Supplementary Information

Targeted Next Generation Sequencing (NGS) Variant Annotation

Manual review and annotation were performed for all single-nucleotide variants, copy-number variations, and translocation calls made by the bioinformatics pipeline. Variants that were previously reported as single-nucleotide polymorphisms in gnomAD were excluded as likely germline variants. Variants were classified as pathogenic if one or more of the following conditions were met: (1) reported in COSMIC as a recurrent event, (2) reported in OncoKB as at least likely oncogenic, (3) compelling evidence of biological effect in the literature. The remaining variants were classified as variants of uncertain significance. The following copynumber alterations were classified as pathogenic: amplifications, homozygous deletions, concurrent copy-number gain/loss and pathogenic mutation involving the same gene (e.g., loss of heterozygosity, amplification of allele bearing an activating mutation) and copy gains or losses of oncogenes/tumor-suppressor genes that are shared across the cohort (>20% of cases).

Supplementary Tables

Table S1: List of all single nucleotide variants/indels detected. SNV: single nucleotide variant; VAF: variant allele fraction; LPV: likely pathogenic variant; VUS: variant of uncertain significance.

Table S2: List of all copy number variants detected. LPV: likely pathogenic variant; VUS: variant of uncertain significance.

Table S3: List of all structural variants detected. LPV: likely pathogenic variant; VUS: variant of uncertain significance.

Table S4: List of all genes covered in targeted next generation sequencing panel (Oncopanel POPv3; 447 genes).

Table S5: TMA and whole tissue section immunohistochemical staining results.

Supplementary Figures

Figure S1: Representative images of *NOTCH2* mutated SMZL stained for NICD2 and total NOTCH2.

Figure S2: Representative images of patient derived xenograft models of triple negative breast cancer stained for total NOTCH1.

Figure S3: Histogram showing *NOTCH2* exon 34 RNA-seq coverage across the DLBCL cohort.

Figure S4: Representative images of *NOTCH2* mutated DLBCL stained for BLC6, NICD2, and total NOTCH2

Table S1: Detected single nucleotide variants and indels, SMZL

Case	Gene	SNV	VAF	Fold Coverage	Variant classification	LPV/VUS
1	*NOTCH2*	c.6967C>T (p.Q2323*), exon 34	4%	149	Nonsense mutation	LPV
1	*KLF2*	c.862C>T (p.H288Y), exon 2	10%	190	Missense mutation	LPV
1	*ABCB11*	c.3524A>C (p.K1175T), exon 26	50%	59	Missense mutation	VUS
1	*BLM*	c.232C>T (p.P78S), exon 3	42%	56	Missense mutation	VUS
1	*BUB1B*	c.1261C>T (p.R421W), exon 9	38%	26	Missense mutation	VUS
1	*CYLD*	c.913+5G>T ()	53%	39	Intronic mutation	VUS
1	*NEIL3*	c.1379T>G (p.F460C), exon 8	41%	53	Missense mutation	VUS
1	*VEGFA*	c.88C>G (p.R30G), exon 1	52%	36	Missense mutation	VUS
2	*NOTCH2*	c.7090C>T (p.Q2364*), exon 34	30%	130	Nonsense mutation	LPV
2	*ARID1A*	c.2757_2758insC (p.Q920Pfs*16), exon 9	31%	125	Frameshift mutation	LPV
2	*NFKBIE*	c.759_762delTTAC (p.Y254Sfs*13), exon 1	45%	217	Frameshift mutation	LPV
2	*ALK*	c.661G>C (p.G221R), exon 1	43%	105	Missense mutation	VUS
2	*C1orf86*	c.273G>A (p.P91P), exon 3	48%	125	Missense mutation	VUS
2	*DOCK8*	c.3010C>T (p.R1004W), exon 25	43%	79	Missense mutation	VUS
2	*MGA*	c.7861C>A (p.P2621T), exon 23	47%	76	Missense mutation	VUS
3	*NFKBIE*	c.782+1G>C ()	30%	152	Splice site mutation	LPV
3	*ARID1B*	c.2765A>T (p.Q922L), exon 9	50%	322	Missense mutation	VUS

3	*BRD4*	c.3404A>G (p.K1135R), exon 16	45%	221	Missense mutation	VUS
3	*CD274*	c.454G>T (p.E152*), exon 4	73%	163	Nonsense mutation	VUS
3	*CTNNA1*	c.665A>G (p.Y222C), exon 6	41%	203	Missense mutation	VUS
3	*KDM5A*	c.3472A>G (p.I1158V), exon 23	52%	273	Missense mutation	VUS
3	*MAFB*	c.539C>T (p.A180V), exon 1	22%	149	Missense mutation	VUS
3	*MGA*	c.2207C>T (p.S736L), exon 6	42%	90	Missense mutation	VUS
3	*MSH6*	c.67G>C (p.A23P), exon 1	42%	235	Missense mutation	VUS
3	*NOTCH3*	c.1379-5C>T ()	58%	252	Intronic mutation	VUS
3	*PRKDC*	c.8578A>G (p.I2860V), exon 64	53%	134	Missense mutation	VUS
3	*RPTOR*	c.3964G>A (p.D1322N), exon 34	46%	238	Missense mutation	VUS
4	*NOTCH2*	c.7165C>T (p.Q2389*), exon 34	22%	666	Nonsense mutation	LPV
4	*MYD88*	c.10_28delGACCGCGC TGAGGCTCCAG (p.A6Pfs*39), exon 1	27%	339	Frameshift mutation	VUS
4	*BRIP1*	c.2905+67T>C ()	47%	165	Intronic mutation	VUS
4	*ERBB3*	c.234+6T>G ()	18%	553	Intronic mutation	VUS
4	*MLH3*	c.3608T>C (p.L1203S), exon 6	47%	491	Missense mutation	VUS
4	*PALB2*	c.48+814G>T ()	46%	294	Intronic mutation	VUS
4	*SH2B3*	c.1058A>G (p.Q353R), exon 6	46%	546	Missense mutation	VUS
4	*TOPBP1*	c.4388G>A (p.C1463Y), exon 27	53%	569	Missense mutation	VUS
4	*WHSC1*	c.928-6T>C ()	20%	210	Intronic mutation	VUS

4	*ZNF217*	c.1795_1796delAC (p.T599Sfs*5), exon 3	39%	895	Frameshift mutation	VUS
5	*TRAF3*	c.772C>T (p.Q258*), exon 8	6%	532	Nonsense mutation	LPV
5	*TRAF3*	c.1387G>A (p.D463N), exon 11	7%	759	Missense mutation	LPV
5	*TNFAIP3*	c.1681C>T (p.Q561*), exon 7	5%	759	Nonsense mutation	LPV
5	*FGFR4*	c.1305C>T (p.G435G), exon 10	48%	587	Missense mutation	VUS
5	*HABP2*	c.1556G>T (p.G519V), exon 13	3%	472	Missense mutation	VUS
5	*NFKBIZ*	c.835C>G (p.Q279E), exon 5	15%	680	Missense mutation	VUS
5	*NOTCH1*	c.301C>T (p.P101S), exon 3	13%	554	Missense mutation	VUS
5	*PMS2*	c.857A>G (p.D286G), exon 8	49%	513	Missense mutation	VUS
5	*RHOH*	c.46G>A (p.G16R), exon 3	2%	548	Missense mutation	VUS
5	*SLC25A13*	c.2026T>C (p.*676Qext*16), exon 18	52%	423	Nonstop extension mutation	VUS
5	*SOX9*	c.1105C>G (p.Q369E), exon 3	43%	137	Missense mutation	VUS
5	*TCF3*	c.1586+75G>A ()	49%	448	Intronic mutation	VUS
5	*TOPBP1*	c.4173+4T>C ()	49%	302	Intronic mutation	VUS
5	*TRAF7*	c.1121T>C (p.M374T), exon 12	48%	291	Missense mutation	VUS
6	*CD79B*	c.552+1G>A ()	13%	581	Splice site mutation	LPV
6	*GATA4*	c.19A>C (p.M7L), exon 2	43%	147	Missense mutation	VUS
7	*KMT2D*	c.15648T>G (p.Y5216*), exon 48	30%	608	Nonsense mutation	LPV
7	*B2M*	c.37_38delCT (p.L15Ffs*41), exon 1	25%	907	Frameshift mutation	LPV

7	*NFKBIE*	c.759_762delTTAC (p.Y254Sfs*13), exon 1	22%	499	Frameshift mutation	LPV
7	*RAD50*	c.3792_3799delTCTG GTAA (p.L1265Hfs*3), exon 25	21%	461	Frameshift mutation	LPV
7	*KAT6B*	c.2373+7G>A ()	50%	277	Intronic mutation	VUS
7	*MAX*	c.172-5C>A ()	44%	314	Intronic mutation	VUS
7	*PML*	c.1710+1396C>T ()	47%	455	Intronic mutation	VUS
7	*TNFAIP3*	c.586A>G (p.I196V), exon 4	36%	352	Missense mutation	VUS
8	*NOTCH1*	c.7183C>T (p.Q2395*), exon 34	16%	225	Nonsense mutation	LPV
8	*TRAF3*	c.212_213insCTT (p.R71_F72insF), exon 2	16%	361	Insertion (1AA) mutation	LPV
8	*DIS3L2*	c.2497-159G>A ()	48%	221	Intronic mutation	VUS
8	*HABP2*	c.365G>T (p.R122L), exon 5	48%	191	Missense mutation	VUS
8	*IDH2*	c.576C>A (p.F192L), exon 5	48%	252	Missense mutation	VUS
8	*LMO1*	c.28G>A (p.V10M), exon 2	43%	136	Missense mutation	VUS
8	*MAP2K2*	c.1142G>C (p.G381A), exon 11	44%	177	Missense mutation	VUS
8	*PBRM1*	c.2932G>A (p.V978I), exon 18	51%	161	Missense mutation	VUS
8	*PHOX2B*	c.29A>C (p.N10T), exon 1	22%	154	Missense mutation	VUS
9	*TP53*	c.576G>T (p.Q192H), exon 6	70%	167	Missense mutation	LPV
9	*TP53*	c.577C>T (p.H193Y), exon 6	68%	169	Missense mutation	LPV
9	*PIM1*	c.549G>C (p.K183N), exon 4	40%	377	Missense mutation	VUS
9	*POT1*	c.1781_1782delGA (p.G594Dfs*4), exon 18	50%	142	Frameshift mutation	LPV

9	*AR*	c.1885+8556G>A ()	47%	182	Intronic mutation	VUS
9	*CALR*	c.1139A>G (p.E380G), exon 9	45%	127	Missense mutation	VUS
9	*CCND3*	c.850C>T (p.P284S), exon 5	46%	396	Missense mutation	VUS
9	*CYLD*	c.725A>G (p.E242G), exon 3	46%	175	Missense mutation	VUS
9	*FANCD2*	c.3963+8C>T ()	44%	125	Intronic mutation	VUS
9	*JAK3*	c.2805+1G>C ()	37%	285	Splice site mutation	VUS
9	*KDM5A*	c.1653+8T>G ()	33%	311	Intronic mutation	VUS
9	*MAP2K2*	c.937C>T (p.R313W)	46%	392	Missense mutation	VUS
9	*NEIL2*	c.790G>A (p.V264M), exon 6	50%	384	Missense mutation	VUS
9	*RAD52*	c.980A>C (p.D327A), exon 11	37%	312	Missense mutation	VUS
9	*VHL*	c.154G>A (p.E52K), exon 1	51%	141	Missense mutation	VUS
10	*NOTCH2*	c.7090C>T (p.Q2364*), exon 34	19%	146	Nonsense mutation	LPV
10	*TP53*	c.406C>T (p.Q136*), exon 5	19%	177	Nonsense mutation	LPV
10	*TP53*	c.569C>T (p.P190L), exon 6	40%	108	Missense mutation	LPV
10	*MYC*	c.221C>T (p.P74L), exon 2	30%	151	Missense mutation	LPV
10	*BCOR*	c.86+8C>G ()	44%	125	Intronic mutation	VUS
10	*CIC*	c.101C>T (p.A34V), exon 2	46%	173	Missense mutation	VUS
10	*NR0B1*	c.1054G>T (p.V352L), exon 1	32%	151	Missense mutation	VUS
10	*TAL1*	c.262G>A (p.V88M), exon 3	53%	13	Missense mutation	VUS
10	*TOPBP1*	c.3304G>A (p.A1102T), exon 20	40%	132	Missense mutation	VUS

11	*NOTCH2*	c.7198C>T (p.R2400*), exon 34	25%	488	Nonsense mutation	LPV
11	*TP53*	c.314G>C (p.G105A), exon 4	2%	390	Missense mutation	LPV
11	*CTNNB1*	c.1161T>A (p.N387K), exon 9	17%	440	Missense mutation	LPV
11	*FAS*	c.847C>A (p.Q283K), exon 9	16%	289	Missense mutation	LPV
11	*ARID1A*	c.4717C>T (p.Q1573*), exon 18	23%	278	Nonsense mutation	LPV
11	*KMT2D*	c.7104delC (p.R2370Afs*14), exon 31	21%	594	Frameshift mutation	LPV
11	*ABCB11*	c.1460G>T (p.R487L), exon 14	18%	259	Missense mutation	VUS
11	*FANCA*	c.1360G>T (p.A454S), exon 15	49%	381	Missense mutation	VUS
11	*IKZF1*	c.640A>C (p.S214R), exon 6	16%	397	Missense mutation	VUS
11	*KMT2D*	c.6649C>T (p.R2217C), exon 31	21%	275	Missense mutation	VUS
11	*MCL1*	c.693G>C (p.M231I), exon 2	20%	403	Missense mutation	VUS
11	*PPARG*	c.480+7delA ()	13%	291	Intronic mutation	VUS
11	*PRKDC*	c.3364+4C>T ()	46%	378	Intronic mutation	VUS
11	*RECQL4*	c.1063C>T (p.R355W), exon 5	25%	402	Missense mutation	VUS
11	*SMO*	c.1040G>C (p.G347A), exon 5	22%	410	Missense mutation	VUS
12	*NOTCH2*	c.7225C>T (p.Q2409*), exon 34	90%	92	Nonsense mutation	LPV
12	*TP53*	c.818G>A (p.R273H), exon 8	83%	65	Missense mutation	LPV
12	*CXCR4*	c.978dupA (p.G327Rfs*21), exon 1	47%	217	Frameshift mutation	LPV
12	*ERCC3*	c.2263G>A (p.D755N), exon 15	43%	100	Missense mutation	VUS

12	*GLI1*	c.358T>C (p.S120P), exon 4	48%	139	Missense mutation	VUS
12	*IKZF1*	c.556G>T (p.D186Y), exon 5	41%	148	Missense mutation	VUS
12	*ITK*	c.1282C>A (p.Q428K), exon 13	55%	101	Missense mutation	VUS
12	*MYD88*	c.289G>A (p.A97T), exon 1	45%	150	Missense mutation	VUS
12	*PALB2*	c.2320A>G (p.K774E), exon 5	53%	103	Missense mutation	VUS
12	*PTCH1*	c.1504-4G>A ()	49%	40	Intronic mutation	VUS
12	*SF3B1*	c.1667T>C (p.I556T), exon 12	61%	31	Missense mutation	VUS
12	*TP53BP1*	c.4528G>A (p.V1510I), exon 21	43%	73	Missense mutation	VUS
12	*WRN*	c.1640C>T (p.S547F), exon 13	48%	43	Missense mutation	VUS
13	*NOTCH2*	c.7225C>T (p.Q2409*)	NA	NA	Nonsense mutation	LPV
13	*TP53*	c.818G>A (p.R273H)	NA	NA	Missense mutation	LPV
14	*KLF2*	c.1049A>G (p.H350R), exon 3	37%	262	Missense mutation	LPV
14	*BARD1*	c.335G>A (p.R112Q), exon 3	47%	90	Missense mutation	VUS
14	*EP300*	c.5441G>A (p.R1814Q), exon 31	37%	246	Missense mutation	VUS
14	*FAT1*	c.13139-1150G>A ()	46%	116	Intronic mutation	VUS
14	*NTRK1*	c.2044C>T (p.R682C), exon 15	48%	97	Missense mutation	VUS
14	*SMARCB1*	c.749C>T (p.T250M), exon 6	46%	312	Missense mutation	VUS
14	*UBE2T*	c.523C>T (p.H175Y), exon 7	46%	165	Missense mutation	VUS
14	*WAS*	c.273+4_273+5insCC ()	33%	340	Intronic mutation	VUS
15	*KLF2*	c.76-1delG ()	23%	526	Splice site mutation	LPV

15	*BRCA2*	c.9271G>A (p.V3091I), exon 25	37%	54	Missense mutation	VUS
15	*FANCB*	c.1079C>T (p.T360M), exon 3	40%	66	Missense mutation	VUS
15	*FOXL2*	c.672_674delAGC (p.A227del), exon 1	40%	390	Deletion (1AA) mutation	VUS
15	*NRG1*	c.14G>T (p.R5L), exon 1	29%	217	Missense mutation	VUS
15	*PAX5*	c.*15C>T (), exon 10	50%	320	3' untranslated region mutation	VUS
16	*NOTCH2*	c.6463G>A (p.E2155K), exon 34	11%	88	Missense mutation	VUS
16	*TP53*	c.376-2A>T ()	54%	110	Splice site mutation	LPV
16	*ARID1B*	c.505_506delGTinsCC (p.V169P), exon 1	52%	26	Indel mutation	VUS
16	*BRCA1*	c.4993G>A (p.V1665M), exon 16	46%	39	Missense mutation	VUS
16	*CDKN1C*	c.632_633insACCGGC (p.P210_A211dup), exon 1	25%	44	Insertion (2AA) mutation	VUS
16	*DIS3L2*	c.795C>T (p.Y265Y), exon 8	44%	169	Missense mutation	VUS
16	*ERCC2*	c.2260G>C (p.E754Q), exon 23	55%	187	Missense mutation	VUS
16	*FANCA*	c.3788_3790delTCT (p.F1263del), exon 38	33%	118	Deletion (1AA) mutation	LPV
16	*FAT1*	c.13660G>A (p.E4554K), exon 27	36%	187	Missense mutation	VUS
16	*MAP3K1*	c.4115-6T>C ()	36%	86	Intronic mutation	VUS
16	*RET*	c.3332C>T (p.T1111M), exon 20	40%	86	Missense mutation	VUS
16	*RPA1*	c.703G>A (p.A235T), exon 9	26%	110	Missense mutation	VUS
16	*SMARCA4*	c.3547-17_3557delGGCACCTCTTCCCCCAGGACCTGCAAGC (), exon 26	8%	167	Splice site mutation	LPV

16	*SOX9*	c.1081C>A (p.Q361K), exon 3	42%	28	Missense mutation	VUS
16	*SUZ12*	c.1223C>G (p.T408R), exon 11	50%	10	Missense mutation	VUS
16	*TCF3*	c.16A>G (p.R6G), exon 2	52%	228	Missense mutation	VUS
17	*FAN1*	c.308C>A (p.P103Q), exon 2	35%	45	Missense mutation	VUS
17	*GNAS*	c.2182G>A (p.D728N), exon 3	43%	114	Missense mutation	VUS
17	*MYCL*	c.496+24A>G ()	46%	94	Intronic mutation	VUS
17	*NKX3-1*	c.395C>T (p.S132F), exon 2	40%	163	Missense mutation	VUS
17	*RAD50*	c.2047G>A (p.V683I), exon 13	51%	113	Missense mutation	VUS
18	*NOTCH2*	c.6882_6891delAACC ACCCCT (p.T2295Gfs*8), exon 34	6%	381	Frameshift mutation	LPV
18	*IDH2*	c.374-8C>T ()	40%	178	Intronic mutation	VUS
18	*RSPO2*	c.56G>T (p.S19I), exon 2	42%	224	Missense mutation	VUS
19	*NOTCH2*	c.6909dupC (p.I2304Hfs*9)	26%	652	Frameshift mutation	LPV
19	*FBXW7*	c.1271_1274dupTATG (p.W425Cfs*13), exon 9	20%	336	Frameshift mutation	LPV
19	*ARHGAP35*	c.4316G>A (p.R1439Q), exon 6	49%	609	Missense mutation	VUS
19	*ATR*	c.3245G>A (p.R1082H), exon 16	44%	259	Missense mutation	VUS
19	*FLT3*	c.2525A>G (p.Y842C), exon 20	50%	332	Missense mutation	VUS
19	*KMT2D*	c.10969C>G (p.L3657V), exon 39	47%	456	Missense mutation	VUS
19	*TLX3*	c.292G>A (p.G98R), exon 1	36%	436	Missense mutation	VUS
19	*TSHR*	c.1493G>A (p.G498D), exon 11	49%	621	Missense mutation	VUS

19	*XRCC3*	c.637G>A (p.D213N), exon 8	48%	392	Missense mutation	VUS
19	*NOTCH2*	c.6909dupC (p.I2304Hfs*9)	26%	652	Frameshift mutation	LPV
20	*SUZ12*	c.910delA (p.N305Tfs*7), exon 8	22%	53	Frameshift mutation	LPV
20	*IGF2*	c.607G>A (p.E203K), exon 5	53%	176	missense mutation	VUS
20	*POLD1*	c.2007-5C>T ()	51%	191	Intronic mutation	VUS
20	*BRAF*	c.1133A>G (p.N378S), exon 8	45%	62	Missense mutation	VUS

Table S2: Detected copy number variants, SMZL

Case	Chromosome	Region	Gene(s) affected in region	Gain/loss	LPV/VUS
1	8	p12-23.1	*GATA4, NEIL2, NKX3-1, PTK2B, WRN, NRG1*	Single copy loss	VUS
2	7	p11.2-22.2	*EGFR, IKZF1, JAZF1, ETV1, RAC1, PMS2, CARD11*	Low copy gain	VUS
2	7	q31.33-36.1	*POT1, SMO, BRAF, PRSS1, EZH2, RHEB*	Single copy loss	LPV
3	7	q31.2-34	*MET, POT1, SMO, BRAF, PRSS1*	Single copy loss	LPV
4	3	q12.3-27.3	*NFKBIZ, CBLB, POLQ, GATA2, MBD4, TOPBP1, FOXL2, ATR, MECOM, TERC, PRKCI, SOX2, ETV5, BCL6*	Low copy gain	LPV
4	7	q22.1-36.2	*CUX1, RINT1, MET, POT1, SMO, BRAF, PRSS1, EZH2, RHEB, XRCC2, PAXIP1*	Single copy loss	LPV
4	11	q22.1-24.2	*YAP1, ATM, SDHD, USP28, HMBS, CBL, ARGHEF12, CHEK1*	Single copy loss	VUS
5	7	q31.2-36.2	*MET, POT1, SMO, BRAF, EZH2, RHEB, XRCC2, PAXIP1*	Single copy loss	LPV
6	3	q12.3-27.3	*NFKBIZ, CBLB, POLQ, GATA2, MBD4, TOPBP1, FOXL2, ATR, MECOM, TERC, PRKCI, SOX2, ETV5, BCL6*	Low copy gain	LPV
6	9	p13.2-24.3	*PAX5, RMRP, CDKN2B, CDKN2A, MTAP, PDCD1LG2, JAK2, CD274, DOCK8*	Low copy gain	VUS
6	18	Whole chromosome	*GATA6, RBBP8, SS18, SETBP1, SMAD2, SMAD4, BCL2*	Low copy gain	VUS
7	1	p36.22		Single copy loss	VUS
7	1	q42.2-43	*FH, EXO1*	Single copy loss	VUS
7	2	p16.1		Low copy gain	VUS

7	3	q27.3		Low copy gain	LPV
7	4	p16.3	*WHSC1*	Single copy loss	VUS
9	3	q22.3-26.32	*ATR, PIK3CA*	Single copy loss	VUS
9	12	p13.1-13.2	*DKN1B*	Single copy loss	VUS
9	12	q15-23.3	*MDM2, TDG*	Single copy loss	VUS
9	17	Whole p arm	*RPA1, TP53, AURKB, MAP2K4*	Single copy loss	LPV
9	17	Whole q arm	*NF1, SUZ12, RHOT1, RAD51D, CDK12, ERBB2, RARA, SMARCE1, STAT3, BRCA1, ETV4, HOXB13, SPOP, EME1, RNF43, RAD51C, TRIM37, PPM1D, BRIP1, CD79B, AXIN2, PRKAR1A, SOX9, H3F3B, RHBDF2, SRSF2, RPTOR, C17ORF70*	Low copy gain	VUS
9	18	q12.3-21.33	*SETBP1, SMAD2, SMAD4, BCL2*	Single copy loss	VUS
11	4	p15.2-16.3	*SLC34A2, WHSC1, FGFR3*	Single copy loss	VUS
11	4	q35.2		Single copy loss	VUS
11	12	Whole q arm	*ERBB3, STAT6, GLI1, CDK4, MDM2, TDG, SH2B3, PTPN11, HNF1A, POLE*	Low copy gain	VUS
12	5	p13.1	*RICTOR*	Low copy gain	VUS
12	5	p13.2-15.33	*IL7R, TERT, SDHA*	Single copy loss	VUS
12	10	Whole chromosome	*GATA3, DCLRE1C, RET, ERCC6, TET1, PRF1, KAT6B, BMPR1A, KLLN, PTEN, FAS, SUFU, NT5C2, SMC3, TCF7L2, HABP2, FGFR2*	Single copy loss	VUS
12	13	q22.1-33.3	*DIS3, ERCC5, LIG4*	Single copy loss	VUS
12	17	Whole p arm	*RPA1, TP53, AURKB, MAP2K4, FLCN*	Single copy loss	LPV

12	18	Whole chromosome	*GATA6, RBBP8, SS18, SETBP1, SMAD2, SMAD4, BCL2*	Single copy loss	VUS
12	19	q13.33-13.41	*BCL2L12, PPP2R1A*	Single copy loss	VUS
12	20	p12.3		Low copy gain	VUS
13	10	Whole chromosome	*GATA3, DCLRE1C, RET, ERCC6, TET1, PRF1, KAT6B, BMPR1A, KLLN, PTEN, FAS, SUFU, NT5C2, SMC3, TCF7L2, HABP2, FGFR2*	Single copy loss	VUS
13	17	Whole p arm	*RPA1, TP53, AURKB, MAP2K4, FLCN*	Single copy loss	LPV
14	3	q26.2-27.3	*MECOM, TERC, PRKCI, PIK3CA, SOX2, ETV5, BCL6*	Low copy gain	LPV
14	7	q22.1-36.2	*CUX1, RINT1, MET, POT1, SMO, BRAF, PRSS1, EZH2, RHEB, XRCC2, PAXIP1*	Single copy loss	LPV
15	3	q13.33-27.3	*POLQ, GATA2, MBD4, TOPBP1, FOXL2, ATR, MECOM, TERC, PRKCI, PIK3CA, SOX2, ETV5, BCL6*	Low copy gain	LPV
15	14	q32.32-32.33	*TRAF3, XRCC3, AKT1, MTA1*	Single copy loss	VUS
15	17	q23.2-25.3	*PPM1D, BRIP1, CD79B, AXIN2, PRKAR1A, SOX9, H3F3B, RHBDF2, SRSF2, RPTOR, C17ORF70*	Low copy gain	VUS
16	1	p36.11-36.12	*ID3*	Single copy loss	VUS
16	2	p15-24.3	*XPO1, REL, FANCL, MSH6, MSH2, EPCAM, SOS1, ALK, BRE, DNMT3A, GEN1, MYCN*	Low copy gain	VUS
16	3	q23-27.3	*MECOM, TERC, PRKCI, PIK3CA, SOX2, ETV5, BCL6*	Low copy gain	LPV
16	7	p22.2-q21.2	*CARD11, PMS2, RAC1, ETV1, JAZF1, IKZF1, EGFR, SBDS*	Low copy gain	VUS

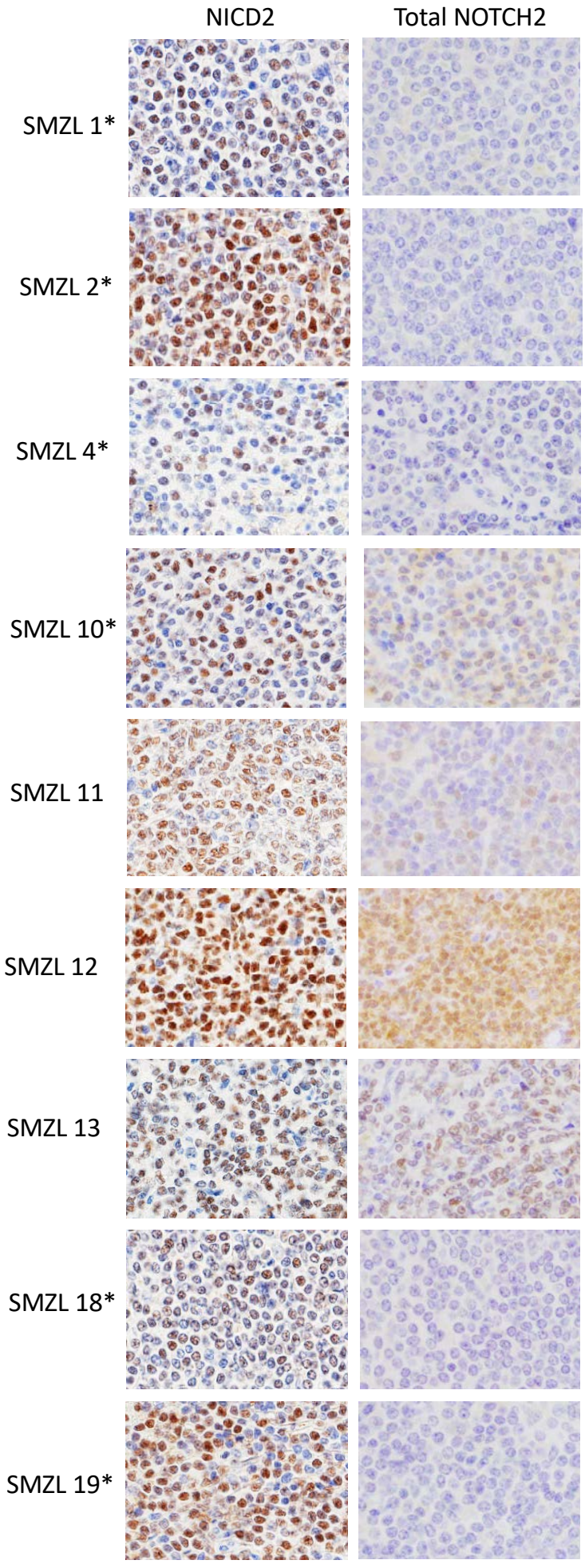
16	8	p11.23-p23.1	*WHSC1L1, NRG1, WRN, PTK2B, NKX3-1, NEIL2, GATA4*	Single copy loss	VUS
16	9	Whole chromosome	*JAK2, CD274, PDCD1LG2, MTAP, CDKN2A, CDKN2B, FANCG, RMRP, PAX5, GNAQ, NTRK2, FANCC, PTCH1, XPA, GALNT12, TAL2, KLF4, ENG, ABL1, TSC1, BRD3, NOTCH1*	SIngle copy loss	VUS
16	10	q23.2-26.13	*BMPR1A, KLLN, PTEN, FAS, SUFU, NT5C2, FGFR2*	Single copy loss	VUS
16	17	p11.2-13.3	*RPA1, TP53, AURKB, MAP2K4, FLCN*	Single copy loss	LPV
16	22	Whole chromosome	*CRKL, MAPK1, SMARCB1, CHEK2, ZNFR3, EWSR1, NF2, EP300, DMC1, XRCC6*	Single copy loss	VUS
18	7	q31.33-36.1	*POT1, SMO, BRAF, PRSS1, EZH2, RHEB, XRCC2, PAXIP1*	Single copy loss	LPV
18	11	q22.3-23.2	*ATM, SDHD, USP28*	Single copy loss	VUS
19	6	q23.3-25.3	*TNFAIP3, ARID1B*	Single copy loss	VUS
19	7	q22.1-36.2	*CUX1, RINT1, MET, POT1, SMO, BRAF, PRSS1, EZH2, RHEB, XRCC2, PAXIP1*	Single copy loss	LPV
19	11	q22.1-23.2	*YAP1, ATM, SDHD, USP28*	Single copy loss	VUS
19	12	q24.33		Low copy gain	VUS

Table S3: Detected structural variants, SMZL

Case No.	Structural variant detected	LPV/VUS
5	19 bp internal deletion (indel) in the *KLF2* gene on chromosome 19. The deletion spans the splice donor site of exon 2 and is predicted to interfere with mRNA splicing, most likely resulting in a prematurely truncated protein	LPV
7	*TNFAIP3* gene on chromosome 6q. The deletion spans the terminal portion of exon 4 and the entirety of exon 5, as well as the intervening intron	LPV
12	Multiple indels involving exon 5 of *CCND3*	LPV
18	20 bp deletion (indel) in exon 2 of *KLF2*	LPV
19	51 bp (i.e., in-frame) deletion in the *ABCB11* gene on chromosome 2q31	VUS

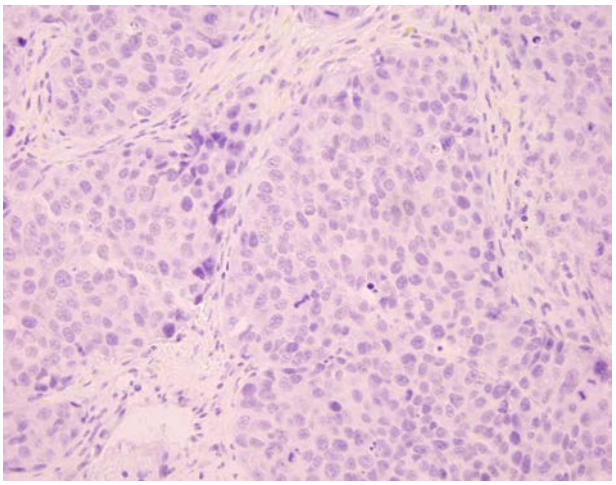
Table S4: Genes covered in Oncopanel POPv3 NGS panel

A. Exonic sequences covered for SNVs and indels
ABCB11,ABL1,ACVR1,AKT1,AKT2,AKT3,ALK,APC,AR,ARAF,ARHGAP35,ARHGEF12,ARIDA,ARID1B, ARID2,ASXL1,ATM,ATR,ATRX,AURKA,AURKB,AXIN2,AXL,B2M,BABAM1,BAP1,BARD1,BCL11B, BCL2,BCL2L1,BCL2L12,BCL6,BCOR,BCORL1,BLM,BMPR1A,BRAF,BRCA1,BRCA2,BRCC3,BRD3, BRD4,BRE,BRIP1,BUB1B,C17ORF70,C19ORF40,C10ORF86,CALR,CARD11,CASP8,CBFA2T3,CBFB, CBL,CBLB,CCND1,CCND2,CCND3,CCNE1,CD274,CD79B,CDC73,CDH1,CDH4,CDK12,CDK4,CDK6, CDK8,CDKN1A,CDKN1B,CDKN1C,CDKN2A,CDKN2B,CDKN2C,CEBPA,CHEK1,CHEK2,CIC,CIITA, COL7A1,CREBBP,CRKL,CRLF2,CRTC1,CSF3R,CTCF,CTLA4,CTNNA1,CTNNB1,CUX1,CXCR4,CYLD, DAXX,DCLRE1C,DDB1,DDB2,DDR2,DICER1,DIS3,DIS3L2,DKC1,DMC1,DNMT3A,DOCK8,EGFR, EGLN1,ELANE,EME1,ENG,EP300,EPCAM,ERBB2,ERBB3,ERBB4,ERCC1,ERCC2,ERCC3,ERCC4, ERCC5,ERCC6,ERG,ESR1,ETV1,ETV4,ETV5,ETV6,EWSR1,EXO1,EXT1,EXT2,EZH2,FAH,FAM175A, FAM46C,FAN1,FANCA,FANCB,FANCC,FANCD2,FANCE,FANCF,FANCG,FANCI,FANCL,FANCM,FAS, FAT1,FBXW7,FGFR1,FGFR2,FGFR3,FGFR4,FH,FLCN,FLT1,FLT3,FLT4,FOXA1,FOXL2,FUS, GALNT12,GATA2,GATA3,GATA4,GATA6,GBA,GEN1,GLI1,GLI2,GNA11,GNAQ,GNAS,GPC3,GREM1, H19,H3F3A,H3F3B,HABP2,HELQ,HFE,HIST1H3B,HIST1H3C,HMBS,HNF1A,HOXB13,HRAS,ID3,ID4, IDH1,IDH2,IGF1R,IGF2,IKZF1,IL7R,ITK,JAK1,JAK2,JAK3,JAZF1,KAT6A,KAT6B,KCNQ1,KDM5A,KDM5 C,KDM6A,KDR,KEAP1,KIF1B,KIT,KLF2,KLF4,KLLN,KMT2A,KMT2D,KRAS,LIG4, LMO1,LMO2,MAF,MAFB,MAP2K1,MAP2K2,MAP2K4,MAP3K1,MAPK1,MAX,MBD4,MCL1,MCM8, MDM2,MDM4,MECOM,MED12,MEF2B,MEN1,MET,MGA,MITF,MLH1,MLH3,MPL,MRE11A,MSH2, MSH6,MTA1,MTAP,MTOR,MUS81,MUTYH,MYB,MYBL1,MYC,MYCL1,MYCN,MYD88,NBN,NEIL1, NEIL2,NEIL3,NF1,NF2,NFE2L2,NFKBIA,NFKBIE,NFKBIZ,NKX2-1,NKX3-1,NOTCH1,NOTCH2,NOTCH3, NPM1,NR0B1,NRAS,NRG1,NSD1,NT5C2,NTHL1,NTRK1,NTRK2,NTRK3,OGG1,PALB2,PARK2,PAX5, PAXIP1,PBRM1,PDCD1LG2,PDGFRA,PDGFRB,PHF6,PHOX2B,PIK3C2B,PIK3CA,PIK3R1,PIM1,PML, PMS1,PMS2,PNKP,POLB,POLD1,POLE,POLH,POLQ,POT1,PPARG,PPM1D,PPP2R1A,PRDM1,PRF1, PRKAR1A,PRKCI,PRKDC,PRSS1,PTCH1,PTEN,PTK2B,PTPN11,PTPN14,PVRL4,QKI,RAC1,RAD21, RAD50,RAD51,RAD51C,RAD51D,RAD52,RAD54B,RAF1,RARA,RASA1,RB1,RBBP8,RBM10,RECQL4, REL,RELA,RET,RHBDF2,RHEB,RHOA,RHOH,RHOT1,RICTOR,RIF1,RINT1,RIT1,RMRP,RNF43,RNF8, ROS1,RPA1,RPTOR,RSPO2,RSPO3,RUNX1,RUNX1T1,SBDS,SDHA,SDHAF2,SDHB,SDHC,SDHD, SERPINA1,SETBP1,SETD2,SF3B1,SH2B3,SH2D1A,SLC25A13,SLC34A2,SLX1A,SLX1B,SLX4,SMAD2, SMAD4,SMARCA4,SMARCB1,SMARCE1,SMC3,SMO,SOCS1,SOS1,SOX2,SOX9,SPOP,SRSF2,SRY, SS18,STAG2,STAT3,STAT6,STK11,SUFU,SUZ12,TAL1,TAL2,TAZ,TCEB1,TCF3,TCF7L2,TDG,TERC, TERT,TET1,TET2,TFE3,TLX3,TMEM127,TMPRSS2,TNFAIP3,TOPBP1,TP53,TP53BP1,TRAF3,TRAF7, TRIM37,TSC1,TSC2,TSHR,U2AF1,UBE2T,UIMC1,UROD,USP28,USP8,VEGFA,VHL,WAS,WHSC1, WHSC1L1,WRN,WT1,XPA,XPC,XPO1,XRCC1,XRCC2,XRCC3,XRCC4,XRCC5,XRCC6,YAP1,ZNF217, ZNRF3,ZRSR2
B. Intronic sequences covered for rearrangement dections
ABL1,ALK,BCL6,BIRC3(API2),BRAF,CAN,CBFB,CIC,CIITA,CRTC1,CRTC3,EGFR,ERG,ESR1,ETV4, ETV5,ETV6,EWSR1,FGFR1,FGFR2,FGFR3,FIP1L1,FOX01,FUS,JAK2,KMT2A,MET,MYB,MYBL1, NAB2,NCOA2,NPM1,NR4A3,NRG1,NTRK1,NTRK2,NTRK3,NUTM1,PDGFB,PDGFRA,PDGFRB,PHF1, PML,PPARG,RAF1,RARA,RELA,RET,ROS1,RSPO2,RSPO3,RUNX1,SLC34A2,SS18,SUZ12, TMPRSS2,TP53, WWTR1,YAP1,YWHAE

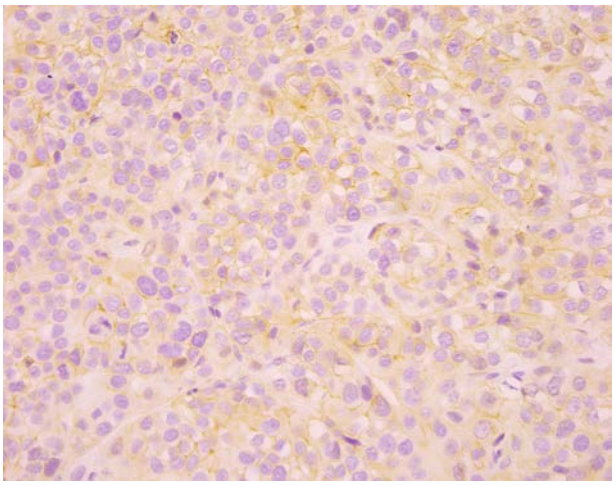


Supplementary Figure S1: Representative images of *NOTCH2* mutated SMZL stained for NICD2 and total NOTCH2 (40X magnification). Tumors with NOTCH2 PEST mutations that remove the C-terminal epitope recognized by the total NOTCH2 antibody are denoted by an asterisk.

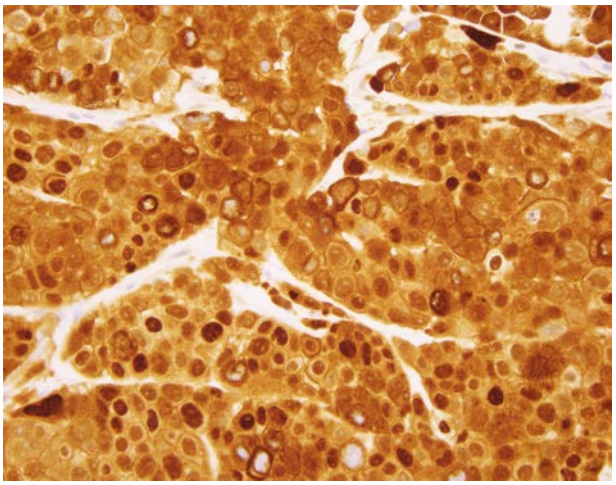
Supplementary Figure S2: Representative images of patient derived xenograft (PDX) models of triple negative breast carcinoma stained for total NOTCH2 protein (40X magnification)



NOTCH2 negative PDX

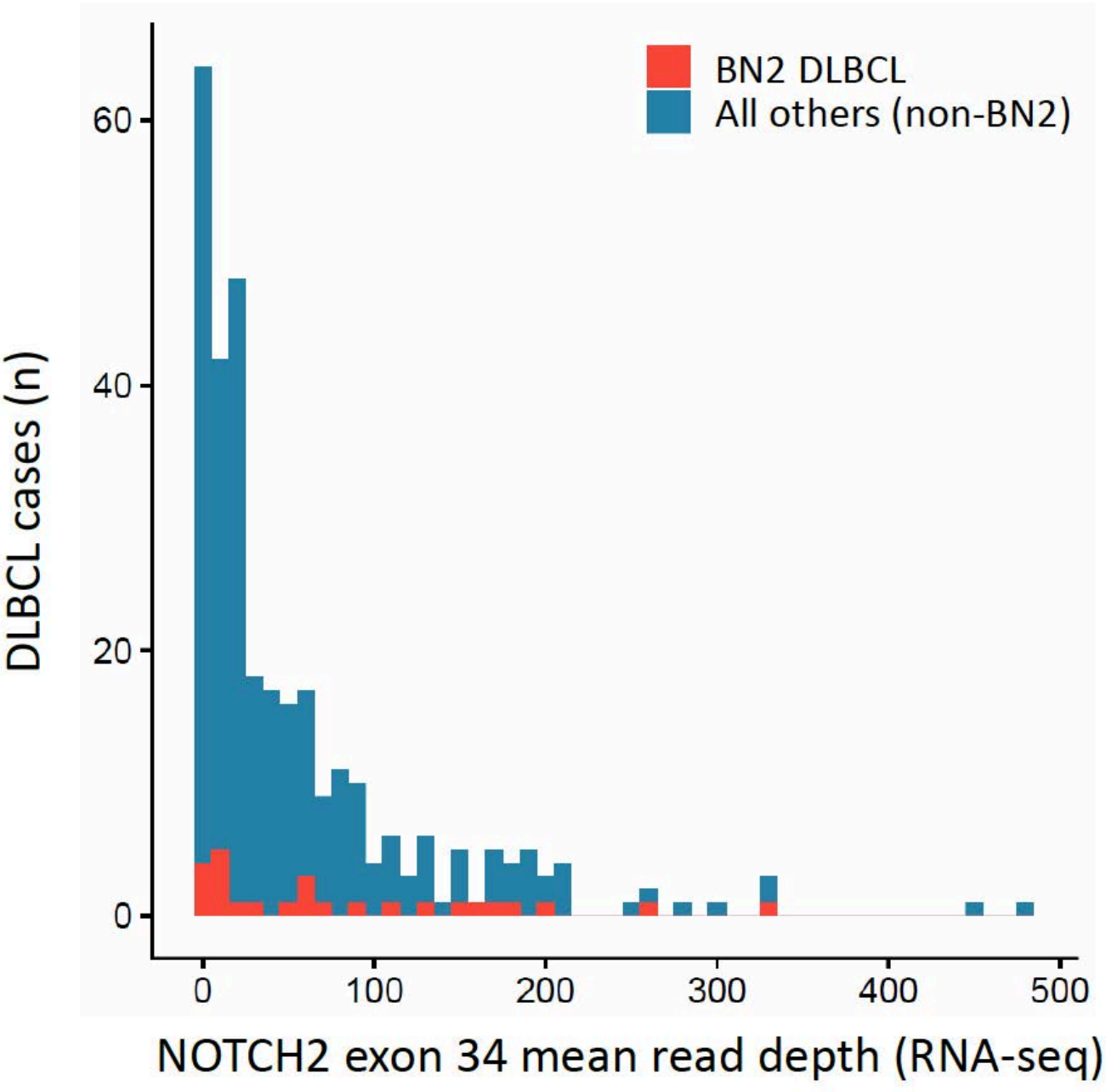


NOTCH2 positive PDX without *NOTCH2* rearrangement



NOTCH2 positive PDX with *PHGDH-NOTCH2* rearrangement

Supplementary Figure S3: Histogram showing *NOTCH2* exon 34 mean RNA-seq coverage across DLBCL cases (n=311)



Supplementary Figure S4: Representative images of *NOTCH2* mutated DLBCL stained for BCL6, NICD2 and total NOTCH2 protein (40X magnification)