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Approaching Liquid Biopsy – A Comparative Overview of Current Biomarker Development in Myotonic Dystrophies

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Clinical Overview and Molecular Pathology

Myotonic dystrophies (DM) are multisystemic disorders caused by pathological repeat expansions in *DMPK* and *CNBP* leading to DM1 and DM2, respectively. Despite substantial phenotypic overlap between the two disease forms, symptom severity and frequency vary. DM1 and DM2 share RNA-mediated alternative splicing pathology, largely attributed to transcribed repeat expansions disrupting the balance between MBNL and CELF1 proteins[1–3].

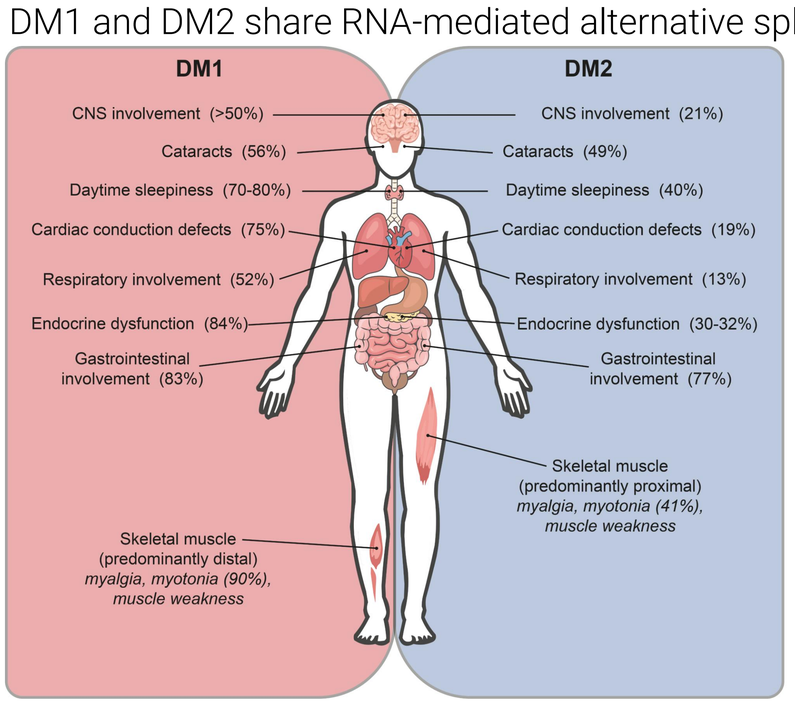


Fig. 1 Overview of common symptoms and their frequencies.

Splicing Biomarkers

Muscle-derived measures of bioavailable MBNL and biomarker panels have been studied, as symptom-related markers of dysregulated alternative splicing. Some of these correlate with parameters of muscle strength and function [6–8], including a composite alternative splicing index developed for DM1 which is currently being used in clinical trials.

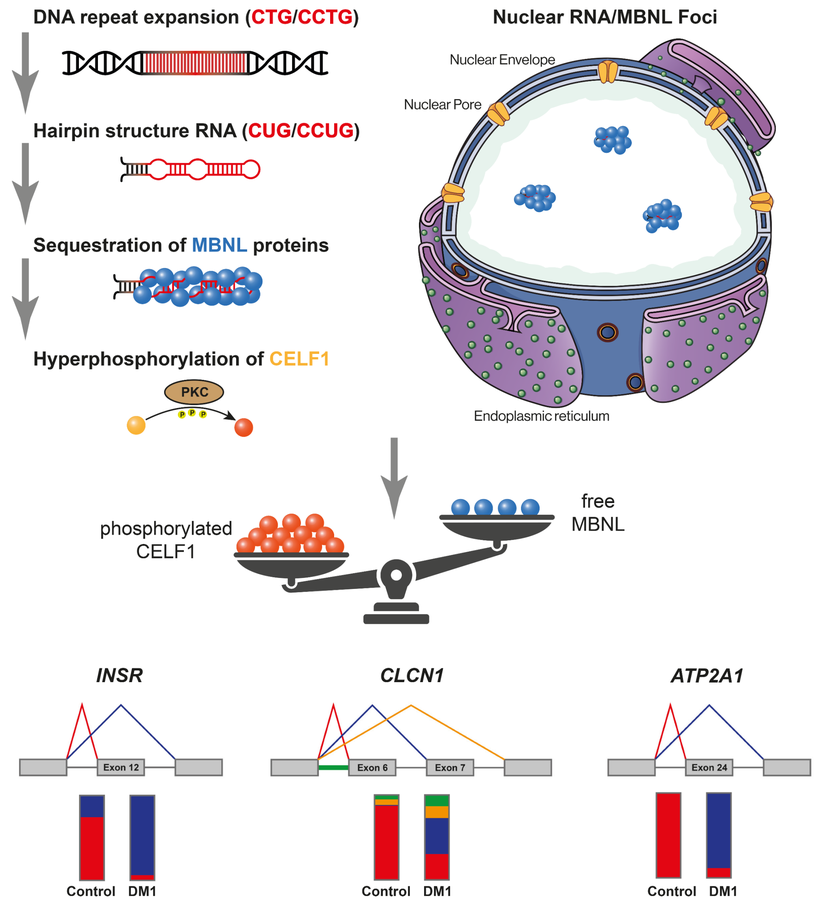


Fig. 2 Molecular mechanism driving pathology in DM1 and DM2.

miRNA Biomarkers

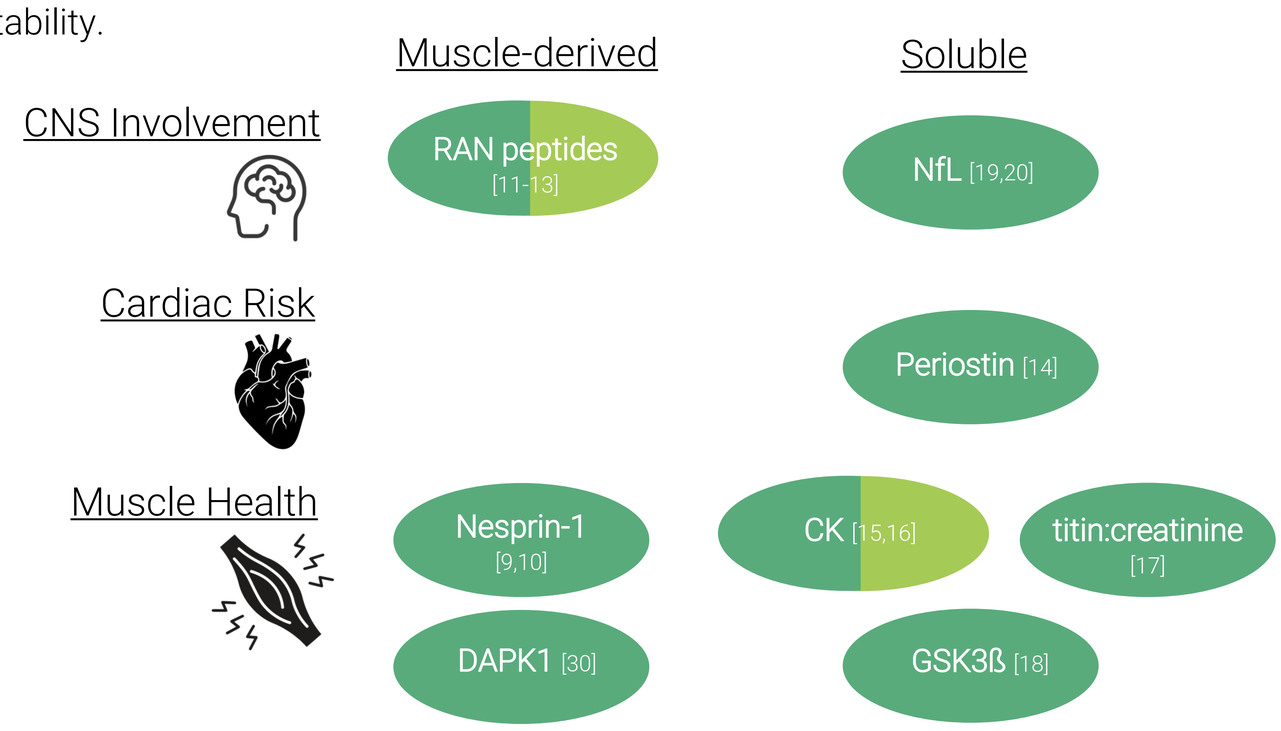
Evidence for miRNA biomarker potential in DM is growing, with increasing focus on circulating myomiRNAs. Functional relevance has been inferred from significantly altered expression of miRNA target genes and assessment of phenotypic correlation, with some serum myomiRNAs (miR-1, miR-133a/b, miR-206) correlating with muscle wastage and functional decline in DM1. Additionally, the mechanistic link between miR-23b and miR-218 and MBNL has shown both biomarker and treatment potential.

However, inconsistent detection and uncertain pathological implications remain challenges impeding clinical implementation of miRNA biomarkers.

miRNA	Studies Reporting Dysregulation				References
	DM1		DM2		
	Muscle	Serum	Muscle	Serum	
miR-1	↑ (1/2)	↑ (3/3)	↑ (1/1)	↑ (1/1)	[21–26]
miR-23b	↑ (1/1)	0	0	0	[27]
miR-24-3p	0	↑ (1/1)	0	0	[28]
miR-27b	0	↑ (1/1)	0	↔ (0/1)	[24]
miR-29b/c	↓ (1/1)	0	0	0	[21]
miR-33	↓ (1/1)	0	0	0	[21]
miR-34a/b/c-5p	↔ (0/1)	0	↓ (1/1)	0	[21,22]
miR-125b-5p	↔ (0/1)	0	↑ (1/1)	0	[22]
miR-133a/b	0	↑ (3/3)	0	↑ (1/1)	[24-26]
miR-140-3p	0	↑ (1/1)	0	↑ (1/1)	[24]
miR-146b-5p	↔ (0/1)	0	↓ (1/1)	0	[22]
miR-193a-3p	↔ (0/1)	0	↑ (1/1)	0	[22]
miR-193b-3p	↑ (1/1)	0	↑ (1/1)	0	[22]
miR-221-3p	↔ (0/1)	0	↓ (1/1)	0	[22]
miR-206	↑ (1/2)	↑ (3/3)	↔ (0/1)	↑ (1/1)	[21-26]
miR-208a	↓ (1/1)	0	↓ (1/1)	0	[22]
miR-218	↑ (2/2)	0	0	0	[27,29]
miR-223-3p	0	↑ (1/1)	0	0	[28]
miR-335	↑ (1/1)	0	0	0	[21]
miR-378a-3p	↔ (0/1)	0	↑ (1/1)	0	[22]
miR-381	↓ (1/1)	0	↓ (1/1)	0	[22]
miR-454	0	↑ (1/1)	0	↑1/1	[24]
miR-574	0	↑ (1/1)	0	↑1/1	[24]

Protein Biomarkers

Proteomic studies reveal distinct protein expression signatures in DM, affecting immunity, metabolism, muscle and mitochondrial function, with mitochondrial dysregulation appearing more prominent in DM2. While symptom-specific muscle-derived and soluble candidate biomarkers have been identified, research has predominantly focused on DM1, and markers tested in DM2 have often shown limited suitability.



Future Directions

- Validate biomarkers in large, longitudinal cohorts
- Improve detection consistency and disease specificity
- Expand DM2-focused research
  - Investigate mitochondrial dysfunction and autoimmunity as potential biomarkers distinct from DM1
- Continue development of minimally invasive biomarkers
  - Particularly serum myomiRNAs

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