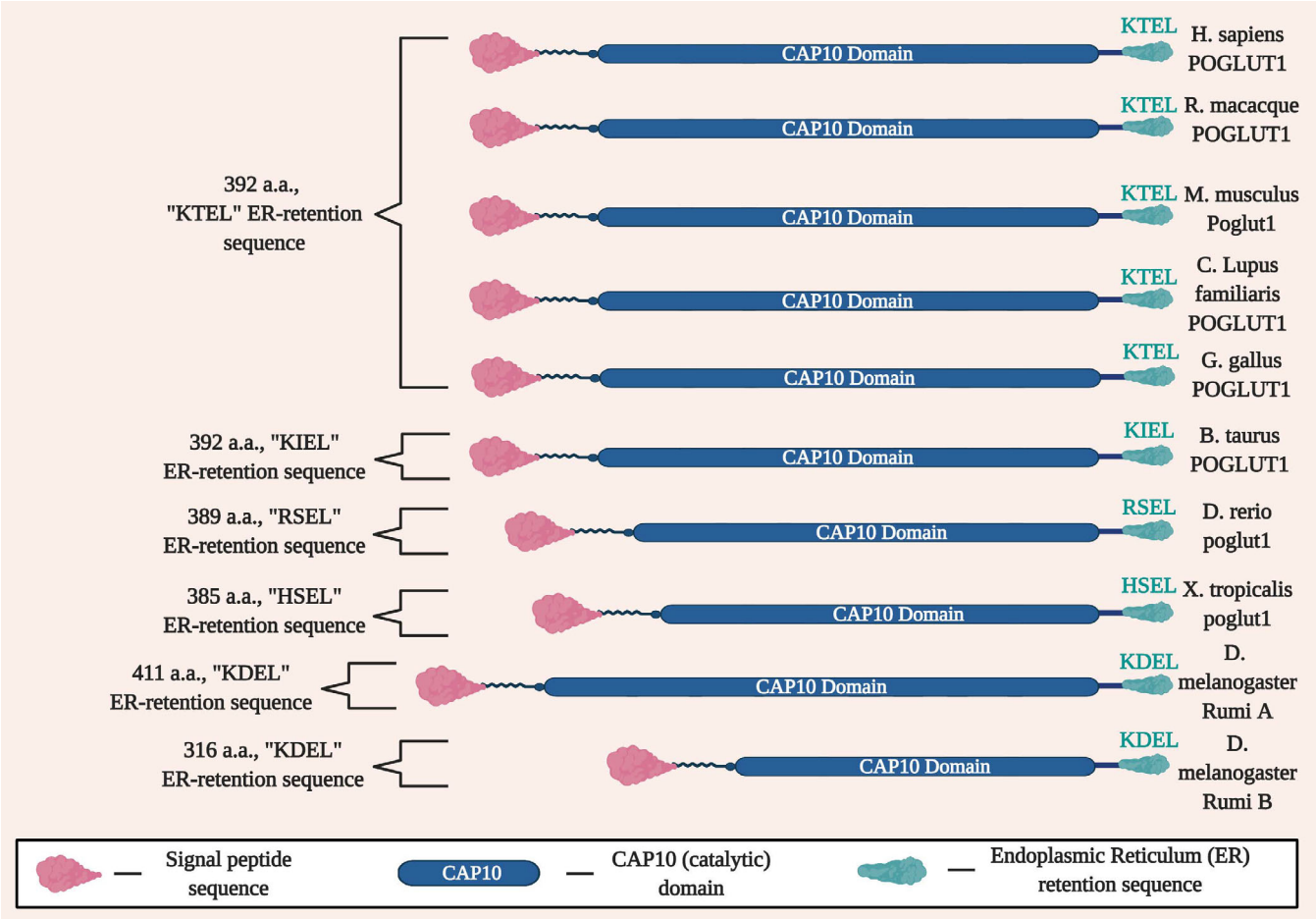

FIGURE 5 Conservation of key domains of POGLUT1 across species, including the signal peptide sequence, CAP10 domain, and the endoplasmic reticulum (ER) retention sequence.

accumulation in one context[98] and depletion in another.[100] This may explain in part why POGLUT1 deficiency has been associated with two different human disease phenotypes.

The most sophisticated animal model of POGLUT1-related muscular dystrophy to date has been developed in *Drosophila*. Rumi deficiency impairs muscle development in *Drosophila*, with more prominent rescue of the phenotype shown with overexpression of wild-type *POGLUT1* compared with *POGLUT1* that harbors a pathogenic variant (c.699 T > G, p.D233E).[91]

1.9 | JAG2-related muscular dystrophy

Biallelic pathogenic variants in *JAG2* were found in a cohort of 13 unrelated families with muscular dystrophy, with severity ranging from an early-onset congenital muscular dystrophy (CMD) phenotype to a later-onset LGMD phenotype.[25] Serum CK levels ranged from normal to four times the upper limit of normal. Some individuals remained ambulatory into adulthood, whereas others lost ambulation in childhood or adolescence. Neck weakness was a prominent feature in a number of affected individuals, and EMG patterns were myopathic in all cases where this test was performed. Muscle biopsy findings included dystrophic patterns and increased fiber size variability.

Affected amino acids are conserved across species (Figure S3),[25] as well as key domains of the protein in general (Figure 6 and Table S3). Several of the affected individuals were found to have a distinct "outside-to-inside" pattern of fatty degeneration on magnetic resonance images of skeletal muscle, similar to the pattern seen in collagen VI–related muscular dystrophy[102] but the reverse of the pattern observed in POGLUT1-related muscular dystrophy.[93] One additional report of JAG2-related muscular dystrophy has since been published,[103] and the milder form of the disease is now classified as LGMD R27. Given the recent discovery of this genetic association, its epidemiology is currently unclear; it may be somewhat rare among muscular dystrophy subtypes.

In contrast to *MEGF10*, *JAG2*'s protein product is an established ligand of the Notch receptors Notch1,[104] Notch2,[105] and Notch3,[104] and furthermore cleaves Notch2.[105] The association between *JAG2* and muscle disease may come as a surprise in view of the complex literature that has accumulated on this gene and its orthologs over the past three decades. The *Serrate* gene was

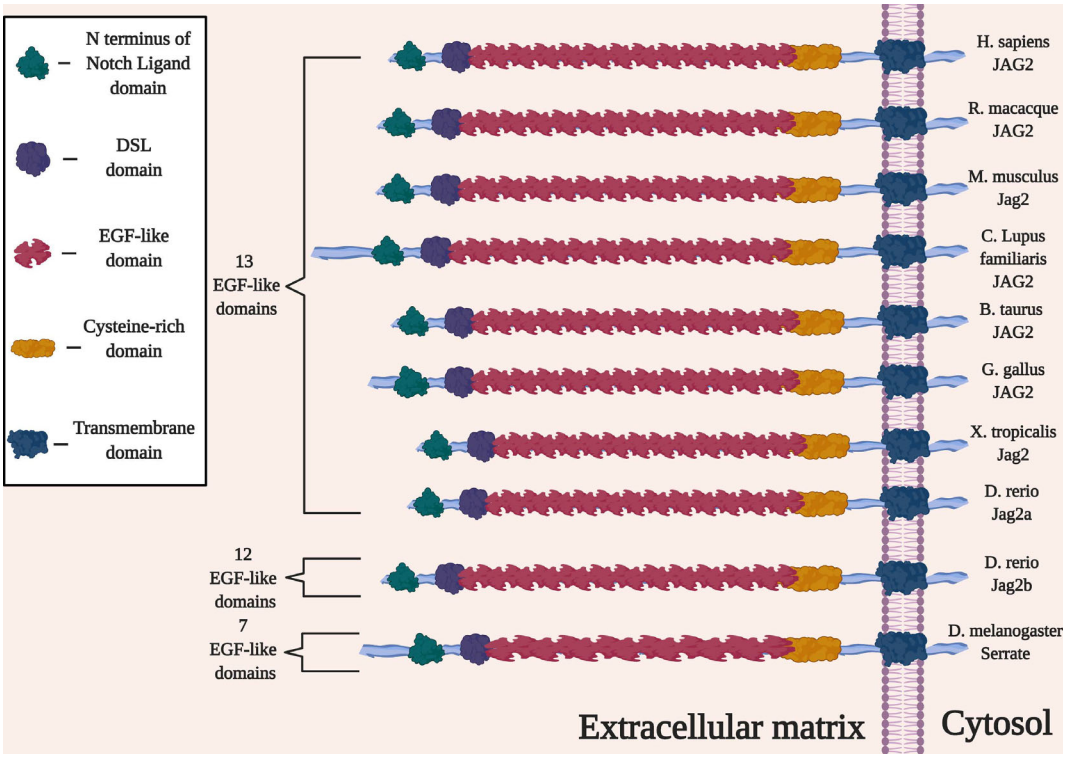

FIGURE 6 Key domains of the JAG2 (Jagged2) protein are conserved across multiple species.

described for *Drosophila* in 1990,[106] followed by the orthologous rat gene *Jagged2*,[107] the murine *Jag2*,[108] and the human *JAG2*.[108–110] The protein products (in humans known as JAG2 or Jagged2) have EGF-like domains[111] and are conserved canonical Notch ligands. In oncology, Jagged2 is known to promote metastasis[112,113] and tumorigenicity[114] in certain types of cancer, potentially due at least in part to pro-angiogenic activity[115]; thus, investigators are examining the means by which to inhibit Notch signaling in cancer biology.[116–118] JAG2 regulation is a potential target for this strategy for selected cancer subtypes.

Even in view of those findings, there are hints suggesting *JAG2*'s link to skeletal muscle disease. JAG2 is expressed in mammalian skeletal muscle,[119] along with several other organs (including the brain,[120,121] gut[122]/enteric nervous system,[123] immune system,[124,125] and ovarian follicles[126,127]). Expression patterns in zebrafish mirror those in mammals.[128–130] At the tissue level, JAG2 is also expressed in mammalian endothelial cells,[131] particularly in arterial vessels,[132] as well as MuSCs.[45] This raises the possibility that JAG2 may mediate signaling between MSCs and endothelial cells and trigger angiogenesis in response to muscle injury.

The regulatory environment upstream of JAG2 is not well characterized in skeletal muscle. However, hnRNP L is an intriguing molecule that is a known splice regulator,[133] and hnRNP L binding sites on the *JAG2* transcript have been identified.[134] Previous reports in the literature have linked hnRNP L to the Notch signaling pathway. Overexpression of hnRNP I (also known as PTBP1), which is a partner of hnRNP L[135] in zebrafish, destabilizes the NICD and inhibits Notch signaling.[136] Studies in mice demonstrated that loss of the Notch inhibitory ligand DLL3 leads to increased levels in two proteins, including hnRNP L.[137] In addition, a screen carried out in *Drosophila* using Notch mutants identified *smooth*, the fly homolog of mammalian *hnRNP L*, as a genetic modifier of Notch.[138] Notably, hnRNP L downstream RNA targets also include *Notch2*,[139] *Notch3*,[134] *Poglut1*,[140] and the Notch inhibitor *Numb*.[134,139] Although these studies point to hnRNP L as a major regulator of several Notch signaling pathway partners,[45] the muscle-specific aspects of this relationship remain to be investigated. Further research is needed, but the studies to date strongly suggest that MEGF10, POGLUT1, and JAG2 interactions synergistically influence Notch signaling (Figure 7).

1.10 | Other links between the Notch signaling pathway and skeletal muscle disease

There are two other muscle disease genes with protein products that may have links to the Notch signaling pathway, with hints of such an association seen in the literature to date: *TRIM32*[141] and *ATP2A1* (SERCA1).[142,143] In addition, *JAG1* is not directly associated with a skeletal muscle disease but a specific variant in *JAG1* appears to have modifying effects on muscular dystrophy.[21]

Biallelic pathogenic variants in *TRIM32* are associated with limb-girdle muscular dystrophy type R8 (LGMDR8, formerly known as LGMD2H).[144] The protein product is a ubiquitin ligase that localizes

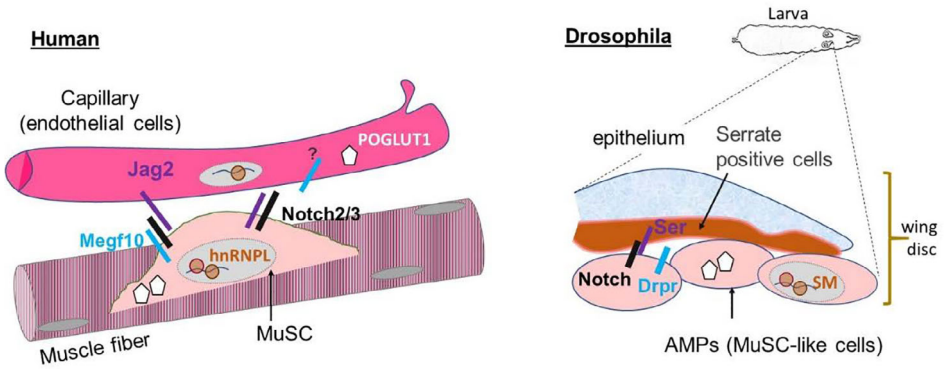

FIGURE 7 Schematic diagram of Notch signaling pathway proteins directly related to human skeletal muscle disease in the muscle fiber vs capillary (left) accompanied by a diagram showing the localization of orthologous proteins in *Drosophila* (right). Human and *Drosophila* orthologous pairs include the proteins JAG2 (Jagged2) and Ser (Serrate), MEGF10 and Drpr (Draper), and HNRNP L and Sm (Smooth). The question mark denotes the potential presence of Megf10 in endothelial cells.

to the Z disk of myofibers, regulates dysbindin,[145] and ubiquitylates thin filament and Z-band proteins.[146] Expression of specific pathogenic variants in *tn* (ortholog of *TRIM32)* leads to myofibrillar abnormalities in *Drosophila*.[147] The link to the Notch signaling pathway arises in the mouse hippocampus, where Trim32 deficiency was found to be associated with upregulation of several relevant genes, including *Notch1* and *Hes1*.[141] This relationship bears exploration for potential relevance to skeletal muscle function and disease.

Brody myopathy is a recessive muscle disorder characterized by childhood-onset muscle stiffness and delayed muscle relaxation[148,149] that is associated with biallelic pathogenic variants in *ATP2A1*,[150] which encodes sarcoendoplasmic reticulum calcium ATPase 1 (SERCA1). The phenotype includes individuals with clinical paramyotonia but without electrical myotonia.[151] The association between SERCA1 and the Notch signaling pathway has been explored primarily in the context of cancer research, with SERCA1 having been identified as a potential therapeutic target.[142,143] Further study of potential interactions between SERCA1 and the Notch signaling pathway in skeletal muscle models may yield novel insights on disease mechanisms and therapeutic targets.

Dominant pathogenic variants in *JAG1* have been associated with Alagille syndrome, a multiorgan system disease that does not have prominent skeletal muscle manifestations,[22,152] familial tetralogy of Fallot,[24] and an axonal form of Charcot-Marie-Tooth disease, known as type 2HH.[23] The protein product JAG1 (also known as Jagged1) is a canonical Notch ligand, along with JAG2 (Jagged2). There have been hints of JAG1 activity in skeletal muscle, including a reduction of JAG1 muscle expression in older humans[153] and in *mdx* mice.[154] JAG1 expression also appears to be induced in activated MuSCs.[155] Intriguingly, a recent study identified a variant in the promoter region of *Jag1* that creates a novel myogenin binding site, increasing *Jag1* expression in skeletal muscle and rescuing Duchenne muscular dystrophy in Golden Retriever dogs.[21]

Recessive pathogenic variants in *PAX7* are associated with a congenital myopathy phenotype, as described in five affected individuals from four unrelated consanguineous kindreds.[156] The disease manifestations include hypotonia, ptosis, and scoliosis, with atrophic fibers and fibroadipose replacement on muscle biopsy. N1ICD expression restores the proliferative potential of Pax7-deficient MuSCs, linking Pax7 to the Notch signaling pathway.[157] Elevated Notch signaling activity has also been associated with an undifferentiated myogenic cell population, characterized by high levels of Pax7 expression.[158]

NOTCH2NLC bears some resemblance to *NOTCH2* and its protein product is also involved in the regulation of Notch signaling. Pathogenic CGG repeat expansions in the 5′ untranslated region of *NOTCH2NLC* have been associated with oculopharyngodistal myopathy (OPDM),[159] neuronal intranuclear inclusion disease (NIID),[160,161] and hereditary essential tremor.[162] Clinical features of this form of OPDM include ptosis, ophthalmoplegia, dysarthria, and muscle weakness.[159]

2 | POTENTIAL THERAPEUTIC TARGETS

Components of the Notch signaling pathway are drawing increasing attention as therapeutic targets. For example, some investigational compounds target γ-secretase, which cleaves the TM from the NICD in the Notch receptor.[163] These and other compounds targeting the Notch signaling pathway have primarily been assessed in nonmuscle diseases[164]; given the emerging body of work linking the Notch signaling pathway to muscle disease, examinations of the effects of some of these compounds in muscle contexts may be warranted. There is also emerging evidence that the Notch signaling pathway is a promising target for therapy in skeletal muscle. Specific small molecule candidate drugs have been found to promote human myotube formation,[165] and sertraline has been found to ameliorate MEGF10 myopathy in cellular, *Drosophila*, and zebrafish model systems.[54]

2.1 | Future directions

Numerous insights into the key contributions of the Notch signaling pathway in skeletal muscle development, maintenance, and repair

have been described. The clinical relevance of the Notch signaling pathway for muscle disease has become apparent over the past decade with the discoveries of three Notch signaling pathway-related muscle disease genes: *MEGF10*, *POGLUT1*, and *JAG2*. Further study of these genes and their encoded proteins, along with exploration of *TRIM32*, *ATP2A1* (SERCA1), and *JAG1* in the same context, are likely to yield a better understanding of skeletal muscle disease. It is likely that additional genes and proteins related to the Notch signaling pathway will be linked to muscle diseases in the future. Sertraline has shown therapeutic effects in models of MEGF10 myopathy, with evidence indicating that it acts via the Notch signaling pathway in this context.[54] This finding, coupled with the potential therapeutic effects of JAG1 augmentation in muscular dystrophy, indicate that the Notch signaling pathway promises to be a robust area of investigation for new therapeutic targets in muscular dystrophy and other skeletal muscle diseases.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated

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