



# Discovering Potential Biomarkers for Uveal Melanoma Targeted Therapy



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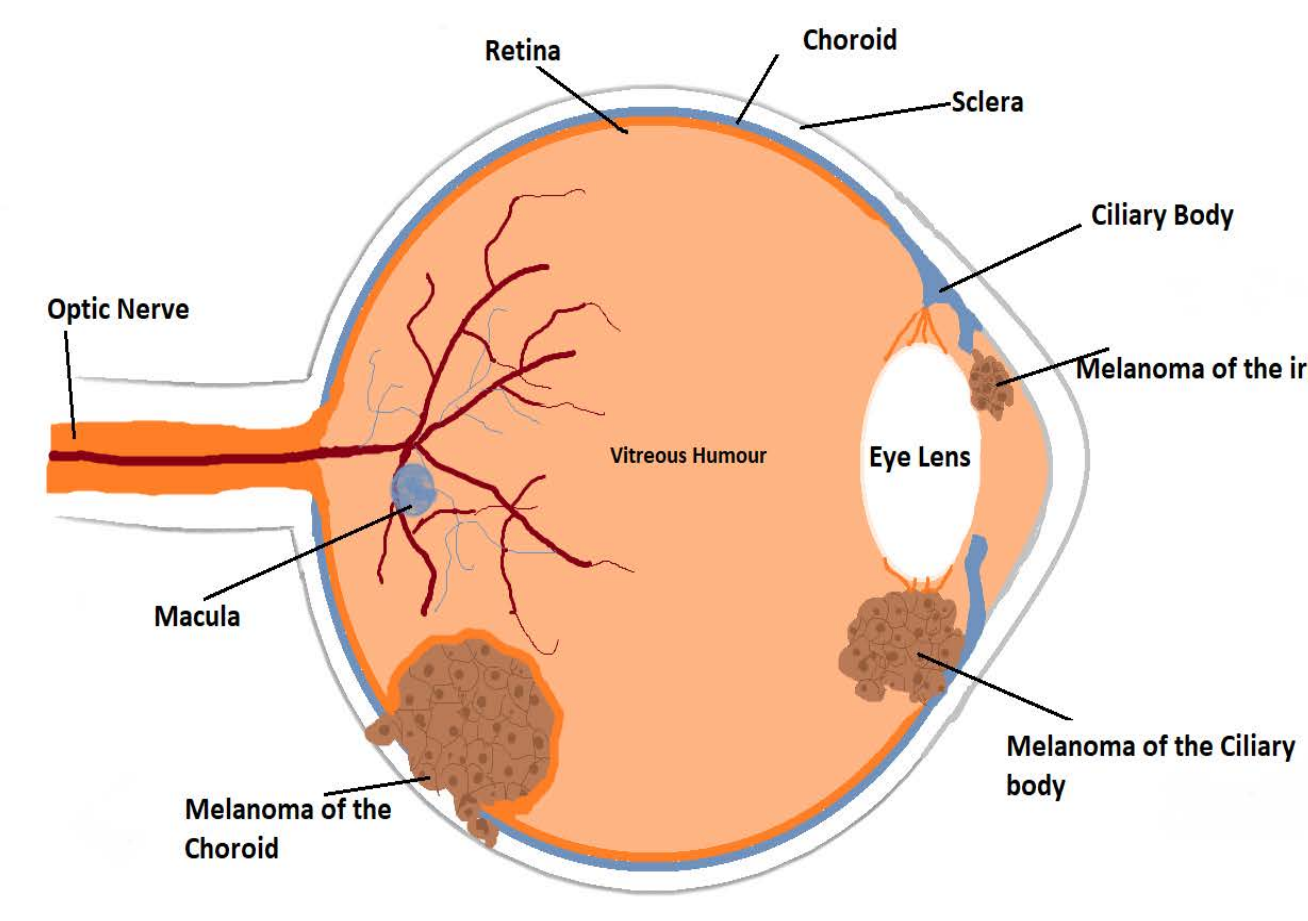
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## Background

Genotype-directed targeted therapy has been widely accepted in the health care regimes for personalized medicine. The identification of genetic alterations in genes is a powerful tool to achieve this goal. The protein-coding region of the human genome is called the exome. Though the exome represents less than 2% of the genome, it contains ~85% of known disease-related variants, making the whole-exome sequence a critical tool to discover biomarkers for the pathological condition. Uveal (ocular) melanoma is a common intraocular tumor, and the exact cause is unknown. In this study, we used publicly available exome databases such as the cancer genome atlas (TCGA) to investigate biomarkers for Uveal melanoma.

## Patients and methods

### Uveal melanoma



### Subjects and Samples

We retrieved about 80 uveal melanoma tumor cases of their genomic and RNA seq data. We analyzed the data using TCGA workflow-Bioconductor in the R package. Table 1 show study subjects age and gender details. Mean age= 59.3 Age range = 22 to 86 Mode age = 59 Male 45; Female 35.

Age	Female	Male	Age	Female	Male
22	0	1	60	1	3
35	1	0	63	0	1
37	1	0	64	1	3
38	0	1	65	0	1
39	0	1	66	2	1
40	0	1	68	0	3
41	1	1	69	0	1
44	1	0	70	1	0
45	0	1	71	1	1
46	1	0	72	0	1
47	2	0	73	0	1
49	1	1	74	1	1
50	2	1	75	1	3
51	2	1	76	1	2
53	0	3	77	1	1
54	1	2	78	4	1
55	1	0	79	1	0
56	1	2	83	2	0
57	1	1	85	1	0
59	1	2	86	0	2

## Results

### UM Mutational Frequency

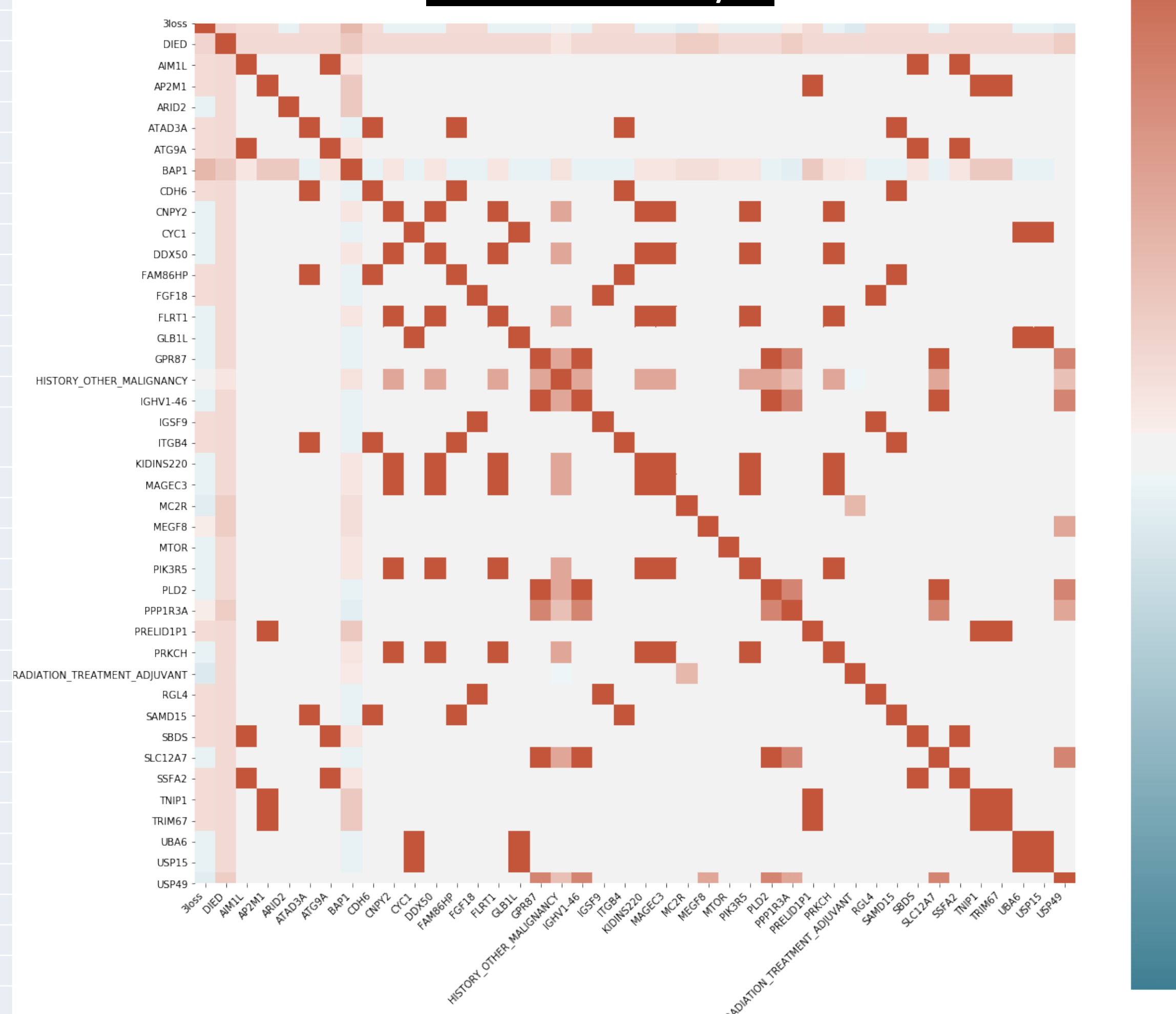
Gene	# Mut	Freq	Is Cancer Gene
APC	2	2.50%	Yes
BAP1	13	16.30%	Yes
COL14A1	3	3.80%	No
CSMD3	3	3.80%	No
CYSLTR2	3	3.80%	Yes
EIF1AX	10	12.50%	Yes
GNA11	36	45.00%	Yes
GNAQ	41	50.00%	Yes
MACF1	3	3.80%	No
MUC16	4	5.00%	No
MYOF	3	3.80%	No
PKHD1L1	3	3.80%	No
SF3B1	18	22.50%	Yes
SRSF2	3	3.80%	Yes
TTN	6	5.00%	No

## Results

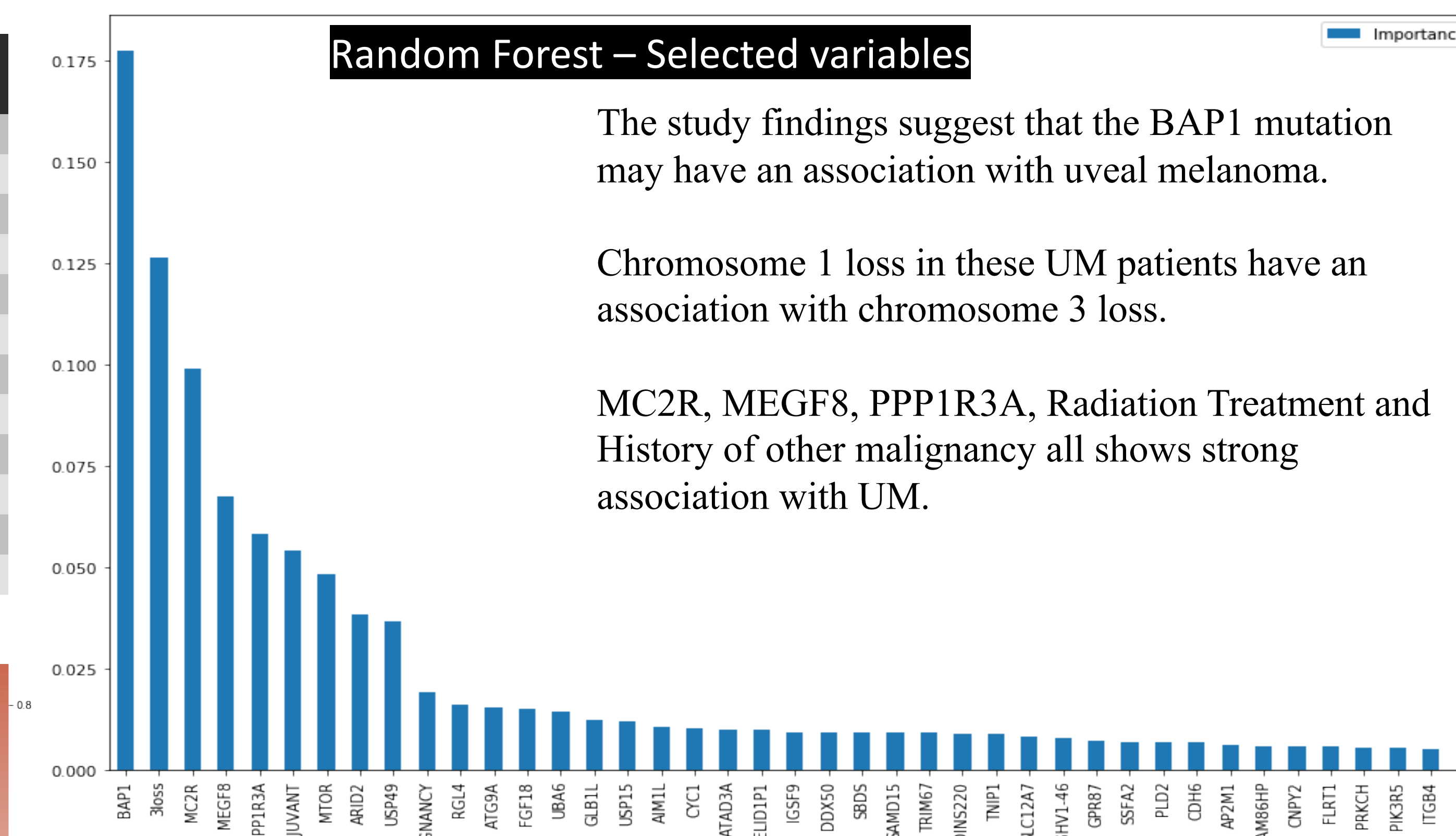
Random Forest Analysis			Logistic Regression Analysis	
Variable	Importance	Variable	Coef	
0	MEGF8	1.56E-02	BAP1	0.525487
1	MC2R	1.12E-02	3loss	0.363163
2	BAP1	1.09E-02	ASPM	0.309756
3	PIK3R5	9.25E-03	PPP1R3A	0.299803
4	USP49	6.82E-03	USP49	0.274206
5	SH2D5	6.59E-03	MTOR	0.267226
6	NPHP3	6.35E-03	FBN1	0.250801
7	PCGF6	6.31E-03	MEGF8	0.245609
8	PPP1R3A	6.05E-03	MC2R	0.245111
9	DBN1	5.98E-03	BRCA2	0.233247
10	PRELID1P1	5.85E-03	FBXL17	0.230739
11	ATG2A	5.75E-03	KIDINS220	0.230739
12	FAM217A	5.73E-03	FLRT1	0.230739
13	CDC40	5.72E-03	EHMT2	0.230739
14	PRDM8	5.72E-03	PRKCH	0.230739
15	VCL	5.68E-03	CNPY2	0.230739
16	ARAP3	5.54E-03	PIK3R5	0.230739
17	UPK1A	5.51E-03	MAGEC3	0.230739
18	SF3B1	5.45E-03	DDX50	0.230739
19	SAMD15	5.37E-03	PLCB4	0.210121
20	KIDINS220	5.32E-03	BMP6	0.207561
21	TMEM44	5.32E-03	ZNF555	0.207561
22	FGF18	5.30E-03	RAB38	0.207561
23	OR9A4	5.13E-03	FGF18	0.207561
24	FAM86HP	5.05E-03	RGL4	0.207561
25	ALKBH7	4.96E-03	PCGF6	0.207561
26	HIRA	4.92E-03	FLNC	0.207561
27	ERCC2	4.86E-03	IGSF9	0.207561
28	IGSF9	4.77E-03	IGHG3	0.207561
29	KDM6A	4.77E-03	BPI	0.207561
30	DDX50	4.76E-03	PRDM4	0.207561
31	SLC22A5	4.67E-03	P2RX1	0.207561
32	MAN2A1	4.52E-03	ADJUVANT	0.205889
33	TNPO1	4.52E-03	SYNE1	0.203696
34	RAB38	4.51E-03	PDGFRA	0.201827
35	OR4M2	4.51E-03	ATAD3A	0.199789
36	DDR2	4.48E-03	ZFC3H1	0.199789
37	CDH6	4.41E-03	PCDH9	0.199789
38	PSG4	4.30E-03	LGALS9	0.199789
39	3loss	4.27E-03	MRPS18C	0.199789
40	GRIN2B	4.26E-03	ITGB4	0.199789
41	LINC00174	4.25E-03	KIAA2013	0.199789
42	FLNC	4.24E-03	FAM86HP	0.199789
43	PCDH9	4.22E-03	SAMD15	0.199789
44	CNOT1	4.22E-03	CDH6	0.199789
45	POU4F1	4.21E-03	LRRC15	0.199789
46	CHML	4.20E-03	PLCB2	0.198886
47	SNTG2	4.19E-03	APC	0.189086
48	TGFBRAP1	4.18E-03	USP15	0.188039
49	LGALS9	4.14E-03	EMID1	0.188039
50	ZNF251	4.11E-03	UBA6	0.188039

Cytogenetics abnormalities	Count of PATIENT
[Not Available]	28
Chromosome 1 loss	3
Chromosome 1 loss Chromosome 3 loss	2
Chromosome 1 loss   Chromosome 3 loss   Chromosome 8q gain	3
Chromosome 1 loss   Chromosome 6p gain   Chromosome 8q gain	1
Chromosome 3 loss	2
Chromosome 3 loss   Chromosome 6p gain	1
Chromosome 3 loss   Chromosome 6p gain   Chromosome 8q gain	5
Chromosome 3 loss   Chromosome 8q gain	18
Chromosome 6p gain	11
Chromosome 6p gain   Chromosome 8q gain	5
Chromosome 8q gain	1

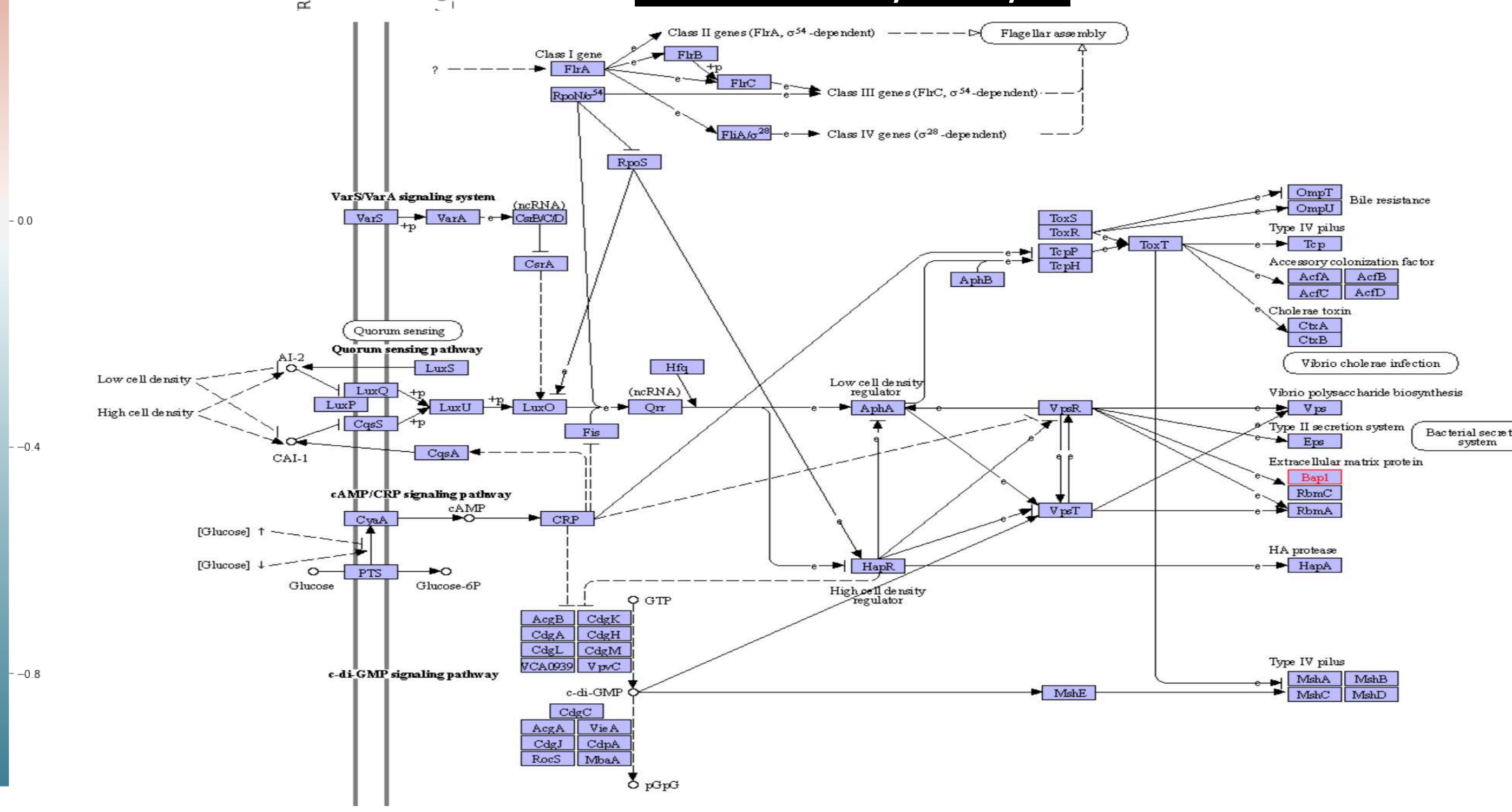
### Correlation analysis



### Random Forest – Selected variables



### KEGG Pathway Analysis



## Conclusions

Several novel biomarkers/SNP were identified and found to be associated with Uveal melanoma, including SF3B1, BAP1, EIF1AX etc. The BAP1 mutated gene has been known to be associated with a unique global DNA methylation profile. This biomarker may be a potential gene-based targeted therapy for Uveal melanoma.

## References

Martine J. Jager, Carol L. Shields, Colleen M. Cebulla, Mohamed H. Abdel-Rahman, Hans E. Grossniklaus, Marc-Henri Stern, Richard D. Carvajal, Rubens N. Belfort, Renbing Jia, Jerry A. Shields & Bertil E. Damato. Uveal melanoma Nature Reviews Disease Primers volume 6, Article number: 24 (2020) [https://epi.dph.ncdohhs.gov/oe/docs/OcularMelanomaInvestigationReport\\_June2015.pdf](https://epi.dph.ncdohhs.gov/oe/docs/OcularMelanomaInvestigationReport_June2015.pdf) <https://portal.gdc.cancer.gov>