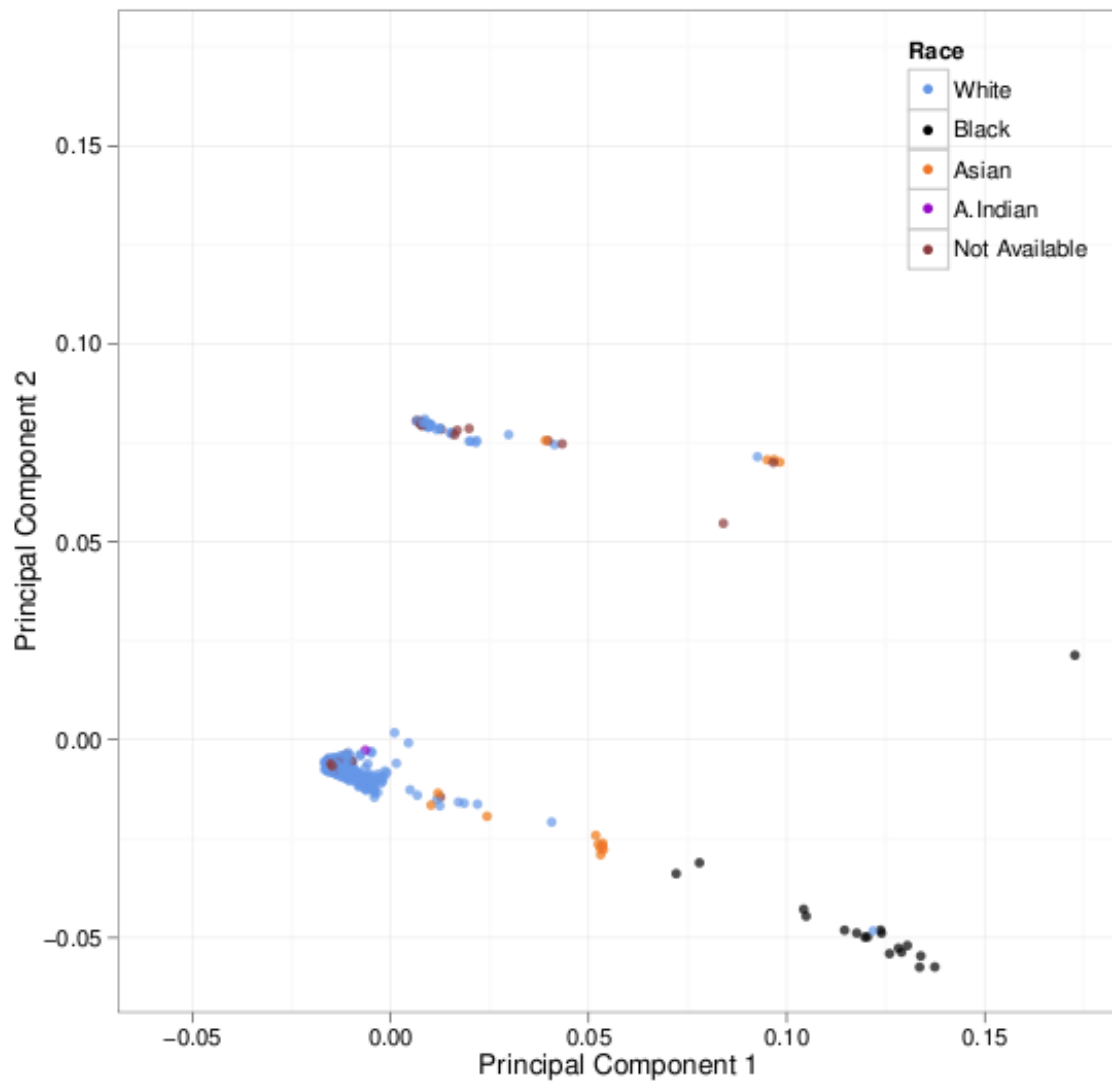
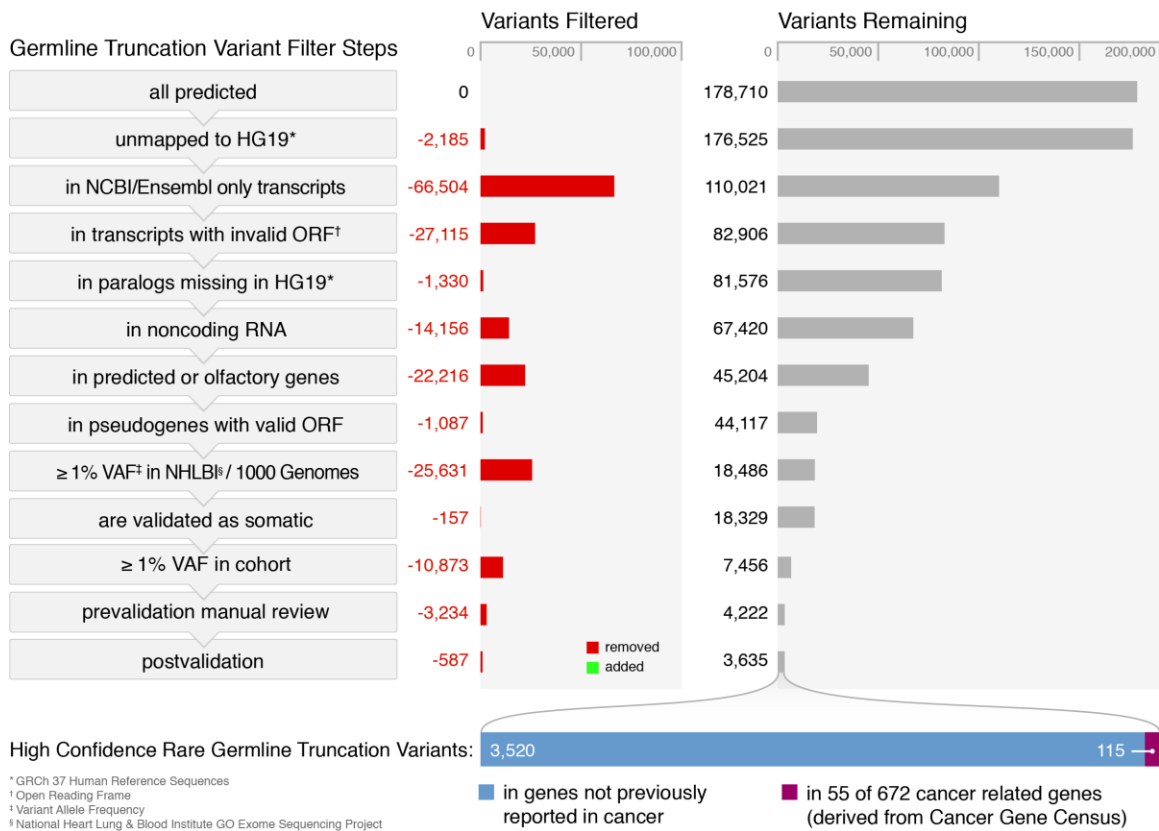


Supplementary Figures



Supplementary Figure 1: Principal Components Analysis (PCA) of TCGA Ovarian Cancer Cases (n=429). The top two principle components were plotted and the points were labeled according to clinically reported ethnicity. PCA clearly distinguished cases with clinically-reported White (blue circles) from Black (black circles) ethnicity, while those with Asian ethnicity clustered between the two groups (orange circles). PCA was used to assign ethnicity group to participants with unknown status (brown circles).

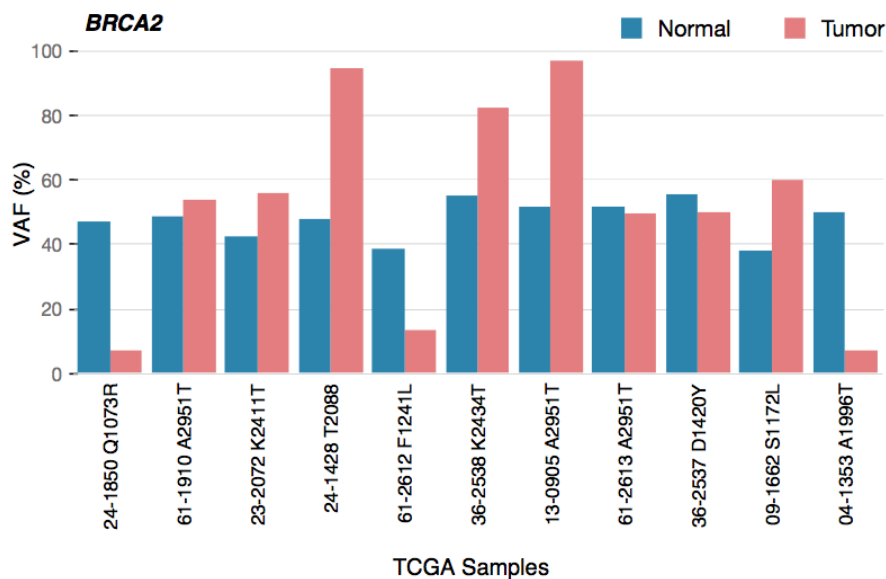
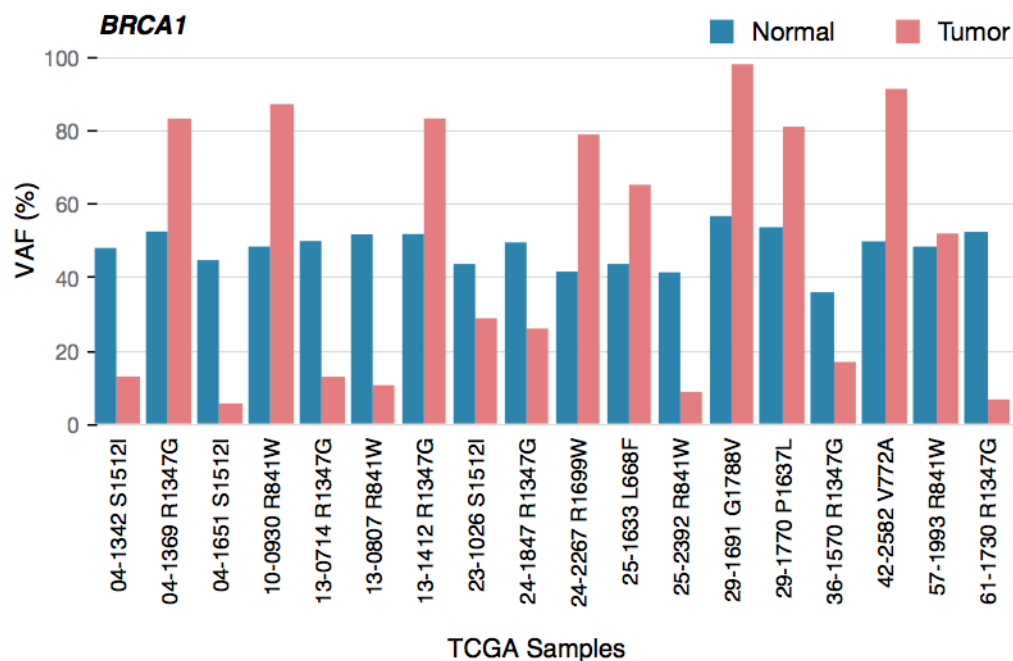
Germline Truncation Variant Discovery in 429 TCGA Ovarian Cancer Cases



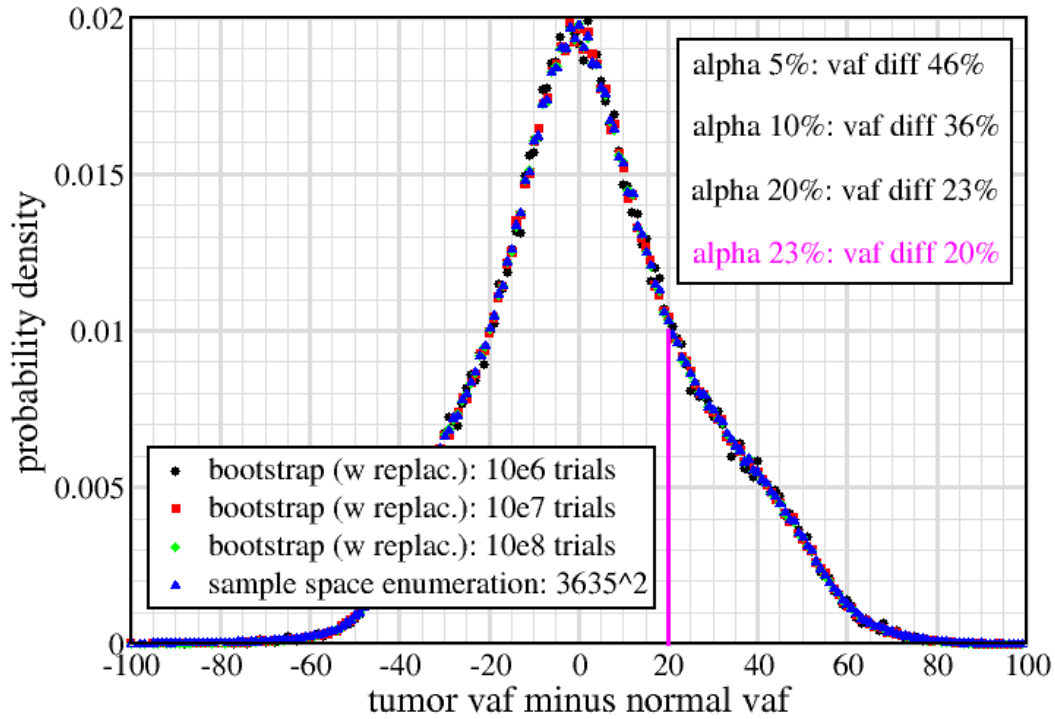
Supplementary Figure 2: Truncation variant filtering process. Shown are the truncation variants identified in 429 ovarian cancer cases. The number of variants removed by each serial filtering step is red. The number of remaining variants after filtering is represented by the gray bar.

All Predicted variants		3,769,601
Filters	Variants in NCBI/Ensembl only transcript	3,650,605
	Variants in noncoding RNA	3,637,328
	Variants in transcript with invalid ORF,LOC and OR	3,018,159
	Variants in pseudogenes with valid ORF	1,363,672
	Variants in NHLBI/1000G $\geq 1\%$ VAF	75,518
	Variants in Caucasians only	57,188
	Variants that are not Condel deleterious	24,813
	Variants $\geq 1\%$ recurrent in cohort	23,915
	Variants that are somatic	23,549
	Expression filter	17,348

Supplementary Figure 3: Missense variant filtering process. The missense analysis was limited to 387 TCGA ovarian cancer cases with White ethnicity. The number of variants remaining after each filtering step described on the left is shown in red boxes.



Supplementary Figure 4: Loss of heterozygosity patterns for *BRCA1* and *BRCA2* deleterious missense variants. Shown are variant allele frequencies in tumor (blue bars) and normal (red bars) sample pairs with rare deleterious variants scored by Condel. *BRCA1* missense variants p.G1788V and p.R1699W were reported as clinically relevant in various BIC and HGMD mutation databases.



Supplementary Figure 5: Empirical distributions for the null hypothesis of Variant Allele Frequency (VAF) differences between tumor and normal Samples. We constructed the distribution for all 3,635 observed events using both bootstrap resampling (with replacement) for one million through 100 million trials and full enumeration of all possible 3635^2 possible tumor-normal-matched events in the sample space. Corrections were made for purity by Equation (1). All methods give a very similar distribution, which reports that a 20% Variant Allele Frequency difference has roughly a 23% false-positive rate (i.e. 23% of the total area under the curve is to the right of the purple threshold).

Supplementary Tables

Supplementary Table 1. Somatic Significant Mutated Genes (SMG) in 429 Ovarian Cancer Cases (FDR cut-off <0.0005)

Gene	Indels	SNVs	Truncations	Total Number of Mutations	Mutation Cases	Mutation Freq	Covd Bps	Mutations per Mbp	P-value CT	FDR CT
<i>TP53</i>	12	246	143	401	399	93.01%	568505	705.36	0.00E+00	0.00E+00
<i>NF1</i>	1	6	20	27	25	5.83%	3665520	7.37	0.00E+00	0.00E+00
<i>BRCA1</i>	0	2	19	21	21	4.90%	5014017	4.19	1.53E-18	8.93E-15
<i>RB1</i>	0	2	12	14	14	3.26%	1158267	12.09	1.89E-16	8.27E-13
<i>CRKRS</i>	1	6	6	13	13	3.03%	2202049	5.9	2.87E-08	1.00E-04
<i>KRAS</i>	0	6	0	6	6	1.40%	302641	19.83	2.22E-07	6.48E-04

Supplementary Table 2. Burden Analysis results for the Truncation variants in cancer genes

Gene	Unique Variant Sites	Variant Count in Control Group	Variant Count in Case Group	Control Alleles (2*sample size of controls)	Case Alleles (2*sample size of cases)	MAF0	MAF1	CAST.greater
BRCA1	16	0	30	1114	774	0.00	0.04	0.00
BRCA2	15	4	25	1114	774	0.00	0.03	0.00
PALB2	3	0	3	1114	774	0.00	0.00	0.04
CHEK2	2	1	3	1114	774	0.00	0.00	0.11
BRIP1	4	1	3	1114	774	0.00	0.00	0.11
ALK	1	0	1	1114	774	0.00	0.00	0.16
FAS	1	0	1	1114	774	0.00	0.00	0.16
HERPUD1	1	0	1	1114	774	0.00	0.00	0.16
IDH1	1	0	1	1114	774	0.00	0.00	0.16
JAK1	1	0	1	1114	774	0.00	0.00	0.16
KIT	1	0	1	1114	774	0.00	0.00	0.16
MYH11	1	0	1	1114	774	0.00	0.00	0.16
NF1	1	0	1	1114	774	0.00	0.00	0.16
PML	1	0	1	1114	774	0.00	0.00	0.16
SLC4A7	1	0	1	1114	774	0.00	0.00	0.16
CDKN2B	1	0	1	1114	774	0.00	0.00	0.16
EGFR	1	0	1	1114	774	0.00	0.00	0.16
ERCC2	1	0	1	1114	774	0.00	0.00	0.16
BLM	5	2	3	1114	774	0.00	0.00	0.21
FANCA	2	1	1	1114	774	0.00	0.00	0.40
ATM	2	1	1	1114	774	0.00	0.00	0.40
PCSK7	1	1	1	1114	774	0.00	0.00	0.40
TET2	2	1	1	1114	774	0.00	0.00	0.40
CARD11	2	1	1	1114	774	0.00	0.00	0.40
FANCD2	4	4	2	1114	774	0.00	0.00	0.65
ERCC5	1	1	0	1114	774	0.00	0.00	0.84
FANCE	1	1	0	1114	774	0.00	0.00	0.84
FBXO18	1	1	0	1114	774	0.00	0.00	0.84
GNAS	1	1	0	1114	774	0.00	0.00	0.84
IKZF1	1	1	0	1114	774	0.00	0.00	0.84
LIFR	1	1	0	1114	774	0.00	0.00	0.84
MITF	1	1	0	1114	774	0.00	0.00	0.84
MLF1	1	1	0	1114	774	0.00	0.00	0.84
MLH1	1	1	0	1114	774	0.00	0.00	0.84
MLL	1	1	0	1114	774	0.00	0.00	0.84
MLLT10	1	1	0	1114	774	0.00	0.00	0.84
MLLT6	1	1	0	1114	774	0.00	0.00	0.84
MUTYH	1	1	0	1114	774	0.00	0.00	0.84
APC	1	1	0	1114	774	0.00	0.00	0.84
ASXL1	1	1	0	1114	774	0.00	0.00	0.84
NCKIPSD	1	1	0	1114	774	0.00	0.00	0.84
PDGFRA	1	1	0	1114	774	0.00	0.00	0.84
PMS1	1	1	0	1114	774	0.00	0.00	0.84
PMS2	1	1	0	1114	774	0.00	0.00	0.84
PRKDC	1	1	0	1114	774	0.00	0.00	0.84

<i>RAD51L1</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>SSX1</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>BRD3</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>BUB1B</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>TET1</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>TOX3</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>XPA</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>CIITA</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>COL7A1</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>DDX10</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>EIF4A2</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>ELF4</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>EML4</i>	1	1	0	1114	774	0.00	0.00	0.84
<i>ERCC3</i>	3	5	1	1114	774	0.00	0.00	0.91
<i>FAT1</i>	2	2	0	1114	774	0.00	0.00	0.92
<i>MSH6</i>	2	2	0	1114	774	0.00	0.00	0.92
<i>MUC1</i>	2	2	0	1114	774	0.00	0.00	0.92
<i>NUMA1</i>	2	2	0	1114	774	0.00	0.00	0.92
<i>CANT1</i>	2	2	0	1114	774	0.00	0.00	0.92
<i>CARS</i>	2	2	0	1114	774	0.00	0.00	0.92
<i>CLTCL1</i>	2	2	0	1114	774	0.00	0.00	0.92
<i>DNMT3A</i>	2	2	0	1114	774	0.00	0.00	0.92
<i>FANCC</i>	1	2	0	1114	774	0.00	0.00	0.92
<i>GOPC</i>	1	2	0	1114	774	0.00	0.00	0.92
<i>TRIP11</i>	1	2	0	1114	774	0.00	0.00	0.92
<i>WRN</i>	4	6	1	1114	774	0.01	0.00	0.95
<i>RNF213</i>	3	3	0	1114	774	0.00	0.00	0.96
<i>ASPSCR1</i>	1	3	0	1114	774	0.00	0.00	0.96
<i>PCM1</i>	1	3	0	1114	774	0.00	0.00	0.96
<i>DDX6</i>	1	5	0	1114	774	0.00	0.00	0.99
<i>SBDS</i>	2	6	0	1114	774	0.01	0.00	0.99
<i>CCND3</i>	1	9	0	1114	774	0.01	0.00	1.00

Supplementary Table 3. Germline truncation and missense variants in somatic SMGs

Gene	Somatic Indels	Somatic SNVs	Somatic Truncations	Somatic Mutation Total	Covered Coding bp	Mutations per Mbp	Germline truncations	Rare Germline Missense
<i>NF1</i>	1	6	20	27	3665520	7.37	1	5
<i>TP53</i>	12	246	143	401	568505	705.36	0	1
<i>BRCA1</i>	0	2	19	21	5014017	4.19	32	18
<i>RB1</i>	0	2	12	14	1158267	12.09	0	2
<i>CRKRS</i>	1	6	6	13	2202049	5.9	0	0
<i>KRAS</i>	0	6	0	6	302641	19.83	0	0
<i>BRCA2</i>	0	3	8	11	4289539	2.56	25	11

Supplementary Table 4. Germline truncations and Somatic mutations in the same gene

Gene	Germline Truncational variant	Somatic variant
<i>PPP1R3A</i>	p.Q662fs	p.S87G
<i>PGAP1</i>	p.R786fs	p.R786fs
<i>TTN</i>	e3+2	p.R30930C
<i>IFI44L</i>	p.Y252*	p.R16P
<i>P2RY11</i>	p.Y300*	p.R103C
<i>KNTC1</i>	p.A412fs	p.Q939fs
<i>PALB2</i>	p.M723fs	p.Q370*
<i>FUT7</i>	p.Q232fs	p.Q232fs
<i>XIRP2</i>	p.R1348*	p.P564T
<i>RETSAT</i>	p.E430*	p.N162K
<i>CYP4A22</i>	p.M300fs	p.L48F
<i>ADCK2</i>	e1+1	p.L101H
<i>ADAM2</i>	e8-2	p.H581P
<i>SCRN3</i>	p.W77*	p.G252R
<i>ABCA8</i>	p.L1365fs	p.G1470A
<i>CLCNKA</i>	p.Q19*	p.A287S
<i>ADCY7</i>	e14-1	p.A1019V
<i>CDK5RAP1</i>	p.Q153*	e9-2

Supplementary Table 5. Two significant subnetworks identified by HotNet using germline truncations and somatic mutations.

Subnetwork	Samples with Mutation
<i>BRCA1, IQGAP2, CHD1L, BLM, HSPA6, SIPA1L1, FANCM, FANCL, SMC1A, CHEK2, MKI67, FANCA, ERCC5, XIAP, BRIP1, LEPRE1, NCOA6, SMC3, EXO1, XPC, MKI67IP, GTF2F1</i>	33.1% (142 / 429)
<i>EGFR, ERBB2, ERBB3, GAB2, LRRK1, BCR</i>	6.8% (29 / 429)

P-values were generated from a two-stage statistical test using a permutation of gene scores.
Significance is defined as P-value < 0.01.