

SUPPLEMENTARY MATERIALS

Clinical Impact of Tumor Mutational Burden in Neuroblastoma

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AFFILIATIONS

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Supplementary Table 1. Characteristics of patients with neuroblastoma according to tumor mutational burden*

Characteristic	Overall† No. (%)	High Tumor Mutational Burden No. (%)	Low Tumor Mutational Burden No. (%)	P value‡
Total	515 (100.0)	107 (100.0)	408 (100.0)	--
Age, months				
<18	141 (27.4)	14 (13.1)	127 (31.1)	<0.001
≥18	374 (72.6)	93 (86.9)	281 (68.9)	
Sex				
Female	201 (39.0)	24 (41.4)	177 (44.2)	0.30
Male	257 (49.9)	34 (58.6)	223 (55.8)	
Unknown	57 (11.1)	--	--	
INSS stage at diagnosis	277 (53.8)	50 (46.7)	227 (55.6)	0.10
Stage 4	238 (46.2)	57 (53.3)	181 (44.4)	
Other				
Histology				
Favorable	106 (20.6)	0 (0)	106 (30.5)	0.04
Unfavorable	251 (48.7)	10 (100.0)	241 (69.5)	
Unknown	158 (30.7)	--	--	
MYCN amplification	359 (69.7)	73 (68.2)	286 (70.6)	0.64
Not amplified	153 (29.7)	34 (31.8)	119 (29.4)	
Amplified	3 (0.6)	--	--	
Unknown				
Mutation count		NA	NA	NA
0	192 (37.3)			
1	130 (25.2)			
2	57 (11.1)			
3	29 (5.6)			
4	16 (3.1)			
5	9 (1.7)			
6	12 (2.3)			
7	8 (1.6)			
>7	62 (12.0)			

* High tumor mutational burden was defined as >3 mutations and low tumor mutational burden was defined as ≤3 mutations. INSS = International Neuroblastoma Staging System; NA = not applicable.

† Of the 515 patients with mutational data, 372 were derived from the TARGET database, 87 from the Amsterdam cohort, and 56 from the German cohort.

‡ Fisher's exact test, two-sided.

Supplementary Table 2. Frequency of mutations in cancer-associated genes in the neuroblastoma cohort ($N = 515$).

Gene	No. of Patients	Frequency, %
<i>ALK</i>	11	2.14
<i>AR</i>	8	1.55
<i>NBPF1</i>	7	1.36
<i>LPP</i>	7	1.36
<i>NBPF10</i>	7	1.36
<i>ZNF717</i>	6	1.17
<i>MYCN</i>	5	0.97
<i>COL5A3</i>	5	0.97
<i>TET2</i>	5	0.97
<i>DNAH2</i>	5	0.97
<i>PTPN11</i>	5	0.97
<i>NF1</i>	5	0.97
<i>ANKRD30BL</i>	5	0.97
<i>NEB</i>	4	0.78
<i>RYR1</i>	4	0.78
<i>MYH1</i>	4	0.78
<i>COL6A3</i>	4	0.78
<i>USP6</i>	4	0.78
<i>TPR</i>	3	0.58
<i>AKAP9</i>	3	0.58
<i>TIAM1</i>	3	0.58
<i>MUC16</i>	3	0.58
<i>TAF1L</i>	3	0.58
<i>AHNAK2</i>	3	0.58
<i>DOCK3</i>	3	0.58
<i>MYH8</i>	3	0.58
<i>IL31RA</i>	3	0.58
<i>AXL</i>	3	0.58
<i>KMT5B</i>	3	0.58
<i>ASB5</i>	3	0.58
<i>CBFA2T2</i>	3	0.58
<i>CNTN5</i>	3	0.58
<i>CSPG4</i>	3	0.58
<i>ATM</i>	3	0.58
<i>ZNF462</i>	2	0.39
<i>FAT4</i>	2	0.39
<i>KMT2B</i>	2	0.39
<i>NALCN</i>	2	0.39

<i>ARHGAP10</i>	2	0.39
<i>PDE8B</i>	2	0.39
<i>WDR87</i>	2	0.39
<i>ARID2</i>	2	0.39
<i>FRMPD2</i>	2	0.39
<i>MITF</i>	2	0.39
<i>MKI67</i>	2	0.39
<i>DAG1</i>	2	0.39
<i>ATP13A5</i>	2	0.39
<i>TSC2</i>	2	0.39
<i>MYOM2</i>	2	0.39
<i>PRKDC</i>	2	0.39
<i>ARID1A</i>	2	0.39
<i>RFESD</i>	2	0.39
<i>DYSF</i>	2	0.39
<i>TMC3</i>	2	0.39
<i>DICER1</i>	2	0.39
<i>ANO8</i>	2	0.39
<i>FAN1</i>	2	0.39
<i>SOS1</i>	2	0.39
<i>LHCGR</i>	2	0.39
<i>GJA3</i>	2	0.39
<i>KRT10</i>	2	0.39
<i>MYH11</i>	2	0.39
<i>PDE6A</i>	2	0.39
<i>LATS2</i>	2	0.39
<i>ATN1</i>	2	0.39
<i>DSC2</i>	2	0.39
<i>MUC17</i>	2	0.39
<i>XIRP2</i>	2	0.39
<i>WWP1</i>	2	0.39
<i>PCDHB12</i>	2	0.39
<i>HGSNAT</i>	2	0.39
<i>GIGYF2</i>	2	0.39
<i>CASR</i>	2	0.39
<i>MLLT6</i>	2	0.39
<i>KDR</i>	2	0.39
<i>SNX21</i>	2	0.39
<i>ITGAE</i>	2	0.39
<i>TTN</i>	2	0.39
<i>NONO</i>	2	0.39
<i>TNXB</i>	2	0.39

<i>BAIAP2L2</i>	2	0.39
<i>TBP</i>	2	0.39
<i>CACNA1A</i>	2	0.39
<i>CACNA1B</i>	2	0.39
<i>USP34</i>	2	0.39
<i>RELN</i>	2	0.39
<i>COL12A1</i>	2	0.39
<i>EPHA6</i>	2	0.39
<i>EP400</i>	2	0.39
<i>DOCK8</i>	2	0.39
<i>TNC</i>	2	0.39
<i>PCLO</i>	2	0.39
<i>TPTE2</i>	2	0.39
<i>APC</i>	2	0.39
<i>KLK14</i>	2	0.39
<i>SIX1</i>	2	0.39
<i>PTPRT</i>	2	0.39
<i>KCNH4</i>	2	0.39
<i>ARFGEF3</i>	2	0.39
<i>MET</i>	2	0.39
<i>NCOR2</i>	2	0.39
<i>FAT1</i>	2	0.39
<i>ARID1B</i>	2	0.39
<i>PTPRC</i>	2	0.39
<i>TTC23</i>	2	0.39
<i>RLIM</i>	2	0.39
<i>NPAP1</i>	2	0.39
<i>RIPOR1</i>	2	0.39
<i>CARD11</i>	2	0.39
<i>KRTAP4-9</i>	2	0.39
<i>TDRD6</i>	2	0.39
<i>HERC1</i>	2	0.39
<i>STAG2</i>	2	0.39
<i>LRIF1</i>	2	0.39
<i>PLXNB1</i>	2	0.39
<i>ESCO2</i>	1	0.19
<i>PARP4</i>	1	0.19
<i>IGFNI</i>	1	0.19
<i>POGLUT1</i>	1	0.19
<i>EPPK1</i>	1	0.19
<i>POLE</i>	1	0.19
<i>ARHGAP26</i>	1	0.19

<i>ROR2</i>	1	0.19
<i>NUP98</i>	1	0.19
<i>FRS2</i>	1	0.19
<i>LRP5</i>	1	0.19
<i>NBN</i>	1	0.19
<i>IRS1</i>	1	0.19
<i>IDH1</i>	1	0.19
<i>CLP1</i>	1	0.19
<i>LRP1B</i>	1	0.19
<i>CIC</i>	1	0.19
<i>DKK2</i>	1	0.19
<i>NOTCH4</i>	1	0.19
<i>SMAD3</i>	1	0.19
<i>EPHA5</i>	1	0.19
<i>BLM</i>	1	0.19
<i>FANCE</i>	1	0.19
<i>CDKN1B</i>	1	0.19
<i>NPM1</i>	1	0.19
<i>ZNF750</i>	1	0.19
<i>NCOA3</i>	1	0.19
<i>MAP2K4</i>	1	0.19
<i>KMT2D</i>	1	0.19
<i>UBXN11</i>	1	0.19
<i>PBRM1</i>	1	0.19
<i>NRAS</i>	1	0.19
<i>ATRX</i>	1	0.19
<i>UHRF1BP1L</i>	1	0.19
<i>RASGRF1</i>	1	0.19
<i>SYNE1</i>	1	0.19
<i>ESR1</i>	1	0.19
<i>DUSP2</i>	1	0.19
<i>TLL2</i>	1	0.19
<i>IL21R</i>	1	0.19
<i>TET1</i>	1	0.19
<i>WRN</i>	1	0.19
<i>IRF8</i>	1	0.19
<i>TPRX1</i>	1	0.19
<i>ZNF727</i>	1	0.19
<i>KMT2A</i>	1	0.19
<i>RNF213</i>	1	0.19
<i>ZFHX3</i>	1	0.19
<i>ROS1</i>	1	0.19

<i>BTLA</i>	1	0.19
<i>GRIN2A</i>	1	0.19
<i>MSH1</i>	1	0.19
<i>IDH2</i>	1	0.19
<i>ACVR1B</i>	1	0.19
<i>CAMTA1</i>	1	0.19
<i>DOT1L</i>	1	0.19
<i>LCPI</i>	1	0.19
<i>KRTAP5-7</i>	1	0.19
<i>NOTCH2</i>	1	0.19
<i>RPL11</i>	1	0.19
<i>PGR</i>	1	0.19
<i>RRAGC</i>	1	0.19
<i>EPHA3</i>	1	0.19
<i>KNL1</i>	1	0.19
<i>AGAP2</i>	1	0.19
<i>CREB3L2</i>	1	0.19
<i>PRDM1</i>	1	0.19
<i>MAPKAP1</i>	1	0.19
<i>FLT4</i>	1	0.19
<i>AMER1</i>	1	0.19
<i>STAG1</i>	1	0.19
<i>AFF3</i>	1	0.19
<i>NUMA1</i>	1	0.19
<i>LILRA6</i>	1	0.19
<i>RUNX1</i>	1	0.19
<i>RUNXIT1</i>	1	0.19
<i>PTEN</i>	1	0.19
<i>BCOR</i>	1	0.19
<i>CBFB</i>	1	0.19
<i>FANCM</i>	1	0.19
<i>TRRAP</i>	1	0.19
<i>NLRP3</i>	1	0.19
<i>STAT6</i>	1	0.19
<i>HELB</i>	1	0.19
<i>RAD50</i>	1	0.19
<i>NEFH</i>	1	0.19
<i>PASK</i>	1	0.19
<i>KMT2C</i>	1	0.19
<i>PPP3R1</i>	1	0.19
<i>NF2</i>	1	0.19
<i>EGFR</i>	1	0.19

<i>MLLT1</i>	1	0.19
<i>MLLT3</i>	1	0.19
<i>ELF4</i>	1	0.19
<i>ASXL2</i>	1	0.19
<i>PC</i>	1	0.19
<i>EP300</i>	1	0.19
<i>TP53</i>	1	0.19
<i>LILRA4</i>	1	0.19

Supplementary Table 3. Characteristics of patients with mutation data compared to those without mutation data available.

Characteristic	Mutation Data No. (%)	No Mutation Data No. (%)	<i>P</i> value*
Total	515 (100.0)	704 (100.0)	
Age, months			
<18	141 (27.4)	168 (23.9)	0.16
≥18	374 (72.6)	536 (76.1)	
Sex			
Female	201 (39.0)	298 (42.3)	0.60
Male	257 (49.9)	406 (57.7)	
Unknown	57 (11.1)		
INSS stage at diagnosis			
Stage 4	277 (53.8)	550 (78.1)	<0.001
Other	238 (46.2)	152 (21.6)	
Unknown		2 (0.3)	
Histology			
Favorable	106 (20.6)	169 (24.0)	0.31
Unfavorable	251 (48.7)	464 (65.9)	
Unknown	158 (30.7)	71 (10.1)	
MYCN amplification			
Not amplified	359 (69.7)	509 (72.3)	0.18
Amplified	153 (29.7)	182 (25.9)	
Unknown	3 (0.6)	13 (1.8)	

* Fisher's exact test, two-sided.

INSS = International Neuroblastoma Staging System.