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Review Article

PPM1D Truncation-associated Overexpression of the Stress-related Protein NQO1 Confers Sensitivity to the Bioactivatable Drug IB-DNQ in Diffuse Intrinsic Pontine Glioma

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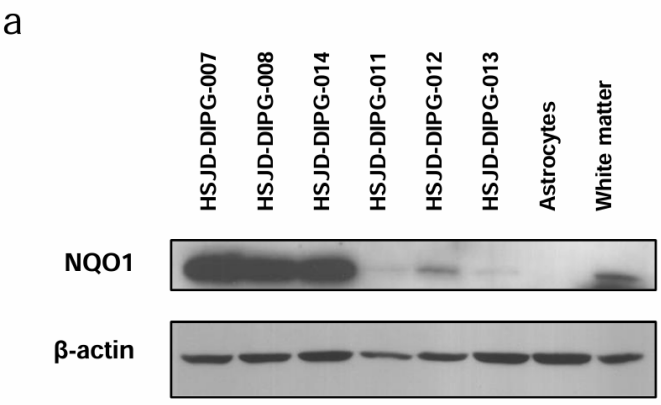
a



b

Target_ID	Location	HSJD-DIPG-007	HSJD-DIPG-008	HSJD-DIPG-014	HSJD-DIPG-011	HSJD-DIPG-012	SU-DIPG-VI
cg03786933	1stExon; 5'UTR	0,03	0,04	0,03	0,02	0,44	0,01
cg09516362		0,02	0,03	0,02	0,02	0,29	0,01
cg09430206		0,02	0,03	0,03	0,03	0,35	0,01
cg09361409		0,03	0,04	0,03	0,03	0,47	0,01

c

Target_ID	Location	HSJD-DIPG-007	HSJD-DIPG-008	HSJD-DIPG-014	HSJD-DIPG-011	HSJD-DIPG-012	SU-DIPG-VI
cg24198493	TSS200	0,48	0,14	0,55	0,17	0,53	0,69
cg00250988	TSS200	0,61	0,30	0,52	0,36	0,57	0,75

Supplementary Figure 1: Related to Figure 1. (a) Western blot of *NQO1* in 6 DIPG cell lines (containing HSJD-DIPG-013 but without SU-DIPG-VI) and normal human astrocytes or normal human white matter as controls. (b) DNA methylation profile of the CpG island promoter for the *NQO1* gene analysed by the EPIC DNA methylation microarray. Single CpG absolute methylation levels (0–1) are shown. Green, unmethylated; red, methylated. (c) DNA methylation profile of the CpG island promoter for the *NSUN5* gene.

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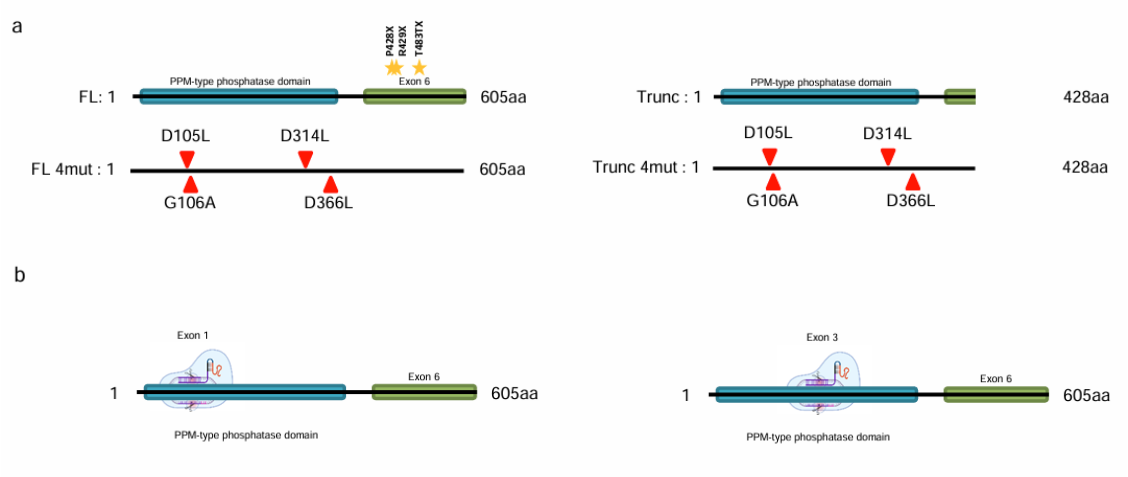

Supplementary Figure 2: Related to Figure 3. (a) Mutational constructs in *PPM1D* transcripts for the full length form (FL; left) or truncated (Trunc; right) that are wild type (up) or mutated (4mut; down). (b) Construction of the CRISPR-Cas9 *PPM1D* model in HSJD-DIPG-007 at exon 1 (left) or exon 3 (right).

Supplementary Table 1: Key resources table.

Reagent or Resource	Source	Identifier
Drugs		
Isobutyl-deoxynyboquinone	Dr. Paul Hergenrother	CAS# 1430798-22-3
GSK2830371	Selleckchem	Cat# S7573
Antibodies		
Mouse monoclonal anti-*NQO1*	Cell signaling	Cat# 3187
Rabbit monoclonal anti-*PPM1D*	Cell signaling	Cat# 11901
Mouse monoclonal anti-*PPM1D*	Santa Cruz	Cat# sc-376257
Rabbit polyclonal anti-p53	Cell signaling	Cat# 9282
Rabbit polyclonal anti-p-p53 (Ser 15)	Santa Cruz	Cat# sc-101762
Mouse polyclonal anti-MDM2	BD Biosciences	Cat# 556353
Rabbit polyclonal anti-p-MDM2 (Ser395)	ThermoFisher	Cat# PA5-13008
Monoclonal anti-β-Actin	Sigma	Cat# A3854
Oligonucleotides		
RT-PCR		
PPM1D Fd	CAACTGCCAGTGTGGTCATC	
PPM1D Rv	CGATTCACCCCAGACTTGTT	
NQO1 Fd	AAAGGACCCTTCCGGAGTAA	
NQO1 Rv	CCATCCTTCCAGGATTTGAA	
MDM2 Fd	TCAATCAGCAGGAATCATCG	
MDM2 Rv	GTGGCGTTTTCTTTGTCGTT	
TP53 Fd	TGAAGCTCCCAGAATGCCAG	
TP53 Rv	CAGTCAGAGCCAACCTCAGG	
GAPDH Fd	TGCACCACCAACTGCTTAGC	

GAPDH Rv	GGCATGGACTGTGGTCATGAG
Cloning	
NQO1 Cloning Fd	aaaaaaaaCTCGAGCCGCCACCATGGTCGGCAGAAGAGCACTGATCGTACTG
NQO1 Cloning Rv	aaaaaaaaGCGGCCGCTCATTTTCTAGCTTTGATCTGGTTGTCAGTTGGG
PPM1D Cloning Fd (fusion A also)	aaaaaaaaTCTAGAGCCGCCACCATGGCGGGGCTGTACTCGCTGGGAGTGAG
PPM1D Cloning FL Rv (fusion D also)	aaaaaaaaGCGGCCGCTCAGCAAACACAAACAGTTTTCCTGTGTTGATGAAGTA AAGGATTTCCAATTTTCTTC
PPM1D Cloning Trunc Rv (fusion D also)	aaaaaaaaGCGGCCGCTCATGGCCATGGATCCTCCTCCAGTGACTTGACTGGTG
PPM1D mut L105-A106 Rv fusion A	GCCGTGGGCCAGGCACACGGCGAAAAAGGCCACGGAGGAACGGCG
PPM1D mut L105-A106 Fd fusion B	GTGTGCCTGGCCCACGGCGGGCGGGAGGCGGCACAGTTTG
PPM1D mut L314 Rv fusion B	CATATTCCAAAGTCCCAGACTCCCCAATATAATATACTTGTGCTTCTGAGGGTC AAGAGTG
PPM1D mut L314 Fd fusion C	ATTATATTGGGGAGTCTGGGACTTTGGAATATGATTCCACCACAAGATGCCATC TCAATG
PPM1D mut L366 Rv fusion C	CACTAGTGTTCAGTGCTCGGAGCATACGCTGCCTCCAG
PPM1D mut L366 Fd fusion D	GTATGCTCCGAGCACTGAACACTAGTGCCATAGTAATCTGCATCTCTCCAGAAGTG
MDM2 Cloning Fd	aaaaaaaaGAATTCGCCGCCACCATGTGCAATACCAACATGTCTGTACCTACTGA
MDM2 Cloning Rv	aaaaaaaaGCGGCCGCTCAGGGGAAATAAGTTAGCACAATCATTTGA
MDM2 mut PCR Fd fusion	TTACACAAGCTTCACAATCACAAGAAAGTGAAGACTATGCTCAGCCATCAAC
MDM2 mut PCR Rv fusion	GGCTGCTATAAATAATGCTACTAGAAGTTGATGGCTGAGCATAGTCTTC
ShRNA	
NQO1 ShRNA 1 Fd	gatccGCGCAGACCTTGTGATATTCTTCAAGAGAGAATATCACA AGGTCTGCGTTTTTTACGCGTg
NQO1 ShRNA 1 Rv	aattcACGCGTAAAAAACGCAGACCTTGTGATATTCTCTCTTGAA GAATATCACAAGGTCTGCGCg
NQO1 ShRNA 2 Fd	gatccGCACTTACGCTGCCATGTATTTCAAGAGAATACATGGCA GCGTAAGTGTTTTTTACGCGTg
NQO1 ShRNA 2 Rv	aattcACGCGTAAAAAACACTTACGCTGCCATGTATTCTCTTGAA ATACATGGCAGCGTAAGTGCg
NQO1 ShRNA 3 Fd	gatccGTCCCAACTGACAACCAGATTTCAAGAGAATCTGGTTGT CAGTTGGGATTTTTTACGCGTg
NQO1 ShRNA 3 Rv	aattcACGCGTAAAAAATCCCAACTGACAACCAGATTCTCTTGA AATCTGGTTGTCAGTTGGGACg
NQO1 ShRNA 4 Fd	gatccGCCATGAACTTCAATCCCATTTCAAGAGAATGGGATTGA AGTTCATGGTTTTTTACGCGTg
NQO1 ShRNA 4 Rv	aattcACGCGTAAAAAACCATGAACTTCAATCCCATTCTCTTGAA ATGGGATTGAAGTTCATGGCg
CRISPR-Cas9 guides	
PPM1D S1	CACCGGACGTTACTCAAATCGTTG
PPM1D AS1	AAACCAACGATTTGAGTAACGTCC
PPM1D S2	CACCGTCGCTTGTCACCTTGCCATG
PPM1D AS2	AAACCATGGCAAGGTGACAAGCGAC