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INTEGRATED TRANSCRIPTOMIC ANALYSIS OF *CIC::DUX4* FUSION SARCOMAS REVEALS ELEVATED PROLIFERATION SIGNALING AND IMPLICATES DNA REPAIR GENE POLE

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2024 ANNUAL MEETING

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Disclosures

I report no financial conflicts of interest

Presented by:

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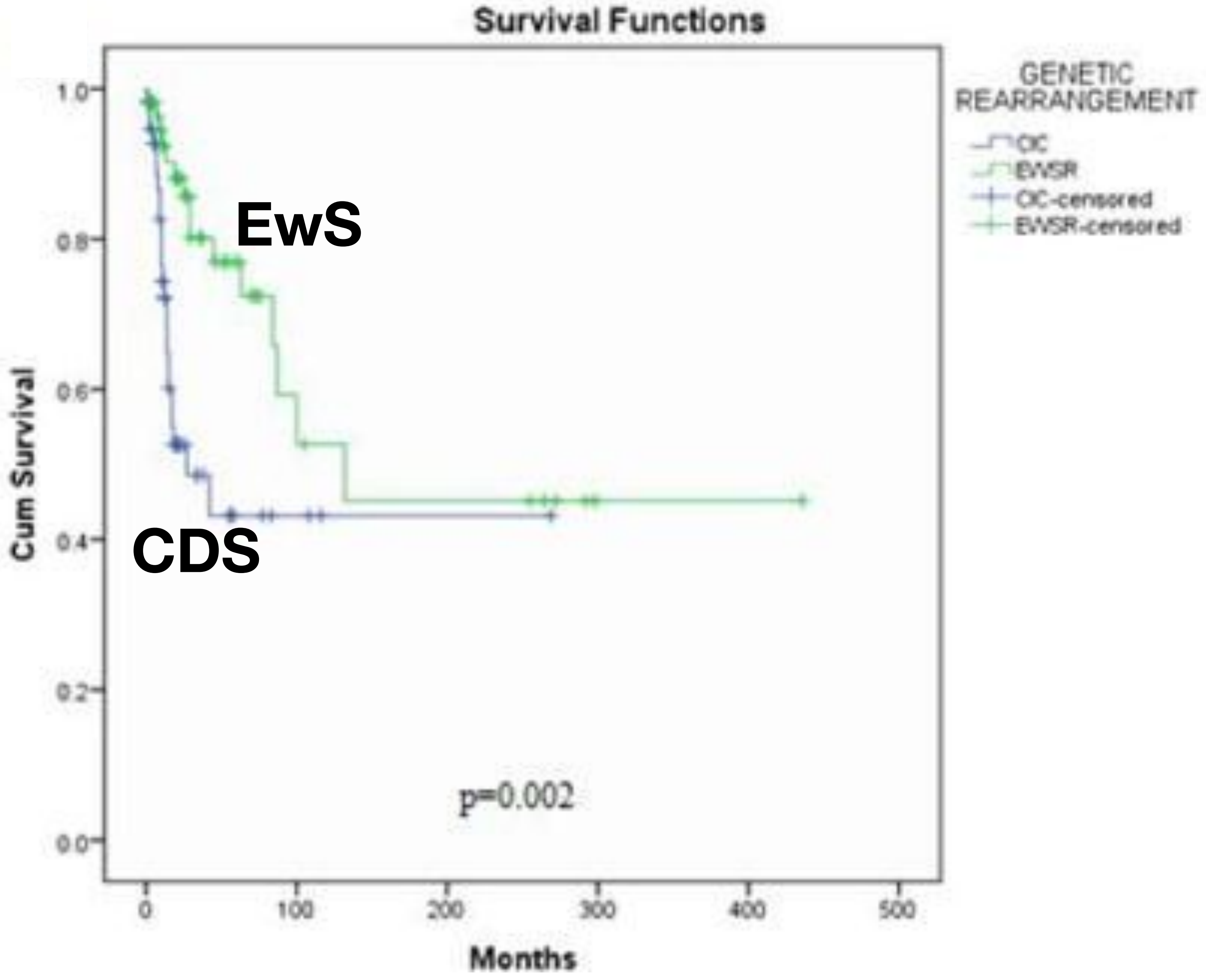
Introduction

- *CIC*::*DUX4* translocation positive sarcomas (CDS)
- Aggressive, chemoresistant
- Overall survival for patients with CDS is worse than other small blue round cell tumors (SBRCT)
- Limited knowledge about the molecular landscape associated with these rare sarcomas



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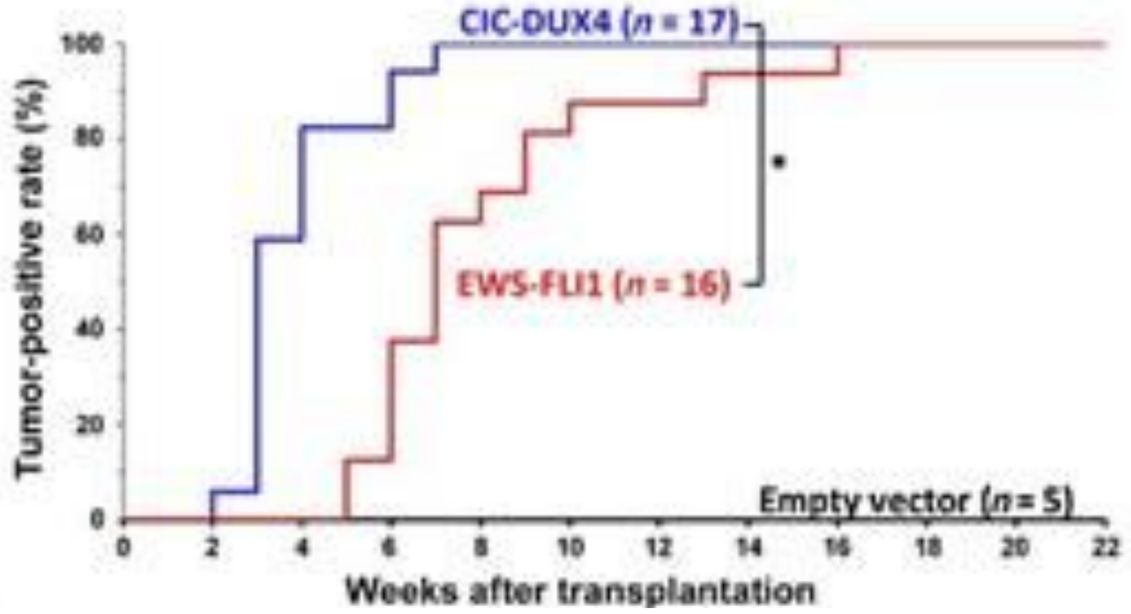

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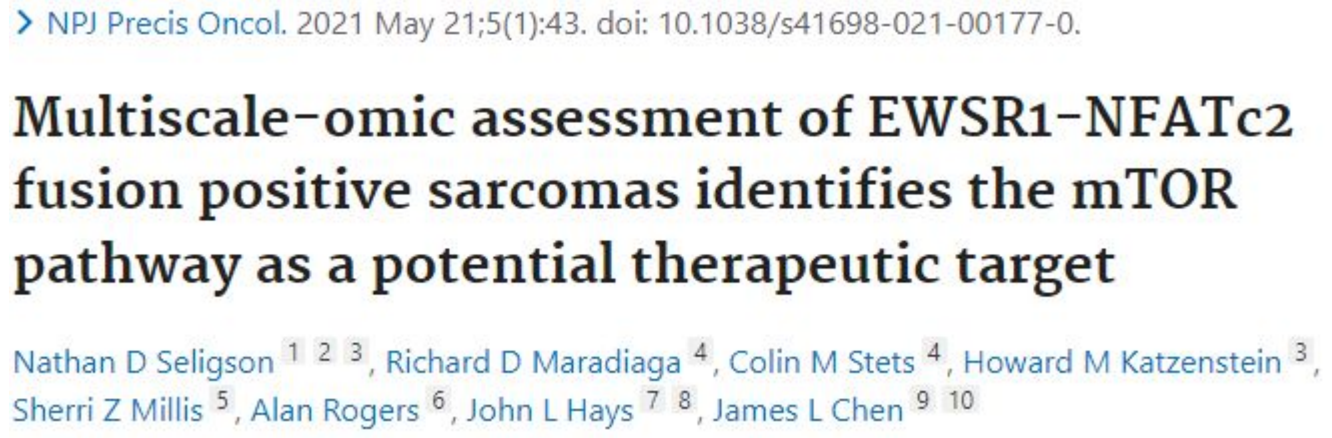
Introduction

- We previously reported that SBRCTs demonstrate unique molecular signatures at the DNA and RNA level
- Defining driver translocation correlates with unique molecular signals
- Molecular signals may be targetable or clinically actionable
- Using a similar methodology, we conduct an integrated molecular analysis of CDS tumors previously unreported and existing molecular data

> Transl Oncol. 2023 Dec:38:101795. doi: 10.1016/j.tranon.2023.101795. Epub 2023 Oct 3.

Gene partners of the EWSR1 fusion may represent molecularly distinct entities

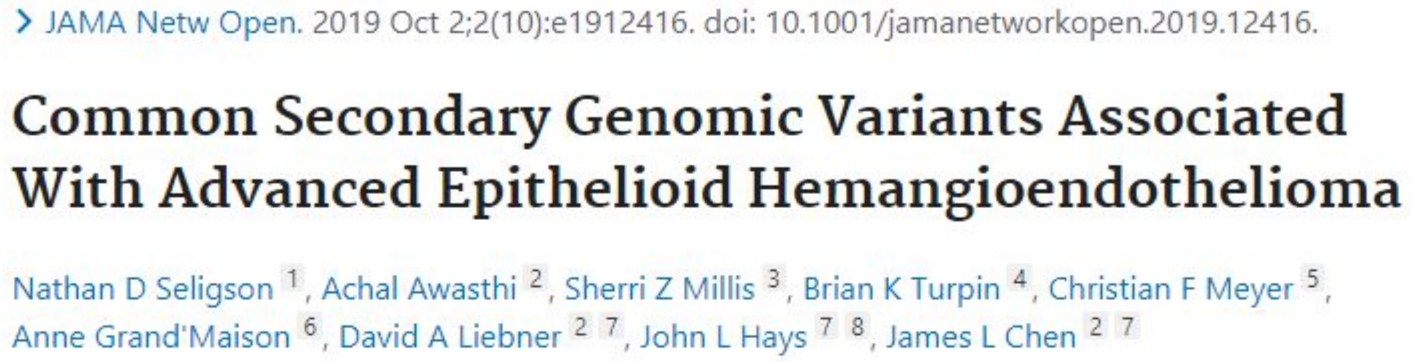
Victoria Walker[1], Dexter X Jin[2], Sherri Z Millis[2], Elham Nasri[3], Diana A Corao-Uribe[4], Aik Choon Tan[5], Brooke L Fridley[6], James L Chen[7], Nathan D Seligson[8]



> NPJ Precis Oncol. 2021 May 21;5(1):43. doi: 10.1038/s41698-021-00177-0.

Multiscale-omic assessment of EWSR1-NFATc2 fusion positive sarcomas identifies the mTOR pathway as a potential therapeutic target

Nathan D Seligson[1,2,3], Richard D Maradiaga[4], Colin M Stets[4], Howard M Katzenstein[3], Sherri Z Millis[5], Alan Rogers[6], John L Hays[7,8], James L Chen[9,10]



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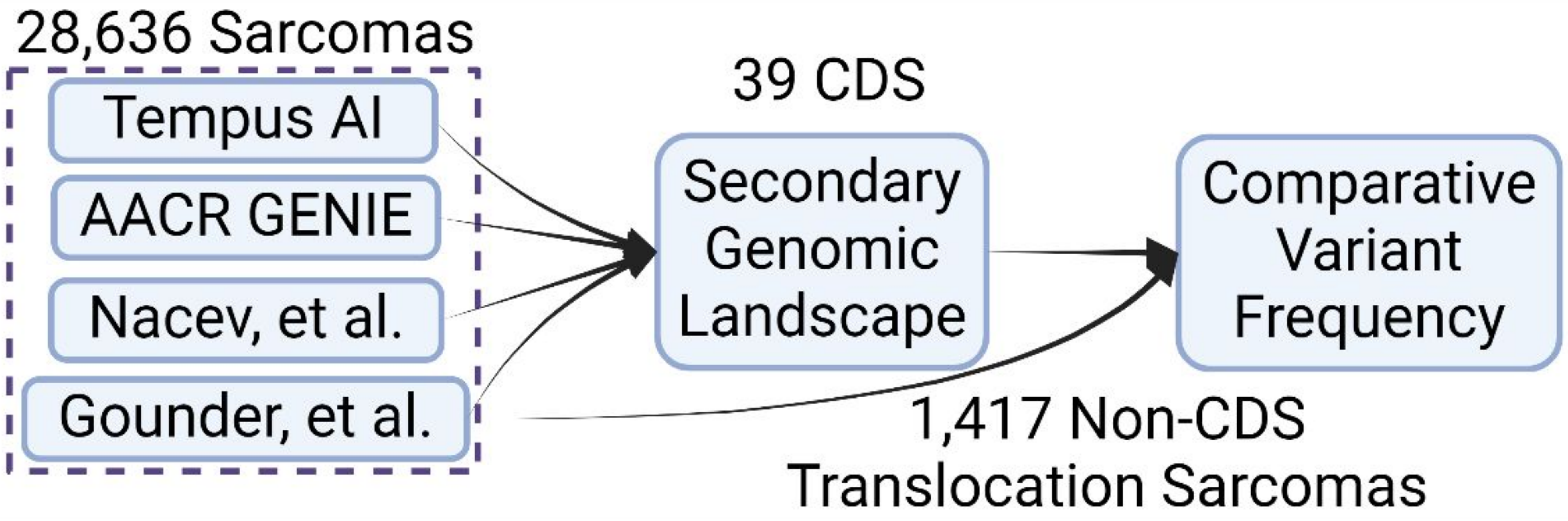
Common Secondary Genomic Variants Associated With Advanced Epithelioid Hemangioendothelioma

Nathan D Seligson[1], Achal Awasthi[2], Sherri Z Millis[3], Brian K Turpin[4], Christian F Meyer[5], Anne Grand'Maison[6], David A Liebner[2,7], John L Hays[7,8], James L Chen[2,7]

Genomic Landscape of CDS



Demographics (DNA Analysis)	
Age [Median (IQR)]; Years	28.5 (18.0-37.8)
≤18 Yeas	12 (30.8%)
Not Reported	2 (5.1%)
Sex	
Female	24 (61.5%)
Male	15 (38.5%)
Tumor Purity (Median [IQR])	51% [29.5-72.5%]
Not Reported	13 (33.3%)
Tumor Mutation Burden	
Median [IQR]; Mutations/Mb	0.8 [0.0-3.0]
Not Reported	19 (48.7%)
Microsatellite Status	
Stable	25 (79.5%)
Not Reported	8 (20.5%)
Sequencing Panel	
FoundationOne®/ FoundationOne® Heme	20 (51.2%)
Tempus xT	6 (15.4%)
MSK-IMPACT468	5 (12.8%)
MSK-IMPACT410	2 (5.1%)
UCSF-NIMV4-TO	3 (7.7%)
UCSF-NIMV4-TN	1 (2.6%)
CHOP-STNGS/FUSIP	1 (2.6%)
DFCI-ONCOPANEL-3	1 (2.6%)

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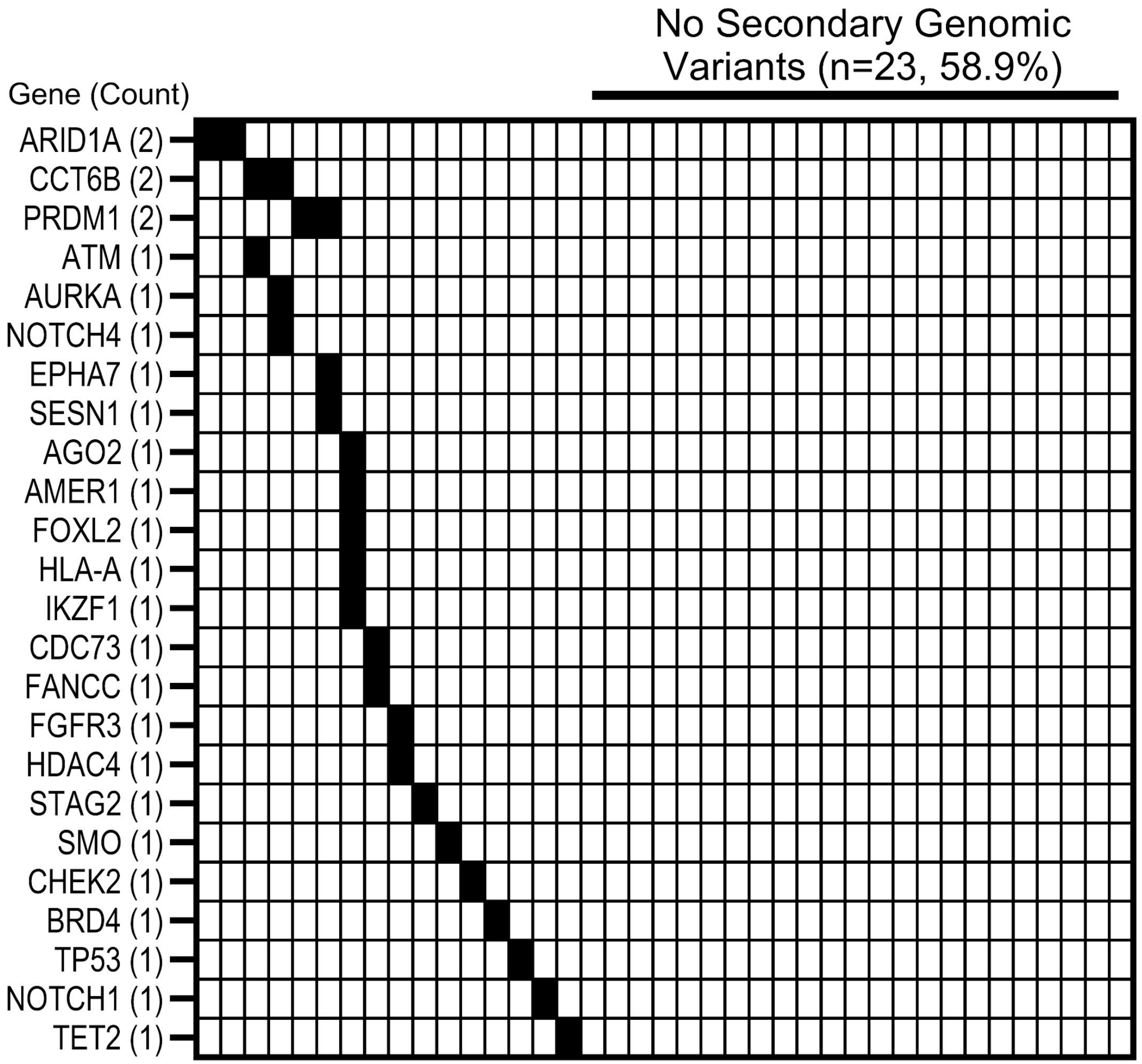
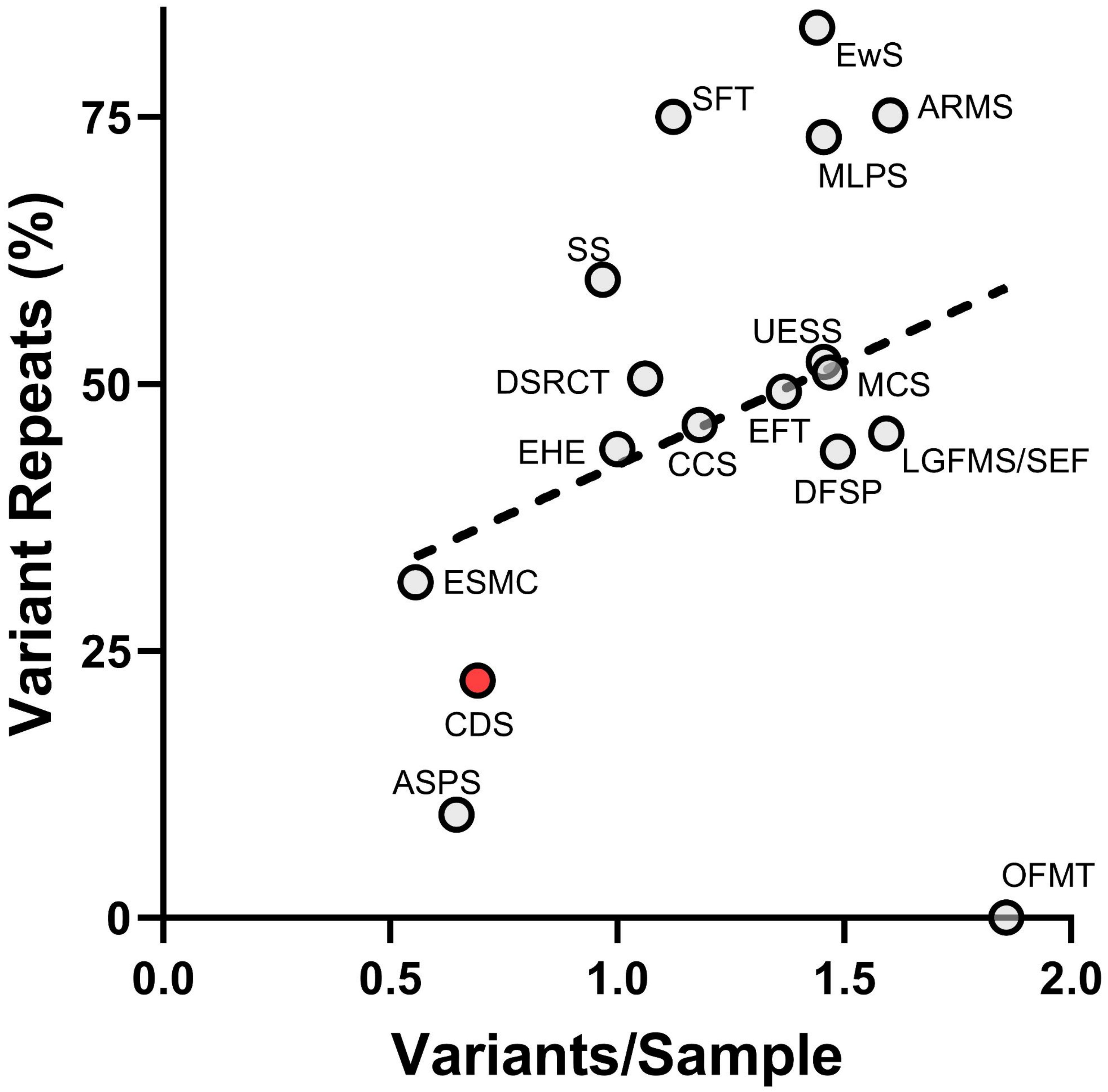
CDS Presents A “Quiet Genome”





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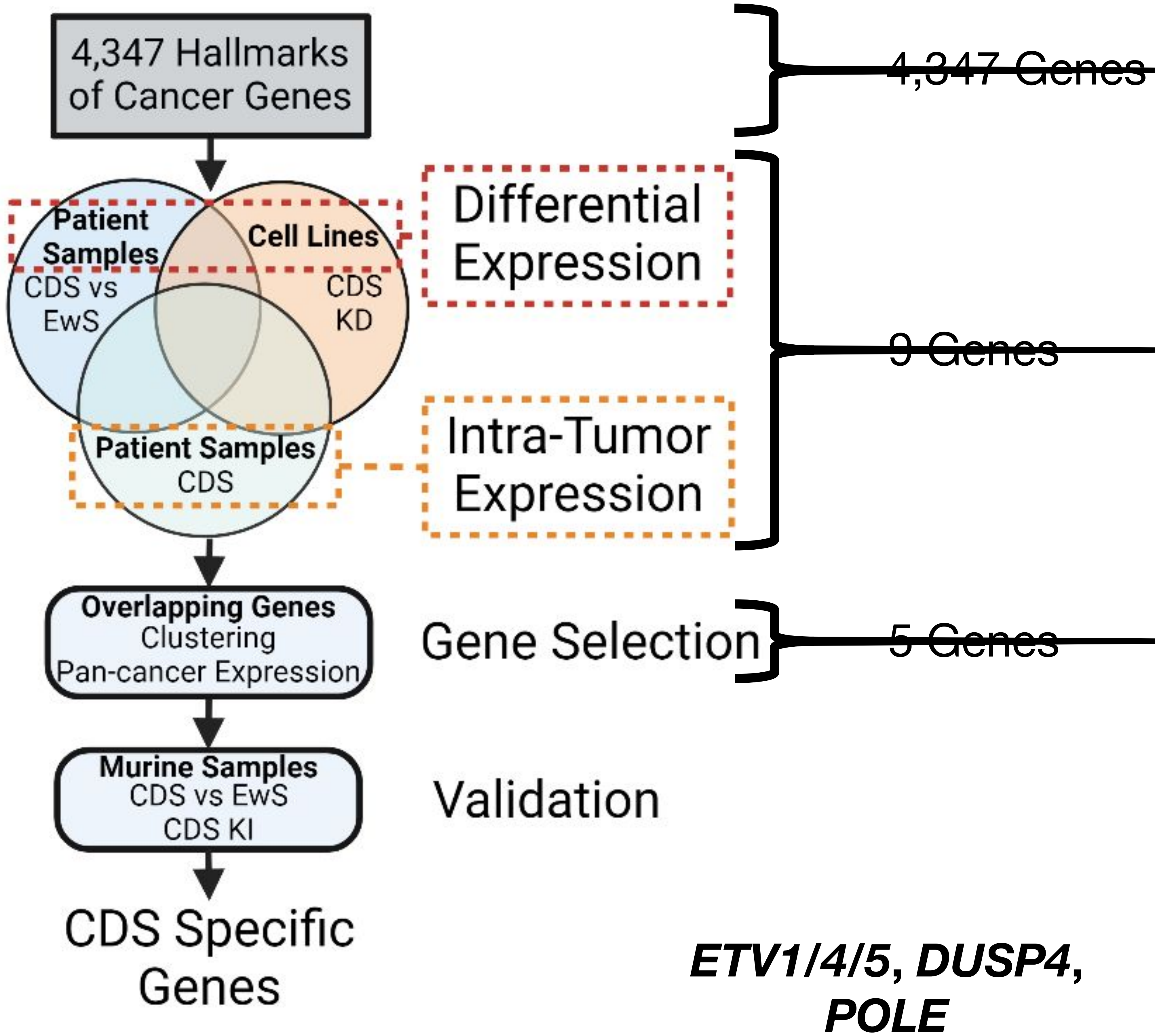
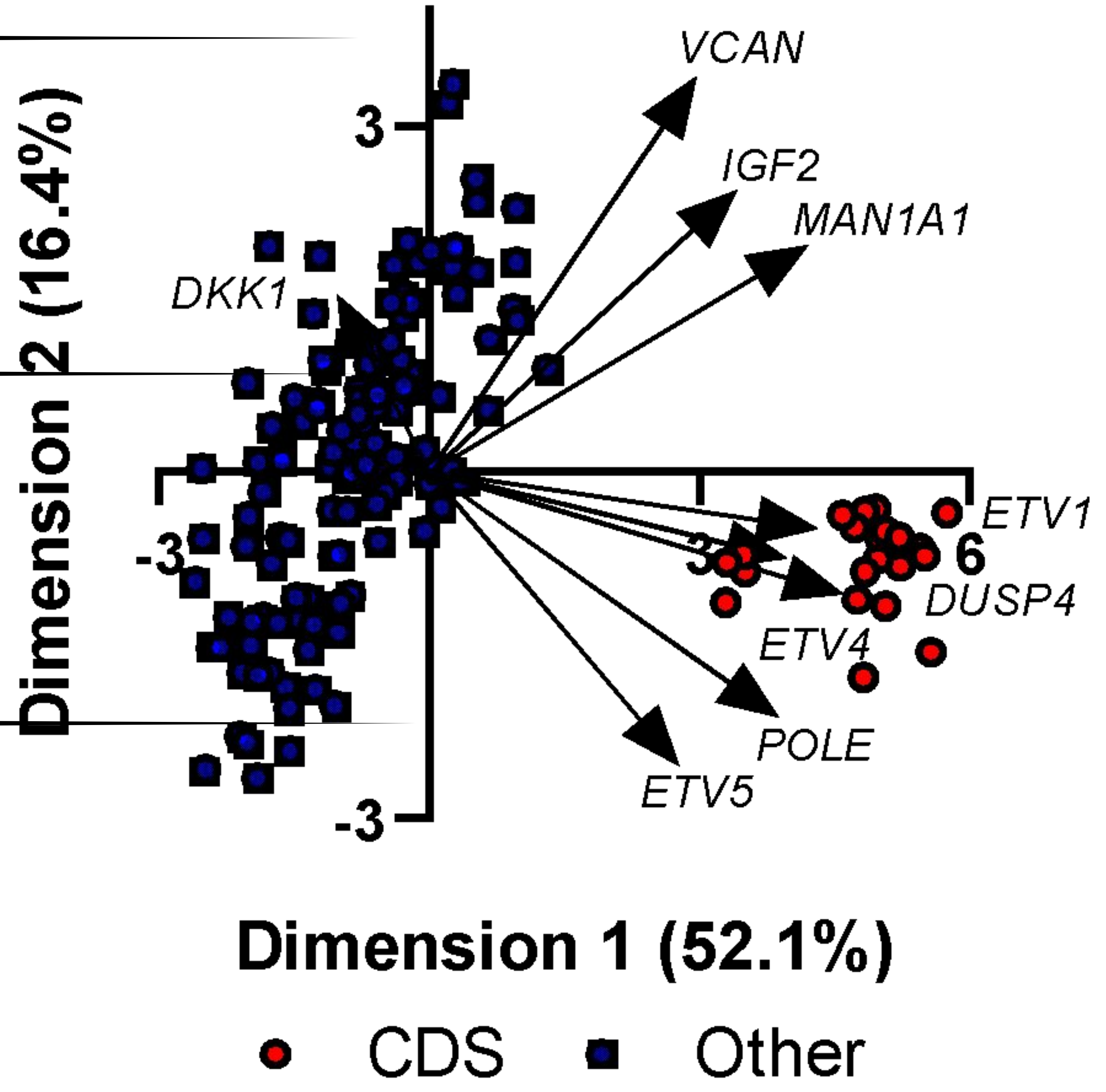
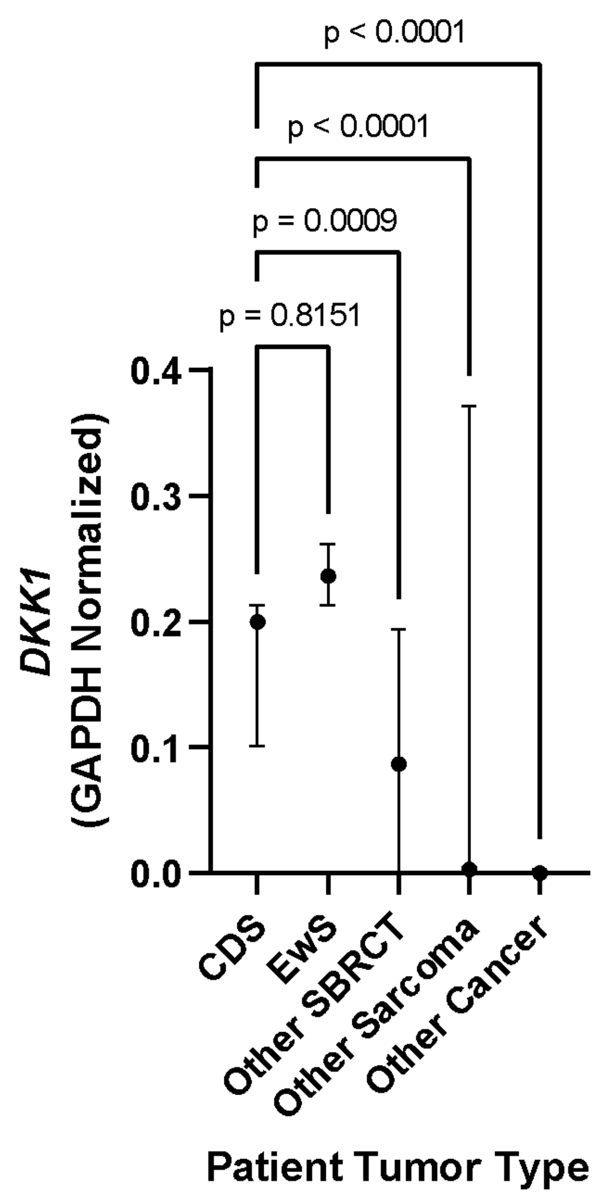
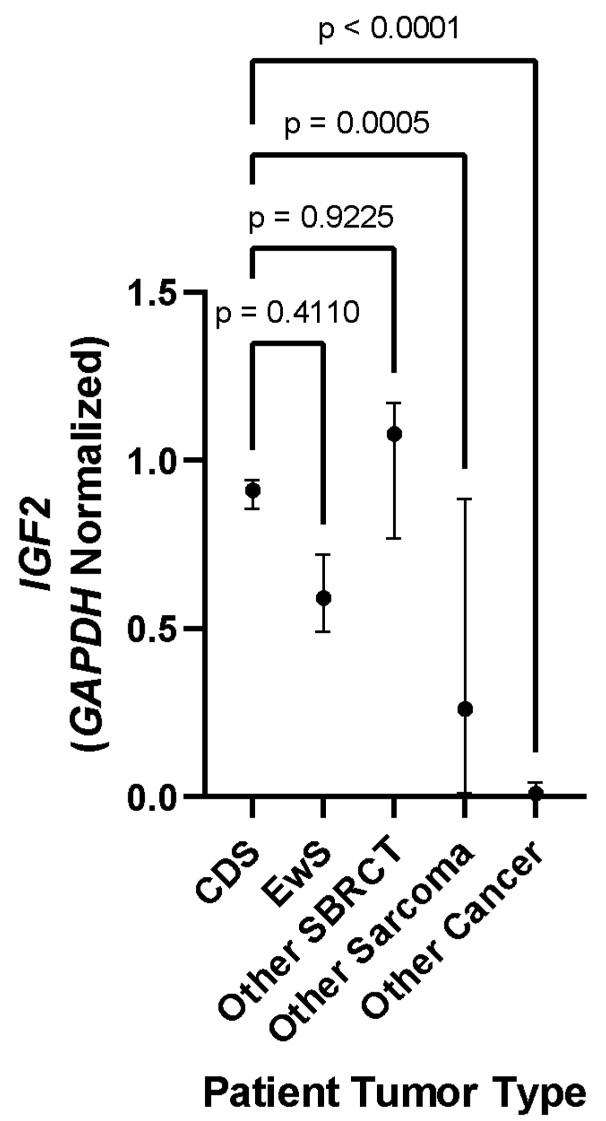
CDS Gene Signature Development



ETV1/4/5, DUSP4, POLE







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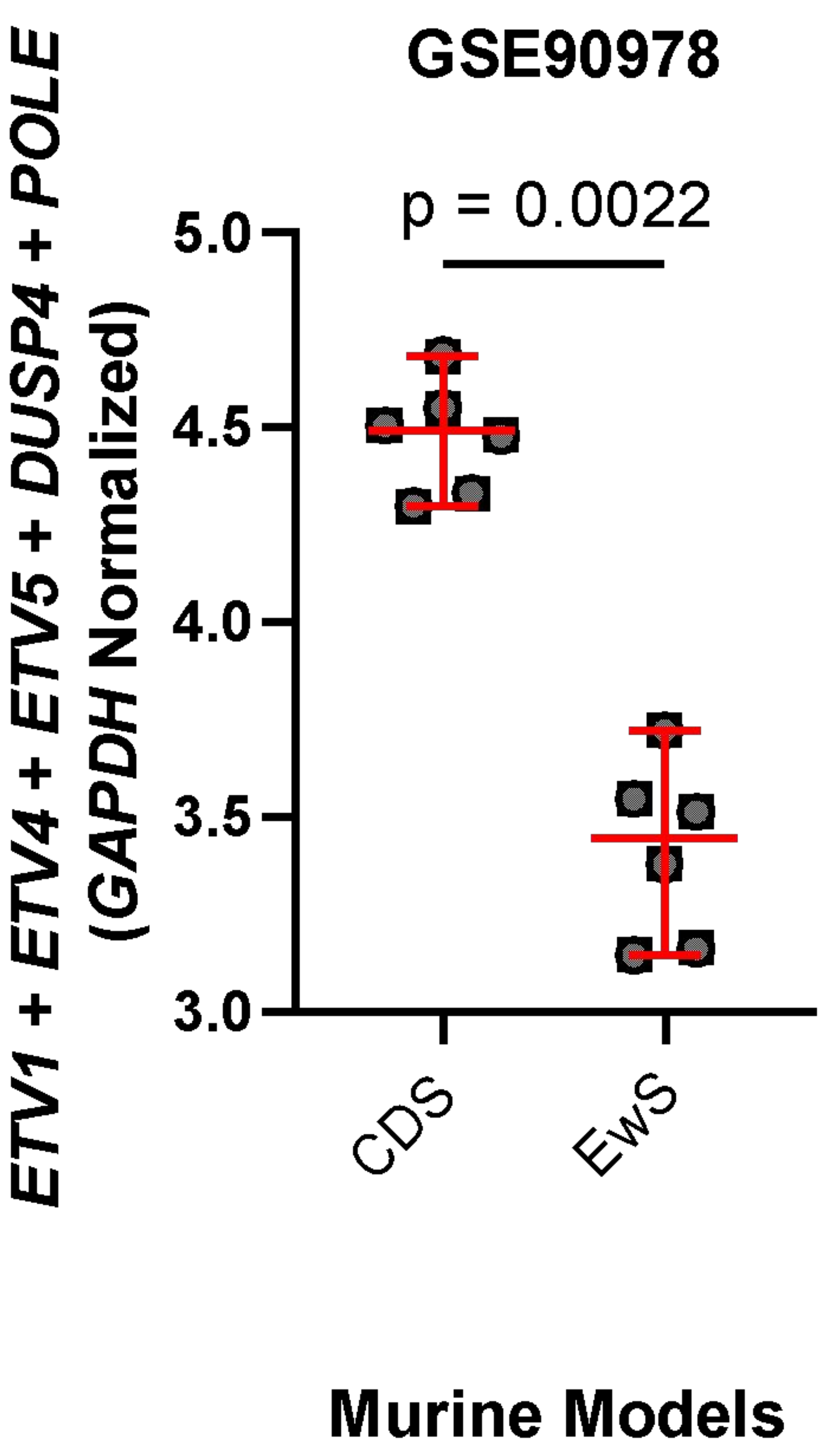
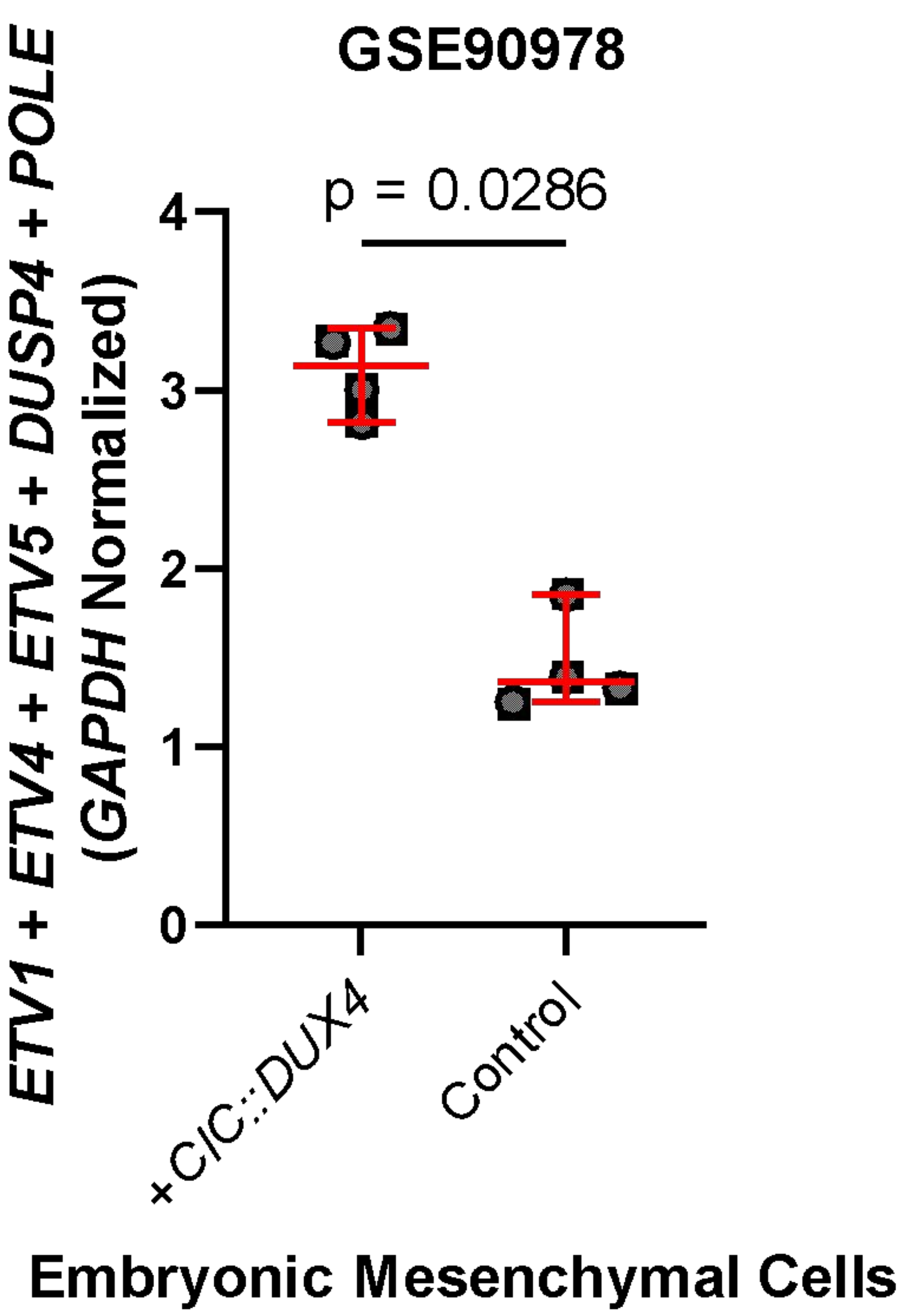
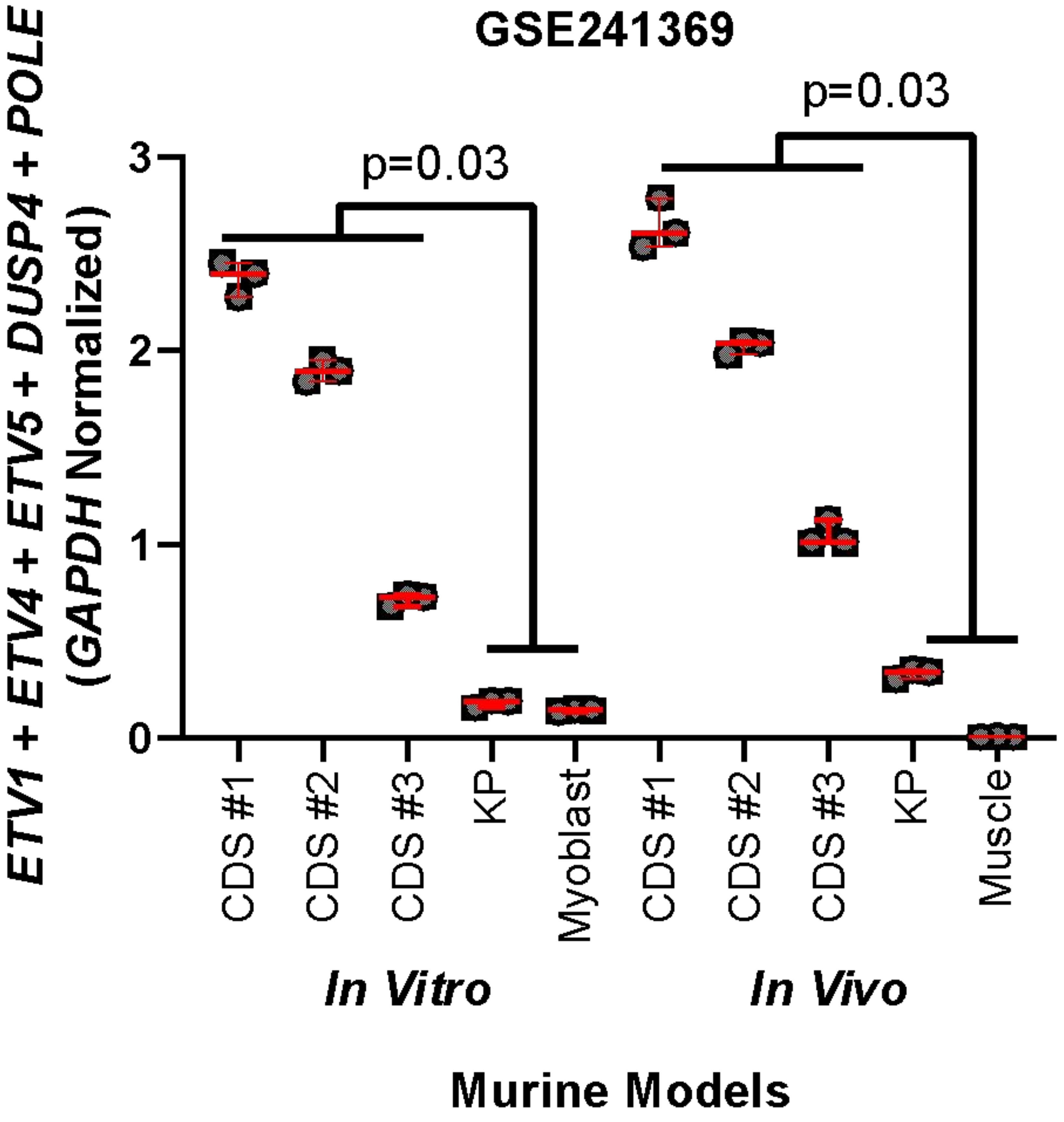
CDS Signature Validation







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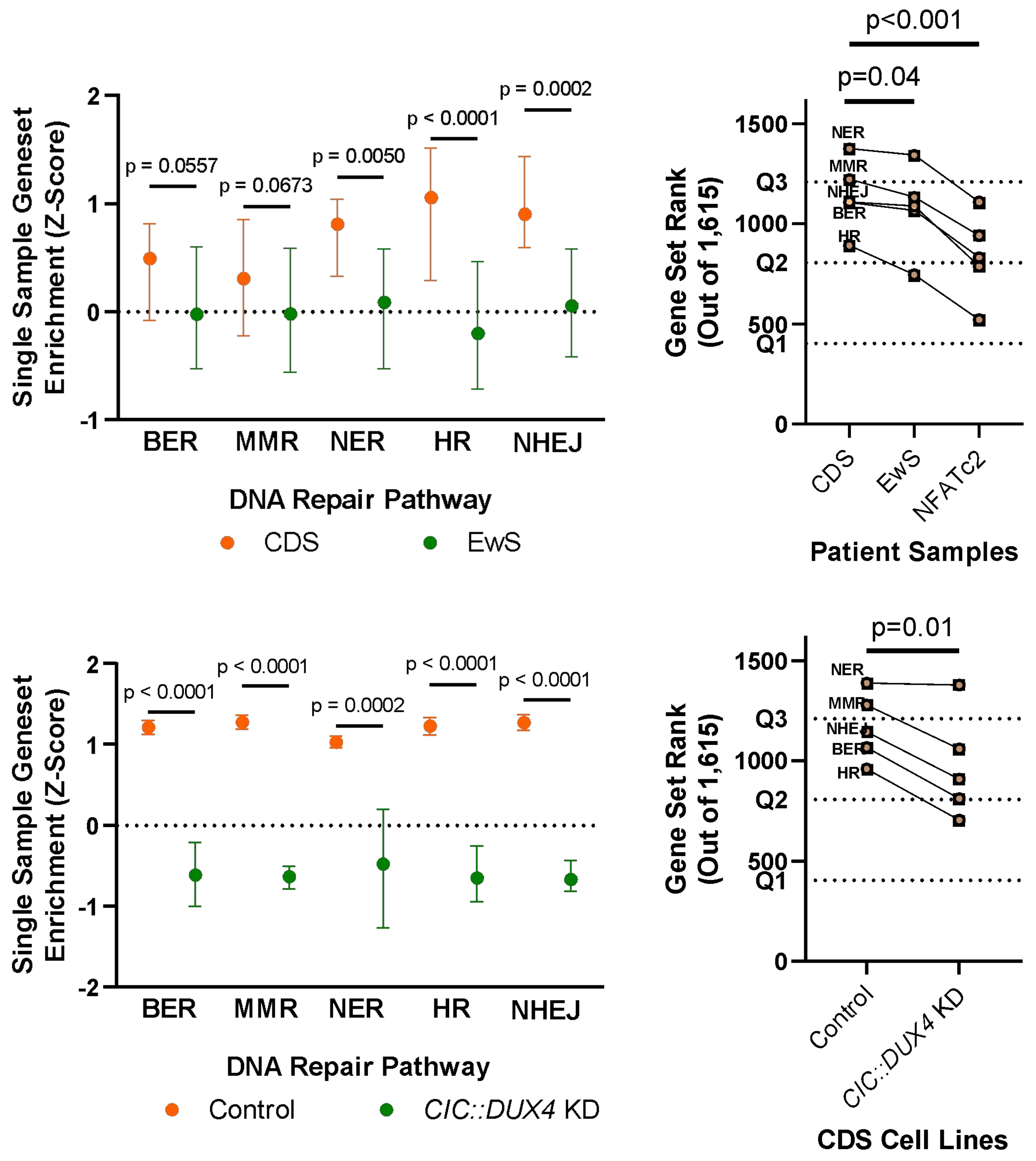
Global DNA Repair Upregulated in CDS

Elevated *POLE* expression has not yet been reported in CDS

POLE is associated with DNA repair
- Typically de-activated in cancer

Reactome database to test expression of DNA repair pathways in CDS



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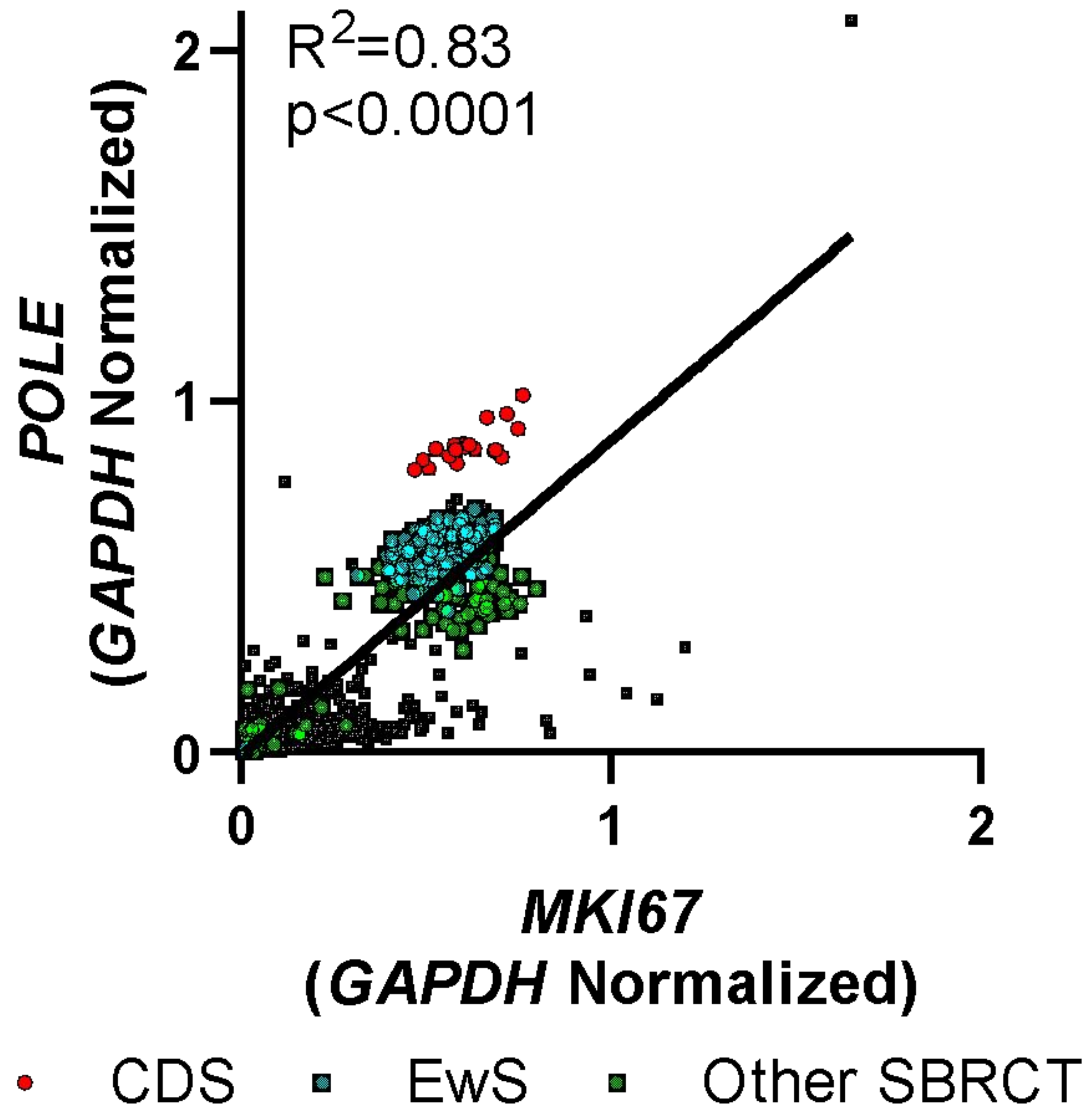
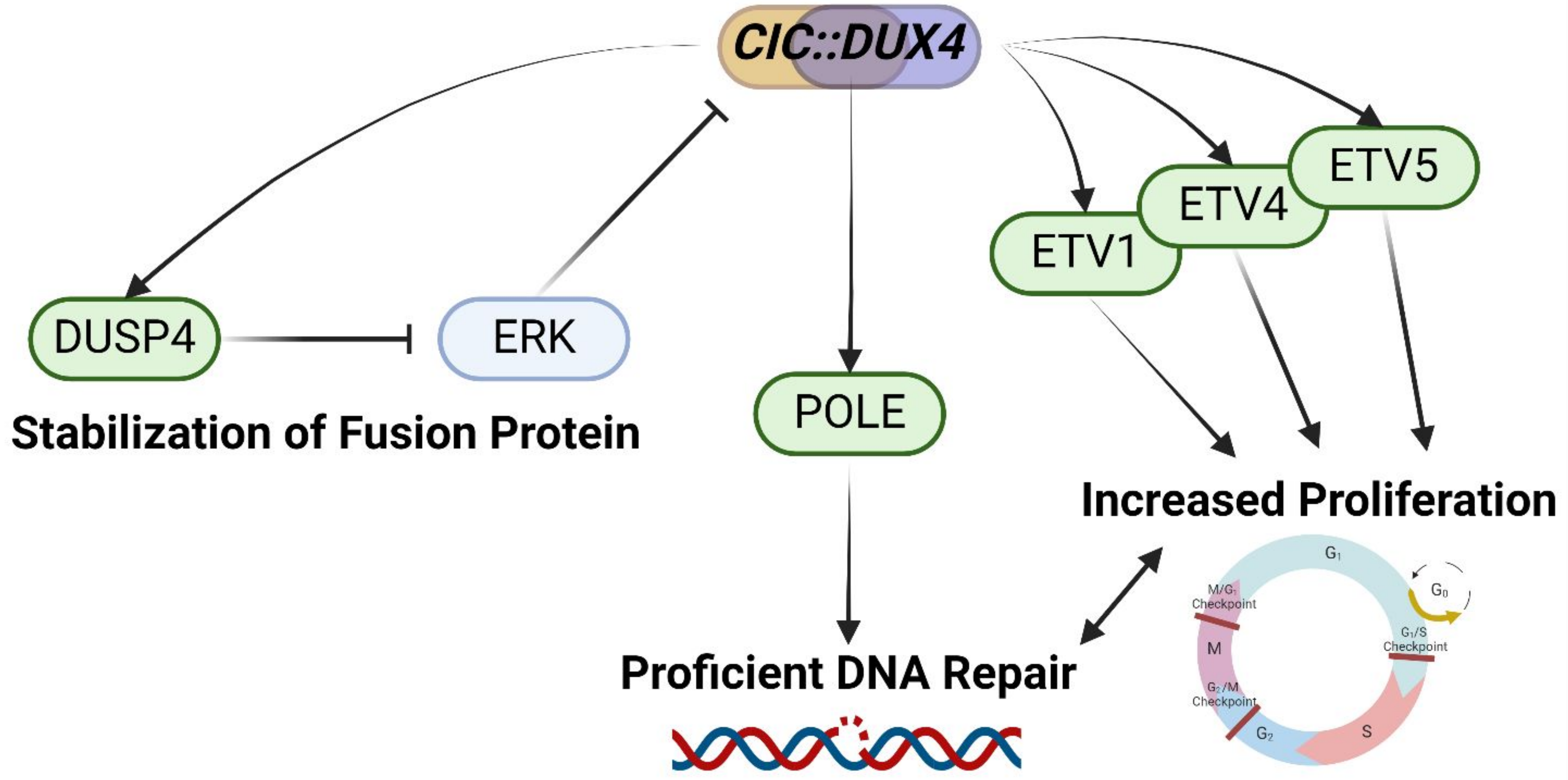
DNA Repair and Proliferation

Given the high proliferation rate of CDS we further investigated the correlation between *POLE* and cellular proliferation (*MKI67*)

- + correlation across cancers
- + correlation in CDS samples alone (r2=0.54, p=0.0002)



Conclusion



CIC::DUX4

DUSP4

ERK

POLE

ETV1

ETV4

ETV5

Stabilization of Fusion Protein

Increased Proliferation

Proficient DNA Repair

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Conclusion

CIC::*DUX4* sarcomas are molecularly distinct from other SBRCT

5-gene gene signature, including *POLE*, is strongly associated with the fusion

- *POLE* has heretofore not been reported in CDS
- Clear markers of proliferation are seen recapitulating prior work

Additional clinical studies are needed to confirm

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Thank You

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Feha Shahalam

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Derek's memory will live on.

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