X-linked Dystrophin (*DMD*) Deactivation as a Genetic Determinant of Male-Biased Gastric Cancer Risk

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Disclaimer

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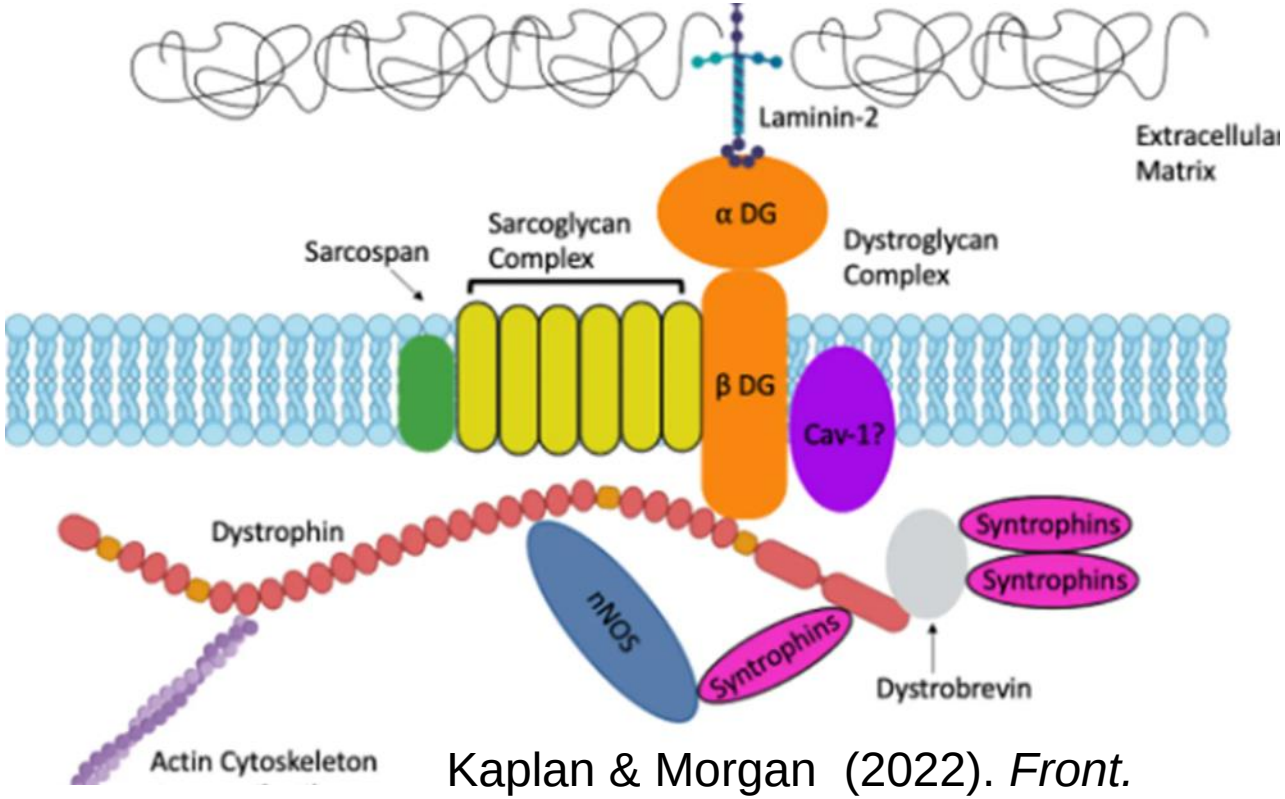
DMD: Protein to Disease

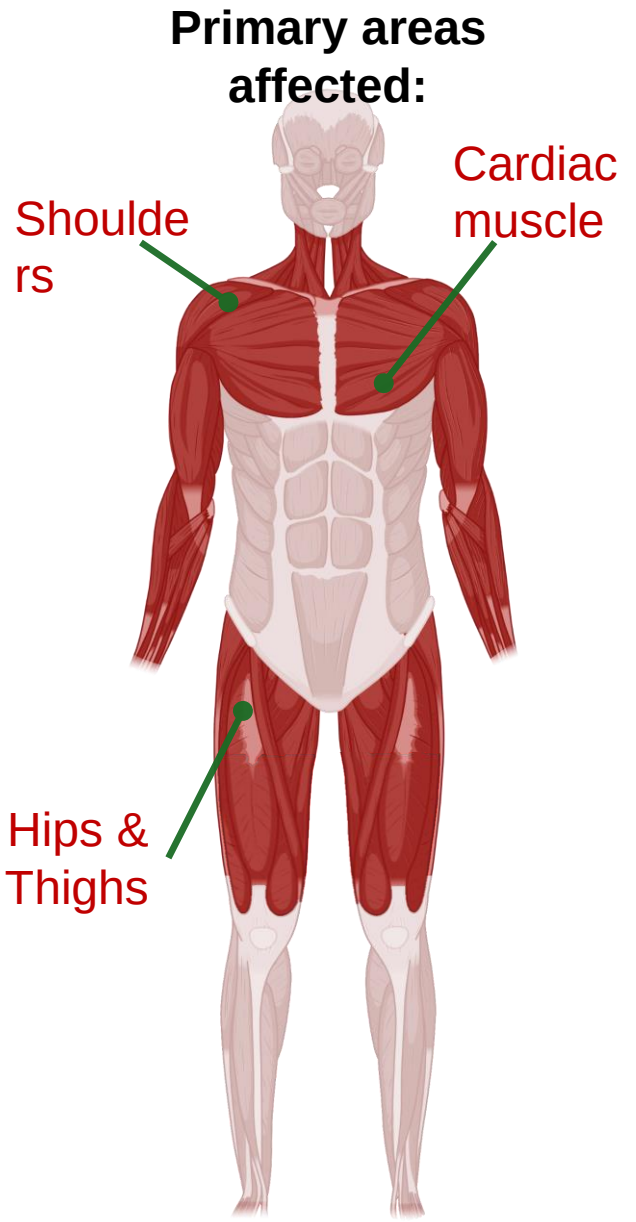
- **Large size:** Dystrophin is translated from the largest known human gene (*DMD* span ~2.4 Mb) and produces a massive **427 kDa** structural protein
- **Structural Anchor:** Dystrophin connects internal actin contractile filaments to the transmembrane dystroglycan complex and extracellular matrix.



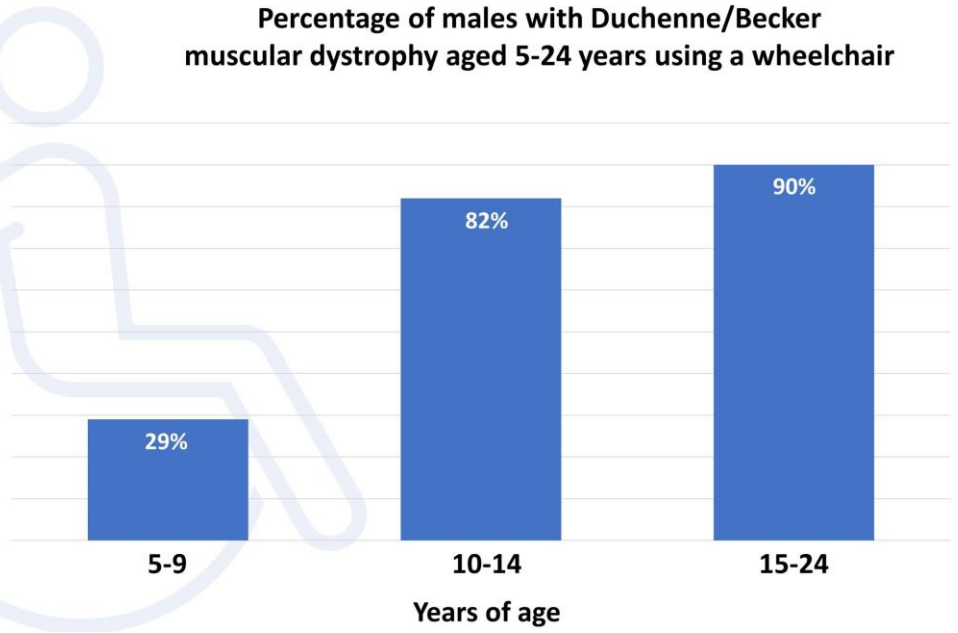
Kaplan & Morgan (2022). *Front. Physiol. 13:1059021.*

- **Shock Absorber:** It acts as a mechanical shock absorber, stabilizing muscle cell membranes during contraction.
- **Loss of Function:** Mutations in the DMD gene lead to absent or non-functional dystrophin protein.
- **Disease Pathology:** Without dystrophin, muscle fibers rupture easily during contraction, causing progressive inflammation, tissue degeneration, and muscle weakness (DMD).

Dystrophin Dysfunction: Duchenne Muscular Dystrophy (DMD)

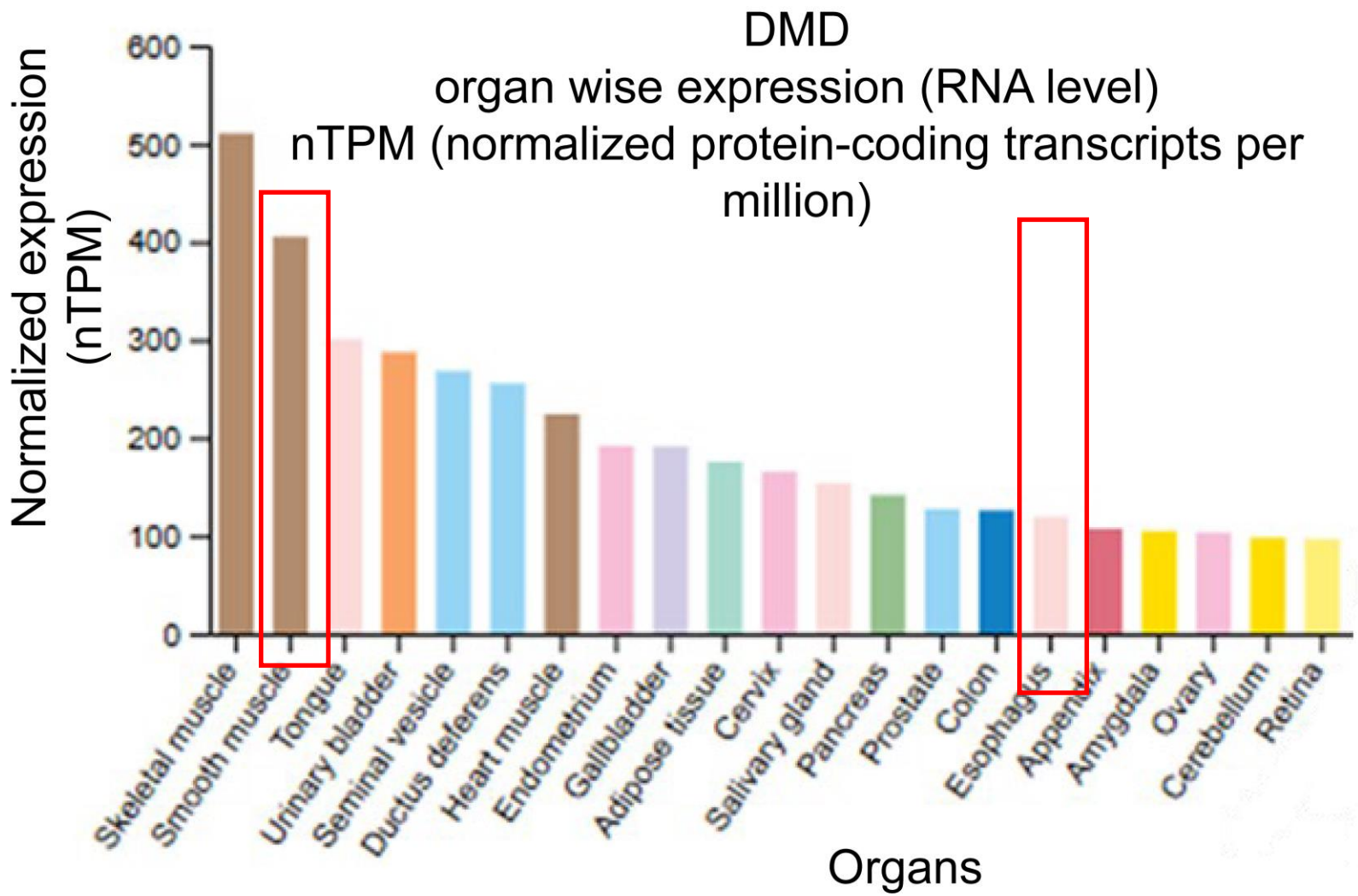


- DMD is a lethal X-linked disorder caused by mutations in the *DMD* gene
- Affects 1 in 5,000 males
- Symptoms:
  - Muscle degeneration
  - Motility dysfunction
- Current diagnosis techniques:
  - Genetic testing results
  - Muscle biopsy results
  - Steroid use



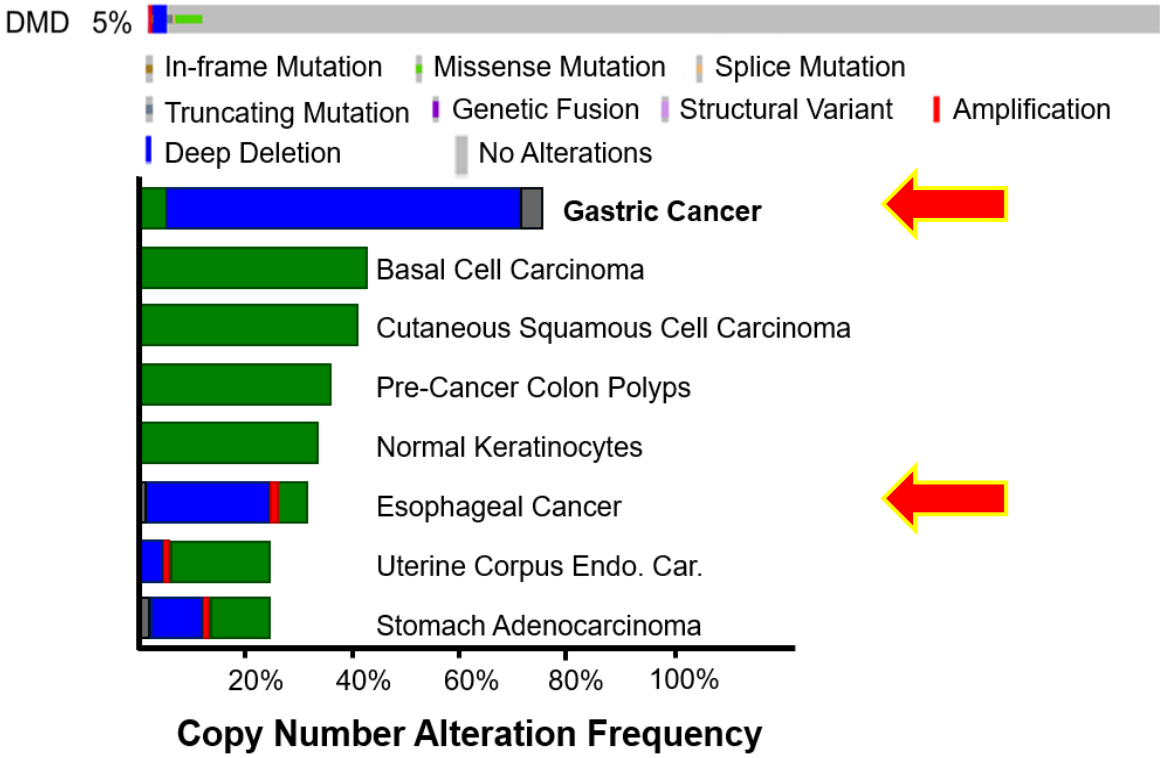
CDC: Centers for Disease Control and Prevention. *Data Summary: Muscular Dystrophy*.

Organ wise differential Expression of DMD



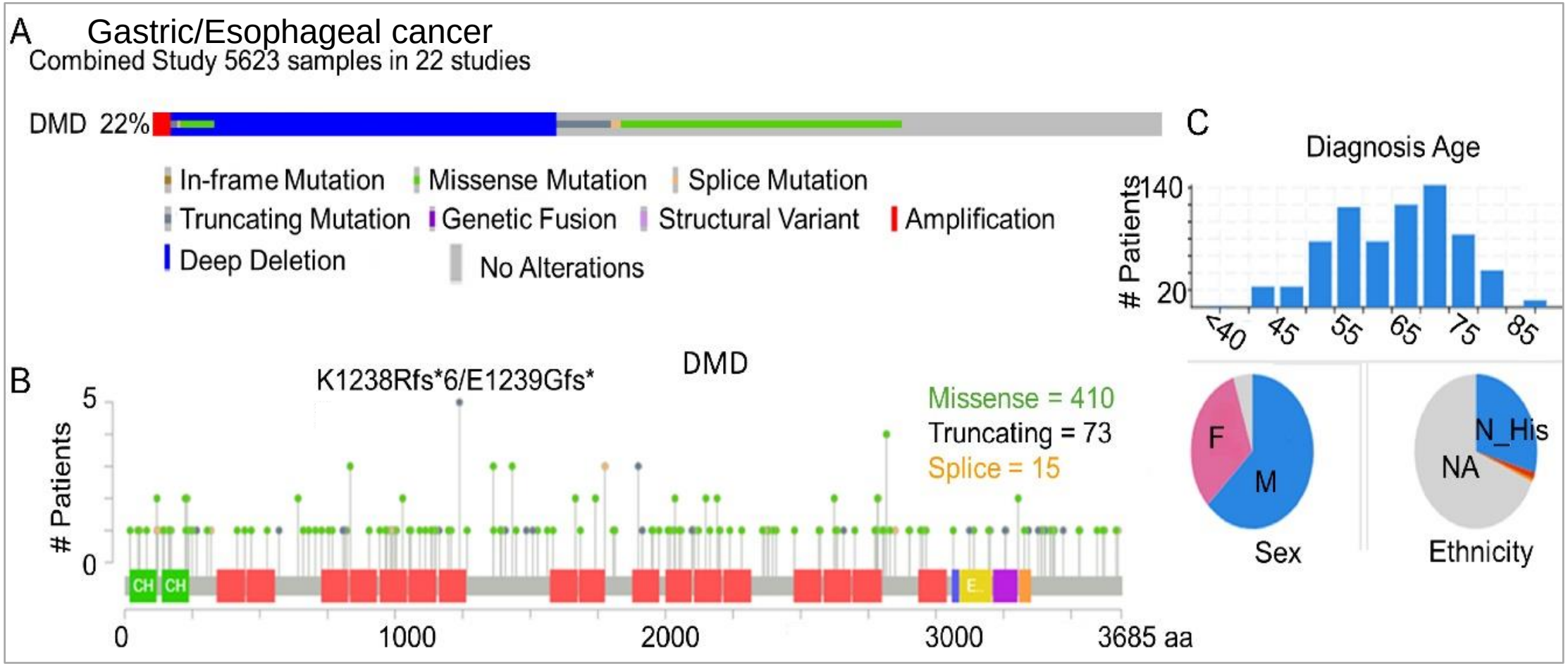
More Than a Muscle Disease: *DMD*'s Emerging Role in Gastric Cancer

"The **lifetime risk of developing gastric cancer is *twice* as higher in men** than in women" – National Cancer Institute



- Potential to utilize DMD as a novel genetic indicator of male-biased gastric cancer
- ***DMD* deletions are prevalent among gastric and esophageal cancers.** (N=105,424 samples, 226 studies)

Dystrophin (*DMD*) and Gastric Cancer



- CNAs constitute 22% of these cancers compared to 5% across all cancers
- *DMD* has >65% frequency in being mutated (deletion and SNV) on the X-chromosome in gastrointestinal tumor samples (N=606)

DMD Gated Genes: Deletions and Amplifications

N=606 (Mutation or Deleted *DMD*- Xp21.2–Xp21.1)

Deleted Loci

Locations	Total Deletions
Xp21	38
Xp22	159
Xq11	10
Xq12	12
Xq13	93
Xq21	54
Xq22	109
Xq23	43
Xq24	50
Xq25	16
Xq26	84
Xq27	36
Xq28	141

Amplified Loci (Compensatory)

Chr/Cytoband	No of Total Genes
3	**19**
8	**176**
17	**13**
11	**11**
6	**11**

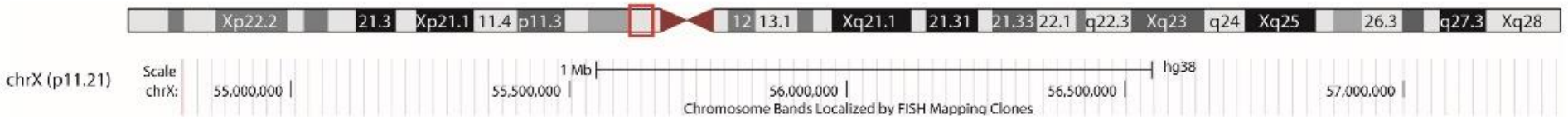
Locations	Total Amplified
8q22	**10**
8q24	**166**

Locations	Total Amplified
3q26	16
3q29	3

Locations	Total Amplified
17q12	13

Deleted and Amplified Genes

X- Chromosome



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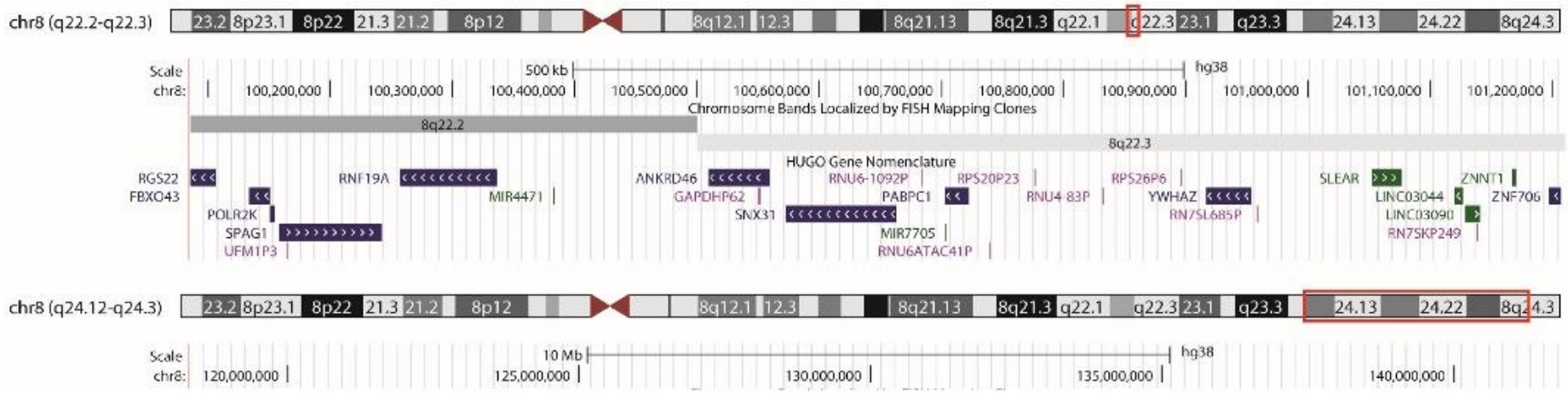
Xq27	36
Xq28	141

Chromosome 8



Locations	Total Amplified
8q22	10
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Rationale & Hypothesis: Connecting DMD & Gastric Cancer

- **Scientific Rationale (The "Tale of Two Diseases")**

→ The role of *DMD* in smooth muscles and its relationship to oncogenesis remains uncovered

- Cancer genomics analyses reveal frequent ***DMD*** **mutations in gastric cancers is often accompanied by oncogene amplifications** (e.g., *MYC, MECOM, MUC20*)
- Shared Pathogenic Signature: Both Duchenne Muscular Dystrophy and Gastric Cancer exhibit profound male bias.

- Predictive Biomarker Potential: Inactivation of the massive *DMD* gene serving as a driver or early predictor for gastric malignancy

HYPOTHESIS

Mutation of the *DMD* gene activates compensatory oncogenic pathways, predisposing smooth muscles to malignancy.

OBJECTIVES

Primary Objectives

- **Bridge the Genetic Axis:** Establish a direct mutational connection between *DMD* loss and gastrointestinal oncogenesis across 100,000+ tumor samples.
- **Identify Predictive Biomarkers:** Uncover shared X-linked and autosomal genetic markers (*MYC*, *MECOM*, *MUC20*) co-amplified during *DMD* inactivation.
- **Cross-Disease Validation:** Validate the DMD–Gastric Cancer biomarker panel using human tissue microarrays (TMAs) and *DMD*-mutated cancer cell lines (SNU-16).

Experimental Pipeline: Establishing the 'DMD Cancer Model'

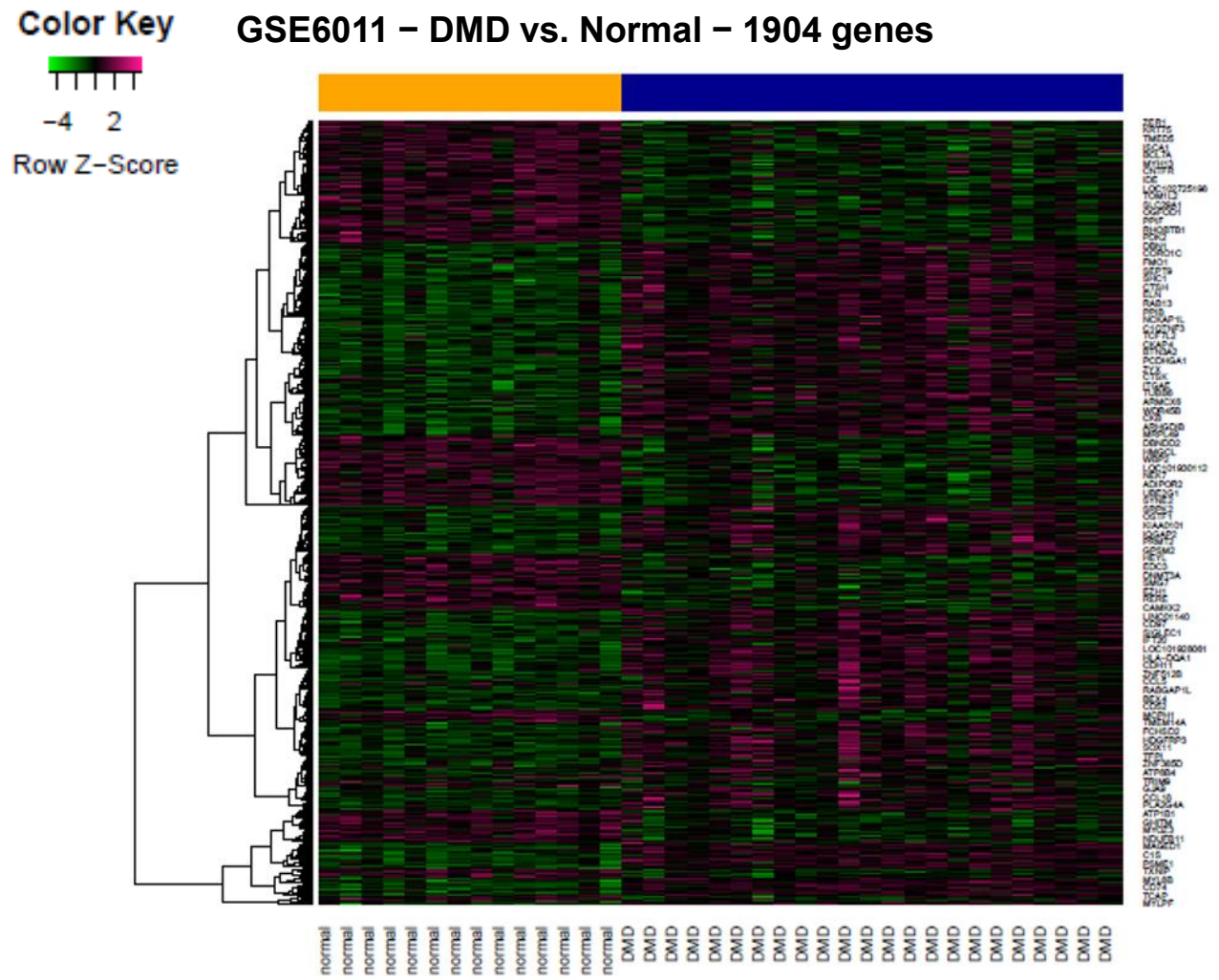
1. **Comparative Transcriptomic Profiling & Signature Cross-Validation**

Classical DMD Signature: Extracted core *DMD*-regulated transcriptomic pathways (dataset-**GEO ID: GSE6011**). *Pescatori et al. (2007) . FASEB J* 2007 Apr;21(4):1210-26
Gastric Cancer Signature: Profiled differential gene expression in gastric cancer and GIST cohorts (**GEO ID: GSE13861**). *Cho et al. (2011). Clin Cancer Res.* 17(7):1850-7.
Cross-Disease Integration: Intersected the classical *DMD* signature with gastric cancer genomic datasets to define a unified **"DMD–Gastric Cancer Common Genetic Signature.“**

2. In Vitro & Tissue-Level Bench Validation
Cell Line Models: Validated expression of top co-regulated targets (*MYC*, *MECOM*, *MUC20*, *FOXO4*) across *DMD*-mutated gastric cancer cell lines (e.g., SNU-16).

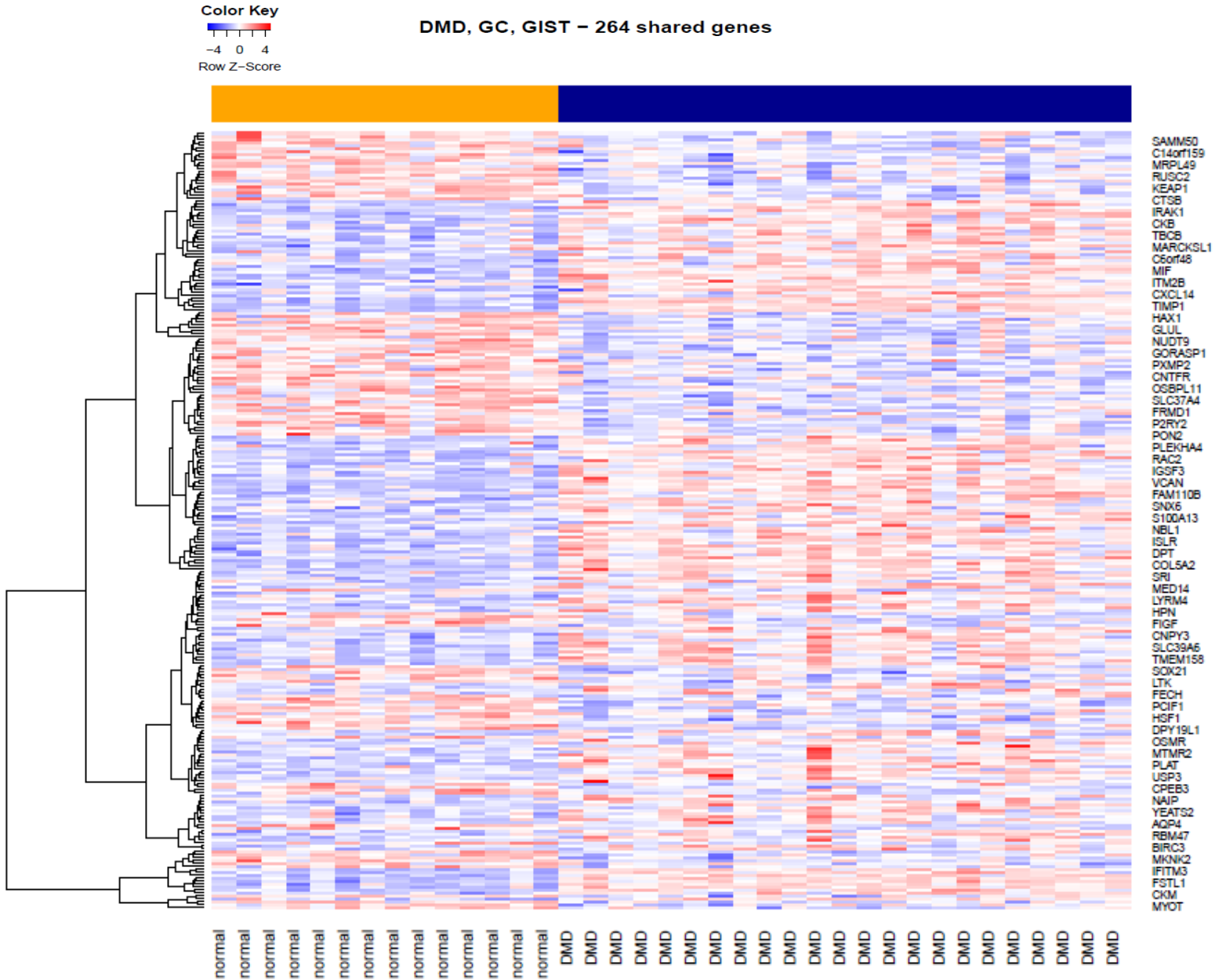
Human Tissue Microarrays (TMA): Confirmed protein-level dysregulation in clinical gastric adenocarcinoma, GEJ, and normal control tissue sections.

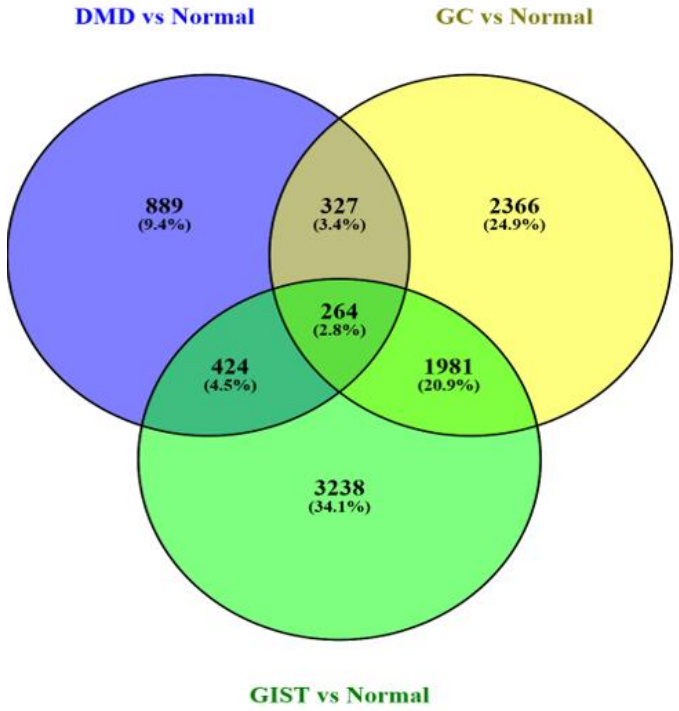
Genetic Overlap- Tale of two Diseases: DMD and Gastric Cancer



All DMD results from NCBI Geo ID: GSE6011
Pescatori et al. (2007) . FASEB J 2007 Apr;21(4):1210-26. PMID: 17264171

Sharing Genetic Signature- DMD/GC axis



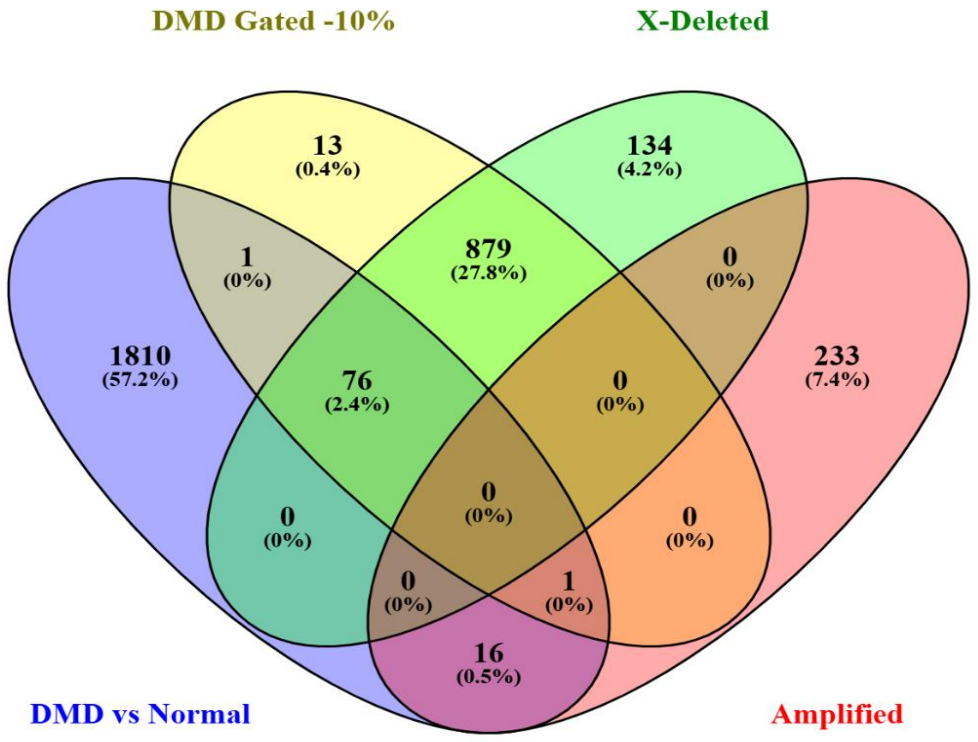


All GC and GIST results from NCBI GEO ID# GSE13861

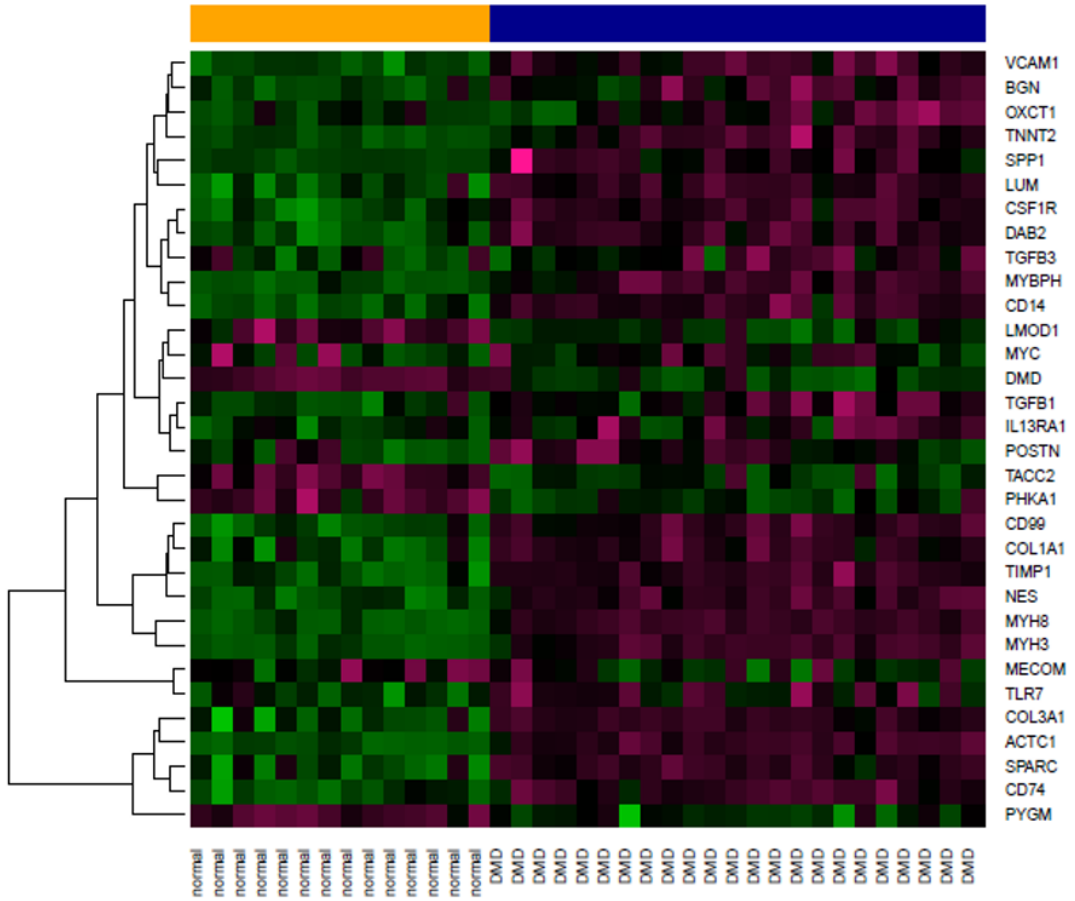
Ref: *Cho et al. (2011). Clin Cancer Res.* 17(7):1850-7. PMID: 21447720

GIST: Gastrointestinal stromal tumor
GC: Gastric Cancer
DMD: Duchenne Muscular Dystrophy

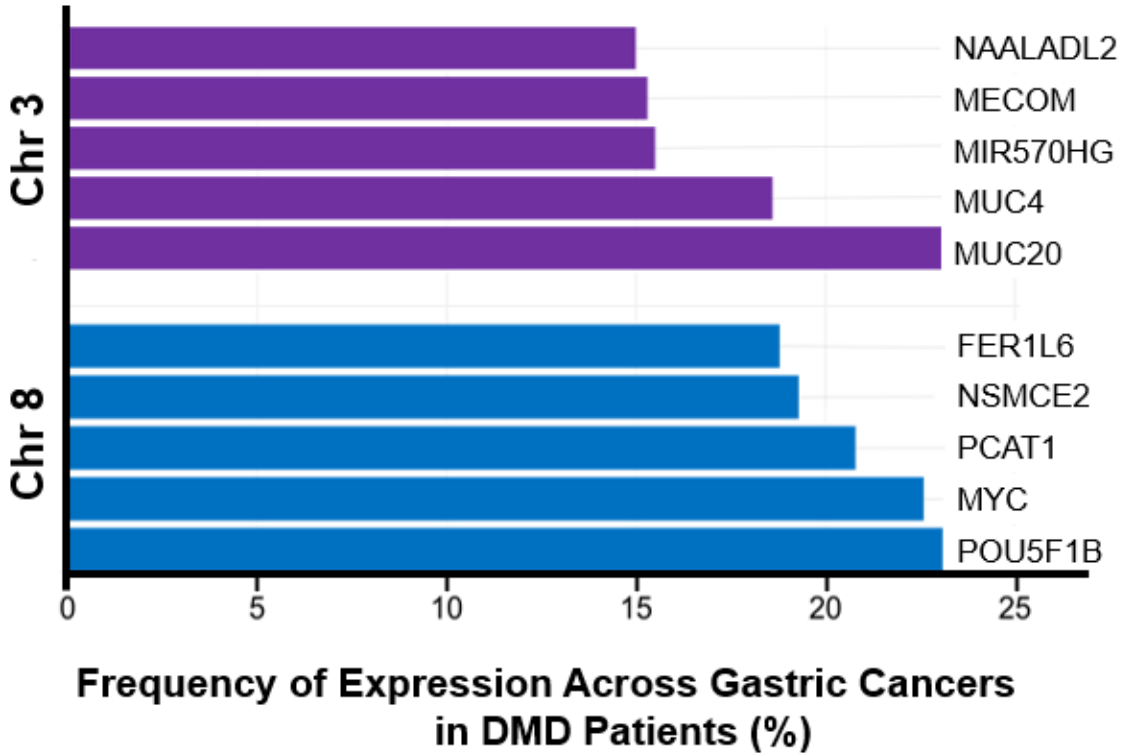
A Common Genetic Signature: classical DMD and ‘cancer-based DMD model’



GSE6011 – DMD vs. Normal – Matched with cancer-based DMD model



Selecting Key Genetic Markers Upregulated in the Presence of *DMD* Mutation



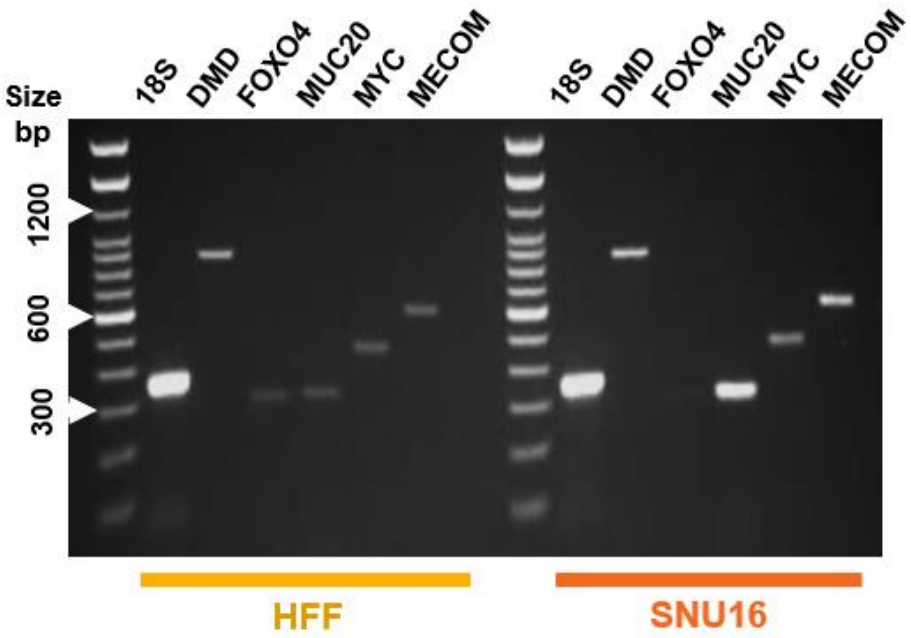
- Top 5 genes represented
- Chromosomes 3 and 8 contain most frequently expressed genes (>20%)
- Select genes to validate: MECOM, MUC20, MYC

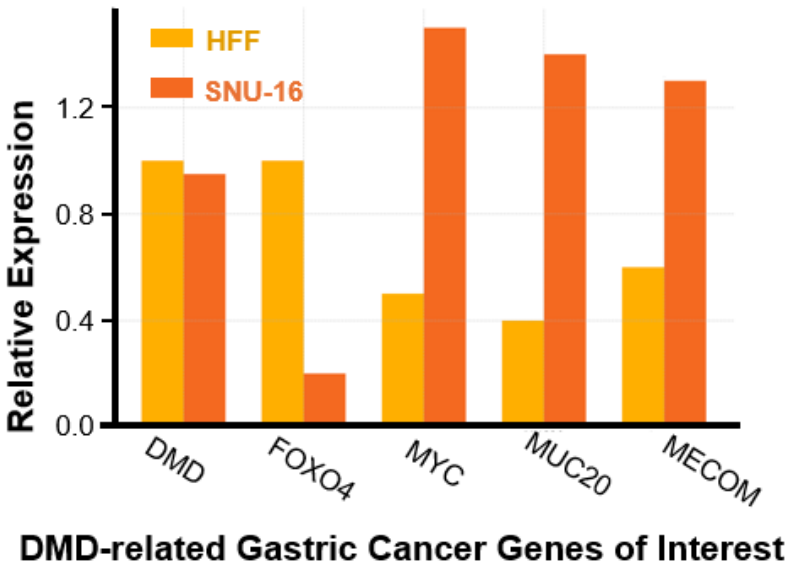
Bioinformatics to Bench

Validating database findings with *in vitro* experiments

DMD Loss Marks an Oncogenic Shift in Gastric Cancer

- Select oncogenes found on chromosomes 3 and 8 are amplified in the presence of *DMD* mutation
- Notable downregulation of FOXO4 on the X-chromosome and high upregulation of MECOM, MUC20, and MYC





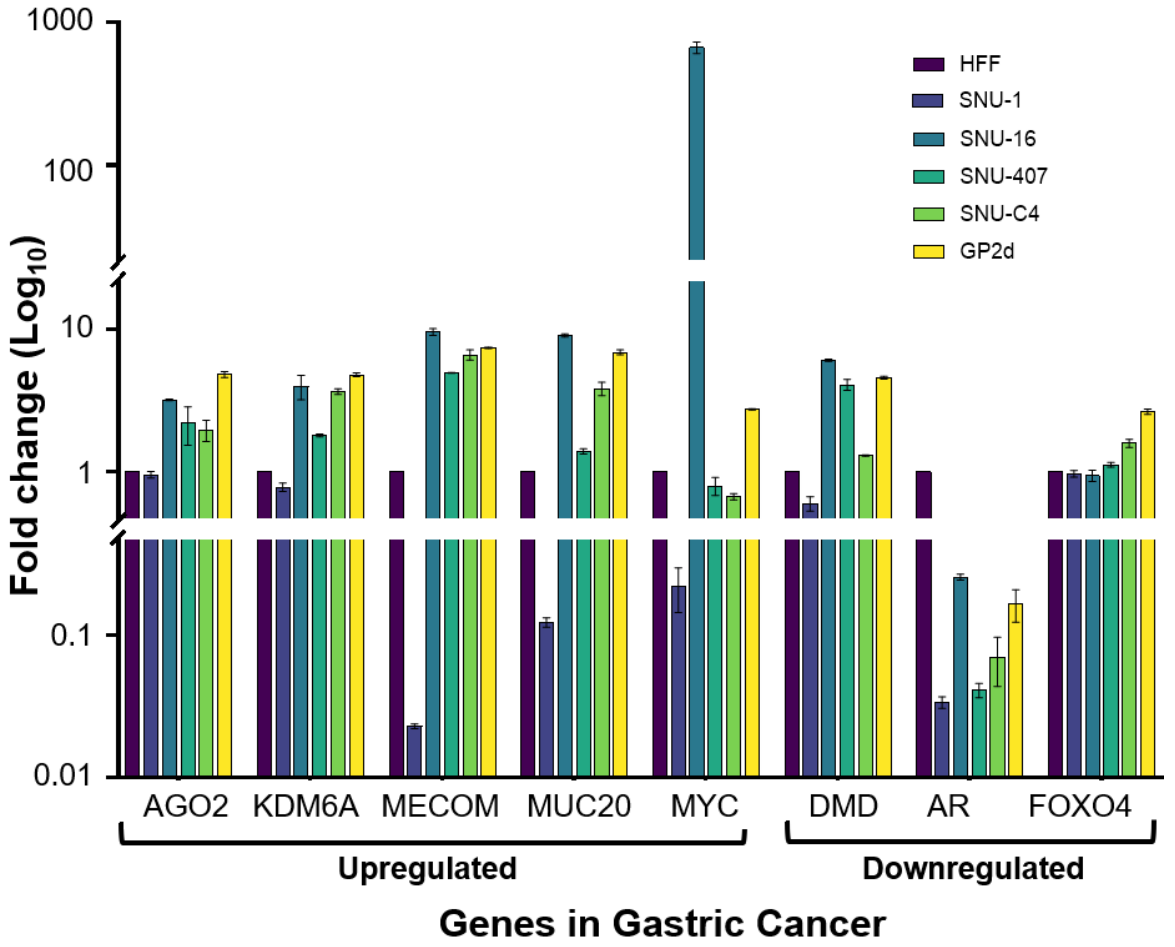
DMD-related Gastric Cancer Genes of Interest

Gene Name	Location	CAN status
DMD	Xp21.2-p21.1	HOMDEL
FOXO4	Xq13.1	HOMDEL
MYC	8q24.21	AMP
MUC20	3q29	AMP
MECOM	3q26.2	AMP

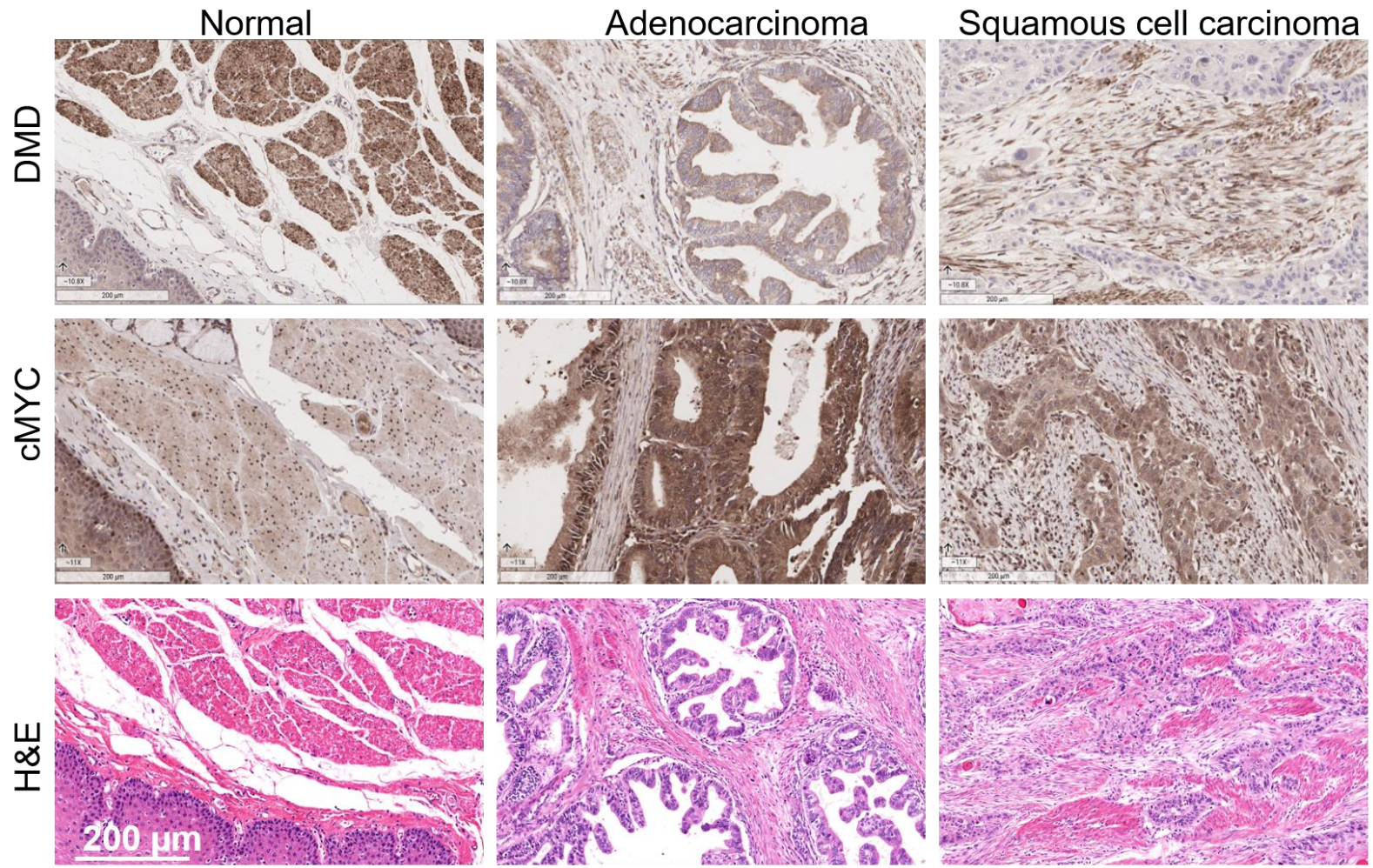
Gene	Oncogenic Role	Regulation Behavior in Gastric Cancer (SNU-16)
MECOM	Progressor	↑
MUC20	Progressor	↑
MYC	Progressor	↑
DMD	Suppressor	↓
FOXO4	Suppressor	↓

Tale of Two Diseases: Validation of Common Genetic Markers

Cell-lines	Type of Cancer	DMD mutation	Variant type
GP2D	Colon Adenocarcinoma	p.K1899NfsTer2	Deletion
SNUC4	Colorectal Adenocarcinoma	p.T3055M/p.E1211KfsTer4	SNV/Deletion
SNU1	Esophagogastric/Stomach Adenocarcinoma (EGC	WT	NA
SNU16	Esophagus/Stomach	p.R2553Ter	SNV
SNU407	Bowel/Colorectal	p.E2015G; p.K1899NfsTer2	SNV/Deletion

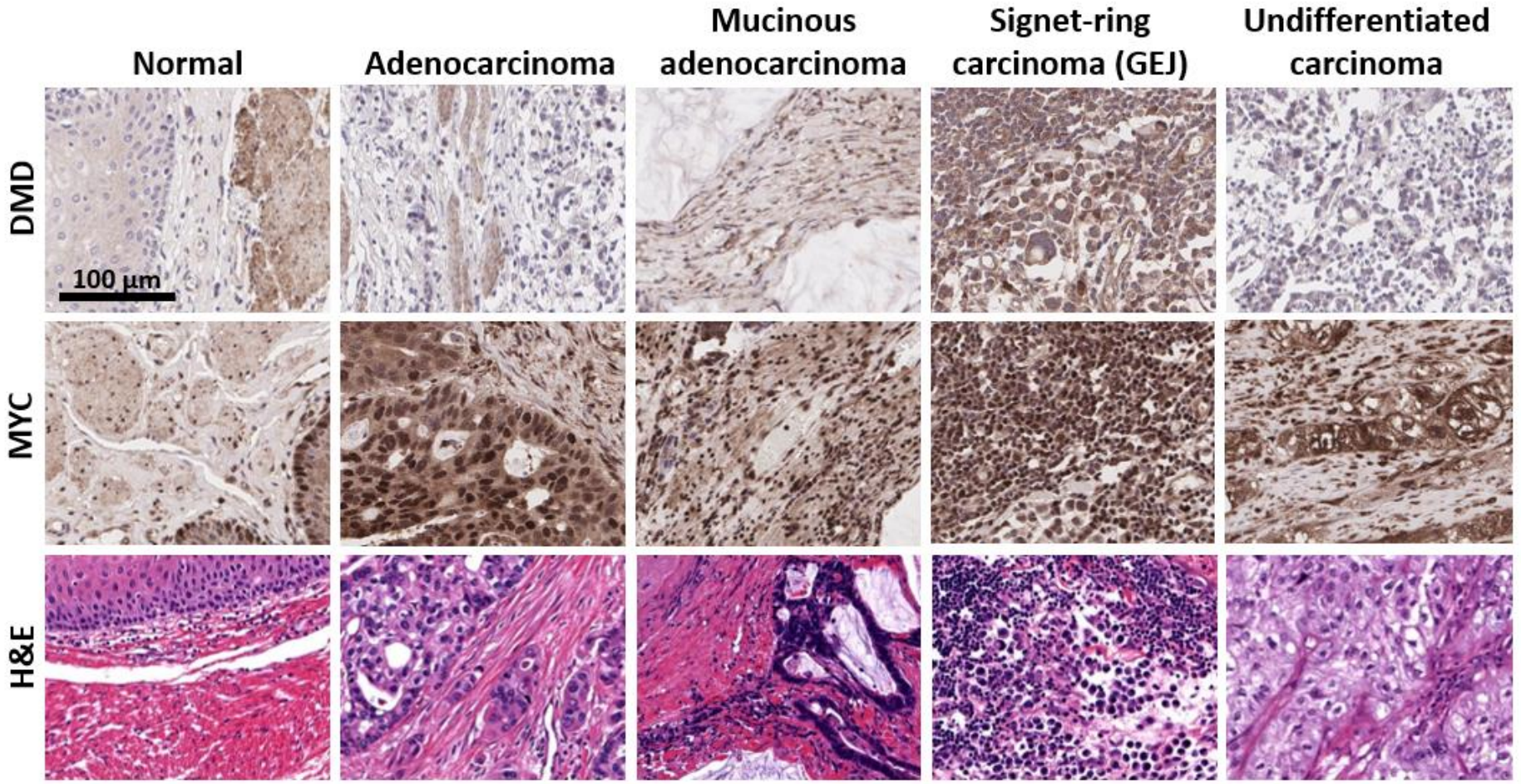


High MYC and Low DMD Define Advanced Gastric Cancers



High MYC and Low DMD Define Advanced Esophageal and Gastric Cancers

Malignant late-stage esophagus and gastroesophageal junction (GEJ) tissues display elevated oncogenic marker (MYC) and decreased DMD expression.



Key Scientific Findings

- **Novel X-Linked Determinant:** Somatic *DMD* mutational inactivation is a distinct genetic indicator of male-biased gastric cancer (~22% frequency in GI vs. ~5% pan-cancer average).
- **Compensatory Driver Cascade:** Loss of *DMD* triggers severe genomic instability and recurrent amplification of oncogenic drivers (*MYC*, *MECOM*, *MUC20*) on chromosomes 3, 8, and 17.
- **Cross-Disease Signature:** Multi-omics integration (GSE6011 & GSE13861) uncovered a 264-gene transcriptomic axis directly bridging inherited muscle dysregulation with GI smooth muscle oncogenesis.

Conclusions & Translational Impact

Broad Impact & Significance:

- This study establishes a unifying, X-linked genetic framework for gender-specific (male) gastric cancer epidemiology. By redefining *DMD* as an X-linked tumor suppressor, we open new avenues for using *DMD* mutational status as an early predictive biomarker for male cancer risk stratification.

Future Translational Steps:

- **Diagnostic Panel Development:** Expand candidate gene repertoire to establish a multi-gene screening panel (*DMD*, *MYC*, *MECOM*) for early gastric cancer detection in high-risk populations.
- **Extended Cell Line & Organoid Validation:** Functional characterization of *DMD*-dependent chromatin and membrane dynamics across additional *DMD*-mutated GI cancer models.
- **Targeted Therapeutics:** Evaluate small-molecule candidates targeting downstream compensatory pathways (*MYC* / *MECOM* axis) for drug repurposing in *DMD*-deficient tumors.

Questions & Discussion

Thank you for your time, attention, and support of military health research.

PRESENTER

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