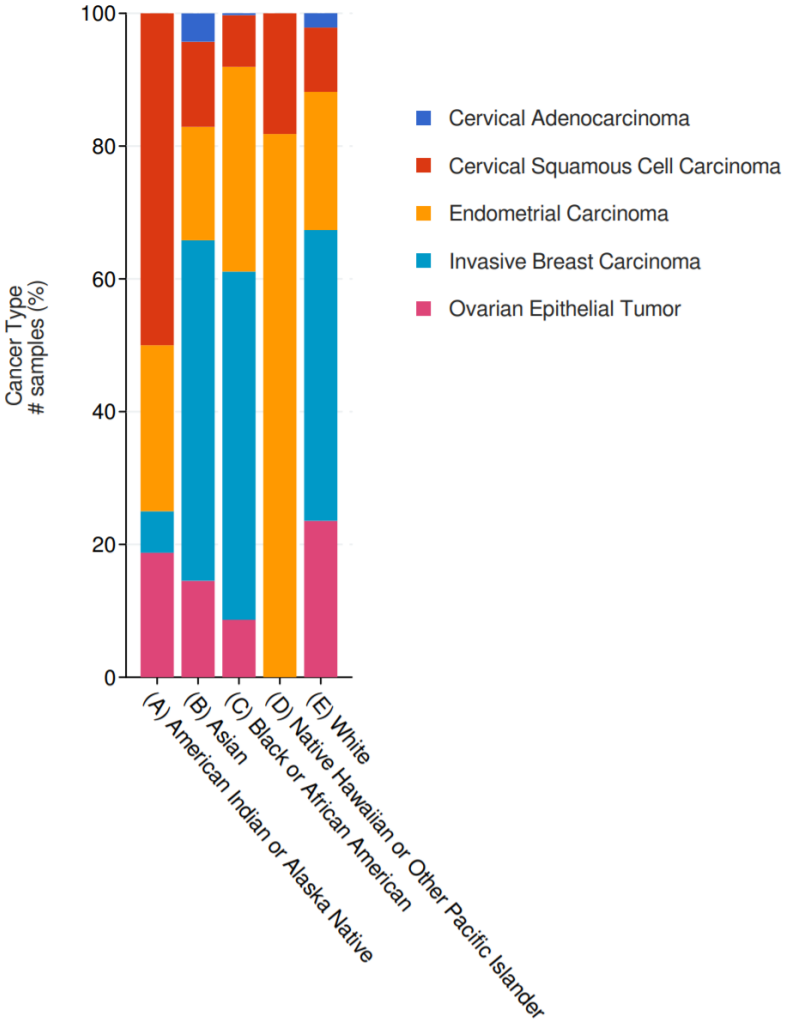
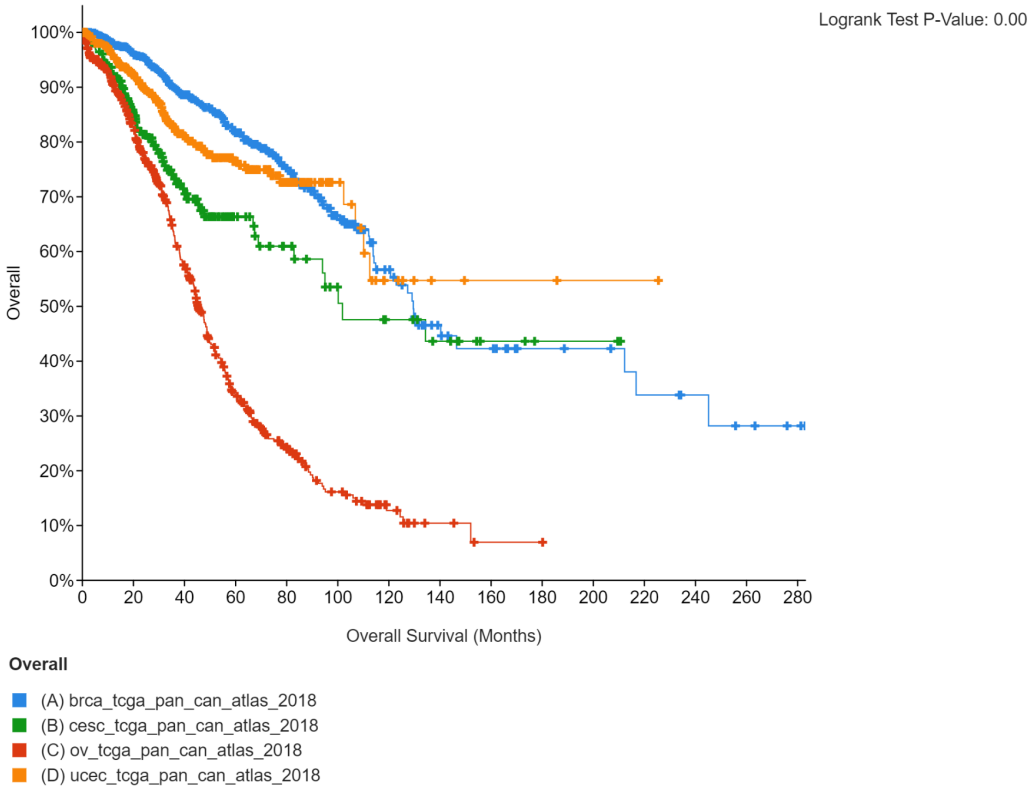
HW4-Adi Falach & Assaf Lovton

Question 1:

1.1:
After removing the NA race, and ordering the clinical data by race type, we can see that there are only 11 samples for Native Hawaiian or Other Pacific Islander. The cancer types divide into 2 groups the first is Endometrial Carcinoma with 9 samples and the second is Cervical Squamous with 2 samples. We would like to point out that only 11 samples is not enough to make this kind of conclusion since it's not large enough to be a representative sample. But if we ignore that and only look at the percentages you will be more likely to have an Endometrial Carcinoma if you are a Native Hawaiian or Other Pacific Islander since 82% of the samples had this kind of cancer for this race group.



1.2:
As we can see in the below graph, the red curve that represents the Ovarian Epithelial Tumor has the lowest value for median- about 60 months.



1.3:

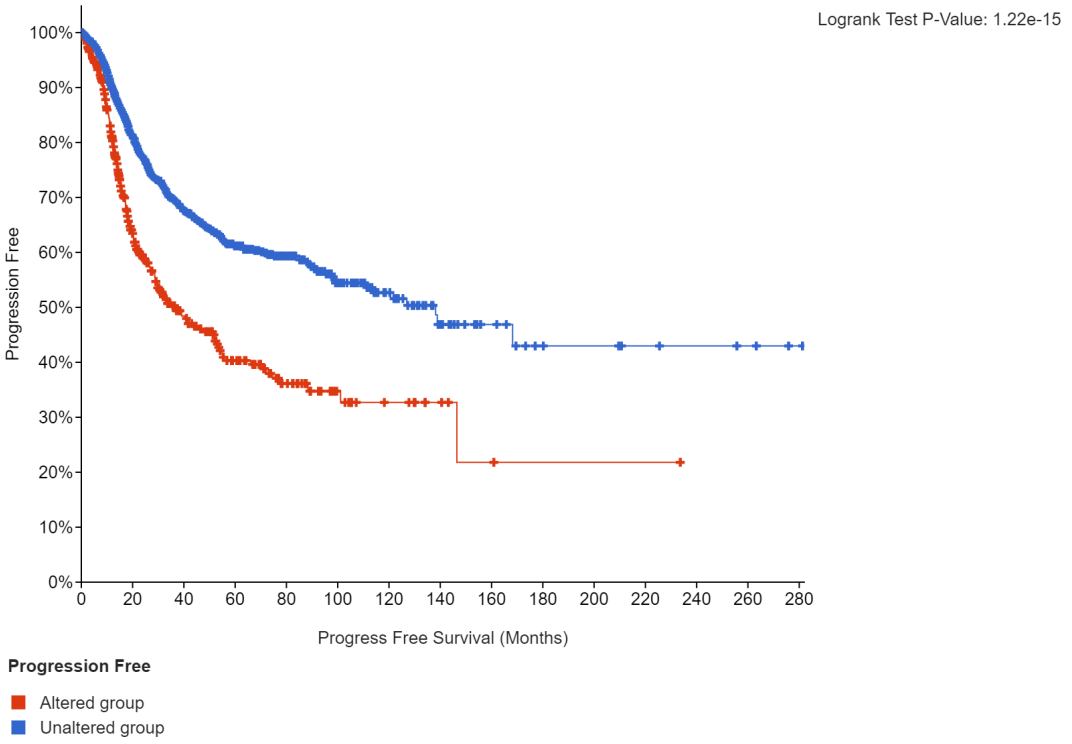
As we can see in the chart below the gene with the highest CNA frequency is MYC. MYC gene encodes a multifunctional, nuclear phosphoprotein that controls a variety of cellular functions, including cell cycle, cell growth, apoptosis, cellular metabolism and biosynthesis, adhesion, and mitochondrial biogenesis.

CNA Genes (2458 profiled samples)

Gene	Cytoband	CNA	#	Freq
MYC	8q24.21	AMP	407	16.6%
PVT1	8q24.21	AMP	400	16.3%
TMEM75	8q24.21	AMP	384	15.6%
CASC8	8q24.21	AMP	383	15.6%
POU5F1B	8q24.21	AMP	377	15.3%
CCAT2	8q24.21	AMP	376	15.3%
CCAT1	8q24.21	AMP	361	14.7%
PRNCR1	8q24.21	AMP	356	14.5%
PCAT1	8q24.21	AMP	354	14.4%
LRATD2	8q24.21	AMP	349	14.2%
LINC00977	8q24.21	AMP	346	14.1%

Search...

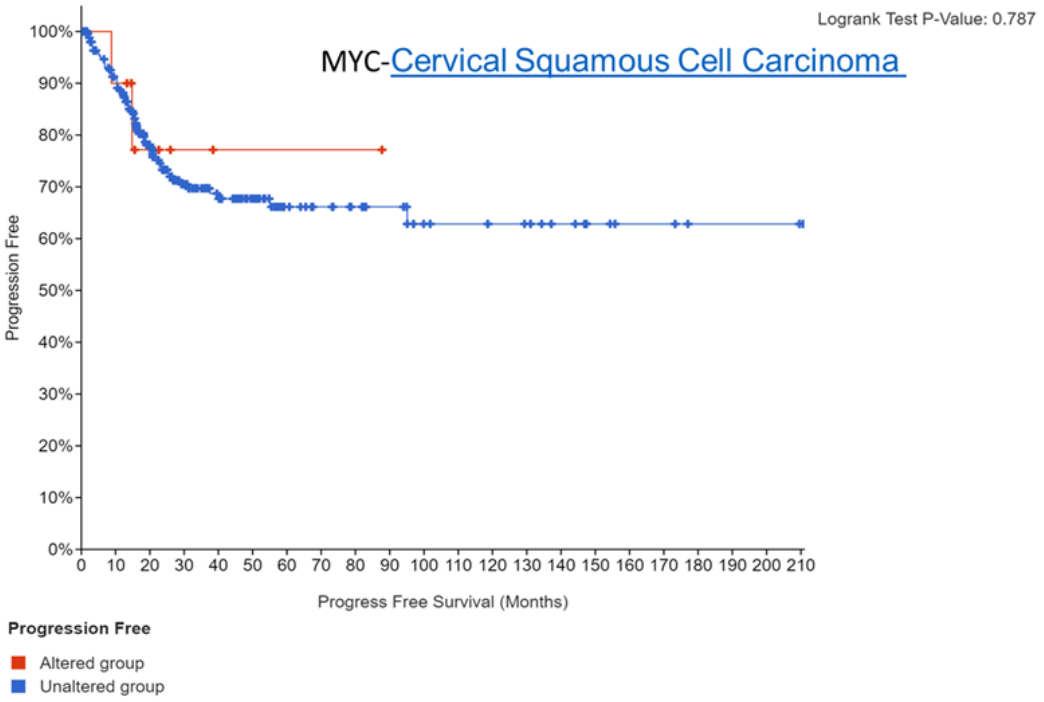
1.4:
Here we can see a progress free survival graph for alterations in MYC gene-red curve vs samples without any alterations in this gene-blue.
We can see that with the MYC alterations the progression free survival Worsened, e.g. looking at 50% progress free rate without the alterations in the MYC gene, we expect 160 months while with the alterations we expect a quarter - only 40 months.



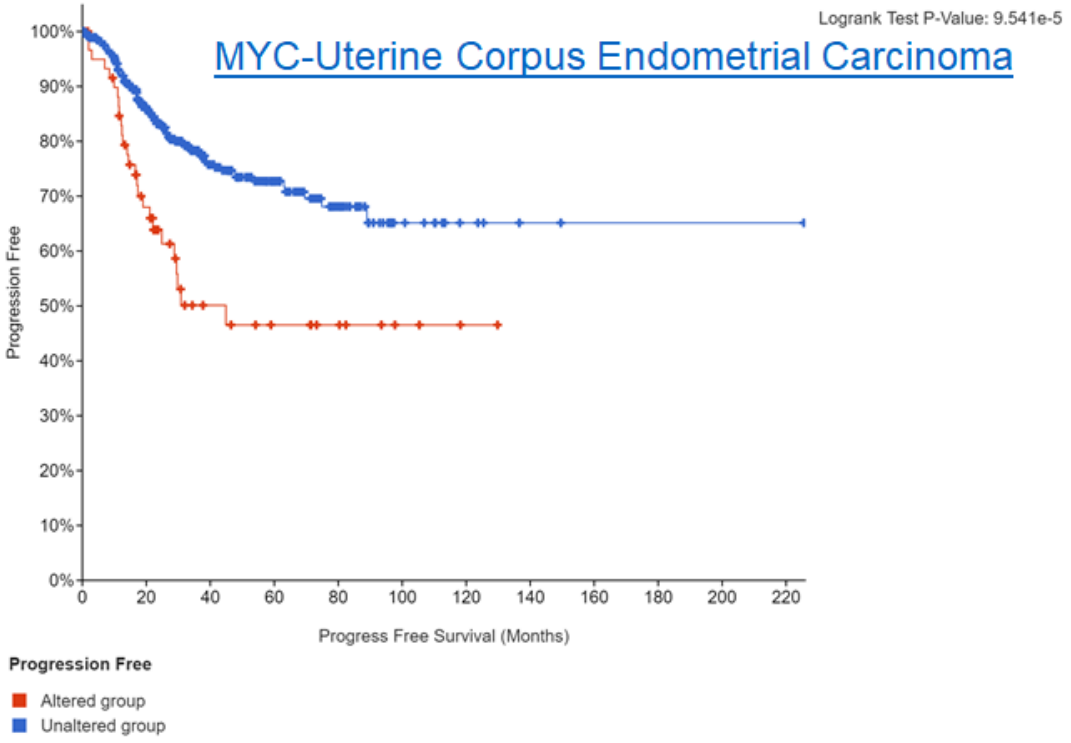
1.5:
A.Cervical Squamous Cell Carcinoma - Shows opposite results from the graph at 1.4-that showed the unaltered had longer progress free survival, since in this graph we can see that the altered group performed better for the first 90 month, but afterwards all of the patients left the trial so there is no further information.
B.Ovarian Serous Cystadenocarcinoma - Shows almost no difference between the alterated group and the unaltered group, therefore also different from the graph at 1.4 that showed the unaltered had longer progression free survival.
C.Uterine Corpus Endometrial Carcinoma - the first graph to show the same results we saw in 1.4 (in same we don't refer to the values but to the trend of the graph and the relation between the related and unrelated groups).
D.Breast Invasive Carcinoma -also shows similar results between the altered and unaltered groups, which also differs from the graph in 1.4

We assume the difference comes from the fact that the graph in 1.4 combines all of the four database's samples. B and D has vers similar results between the altered and unaltered so in average they won't affect the combined graph, A had a very small positive result for the altered group and C had a very negative (altered is had a much lower progression free rate) result so the graph that combines ABCD will resemble the most to graph C

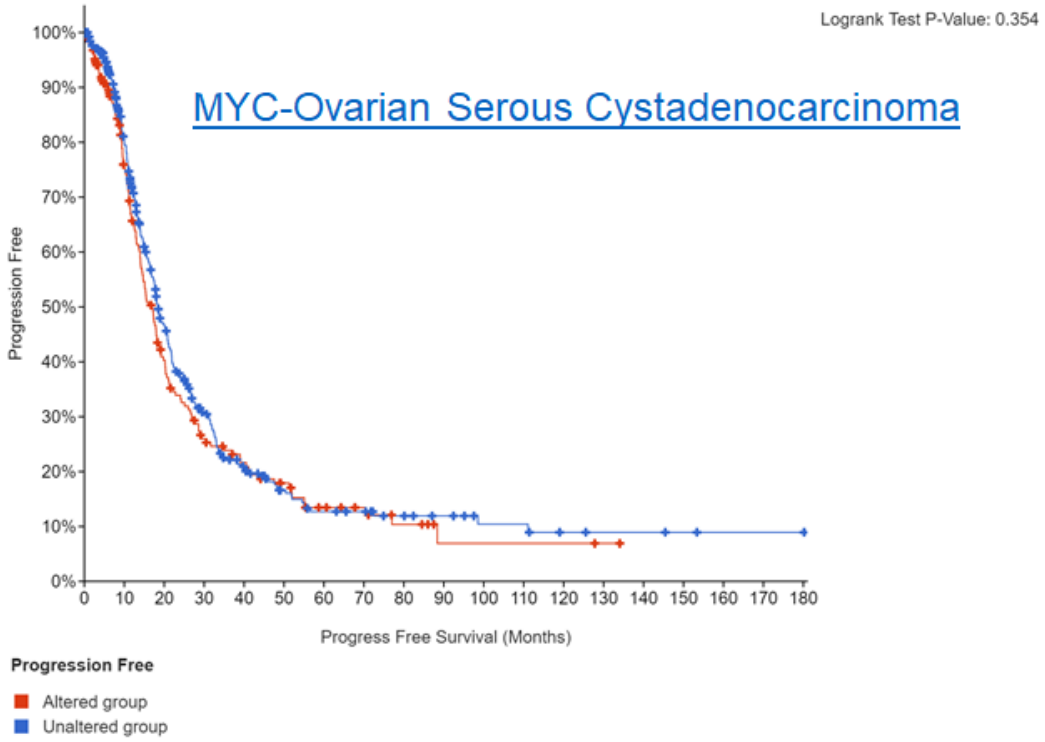
graph A:



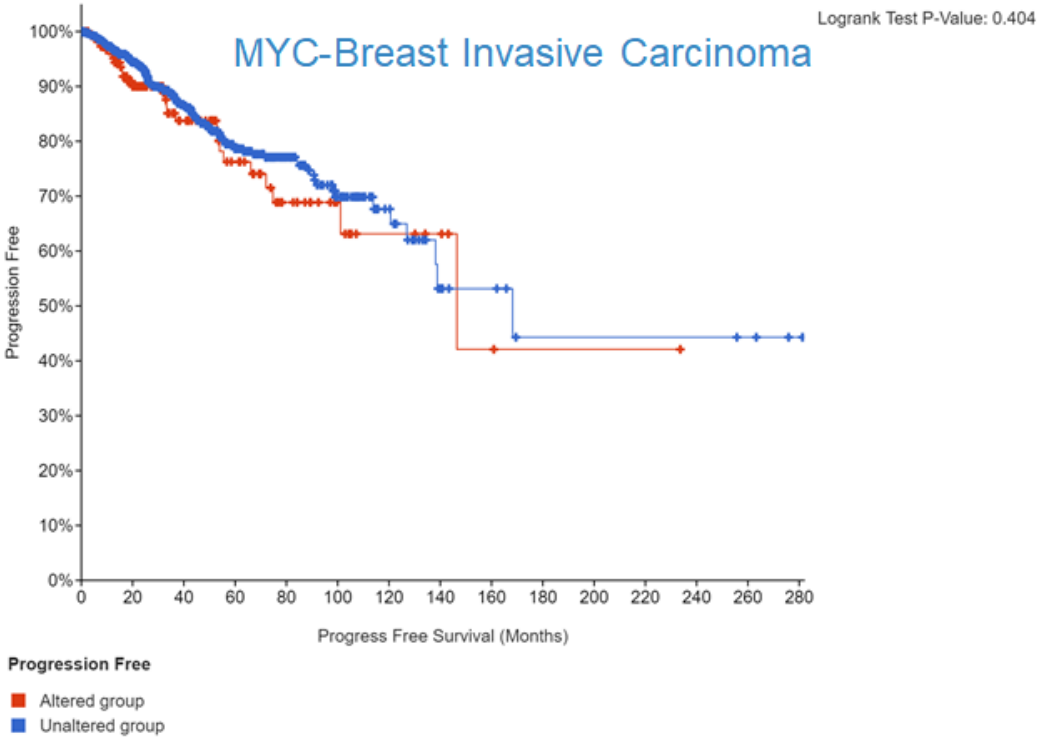
graph B:



graph C:

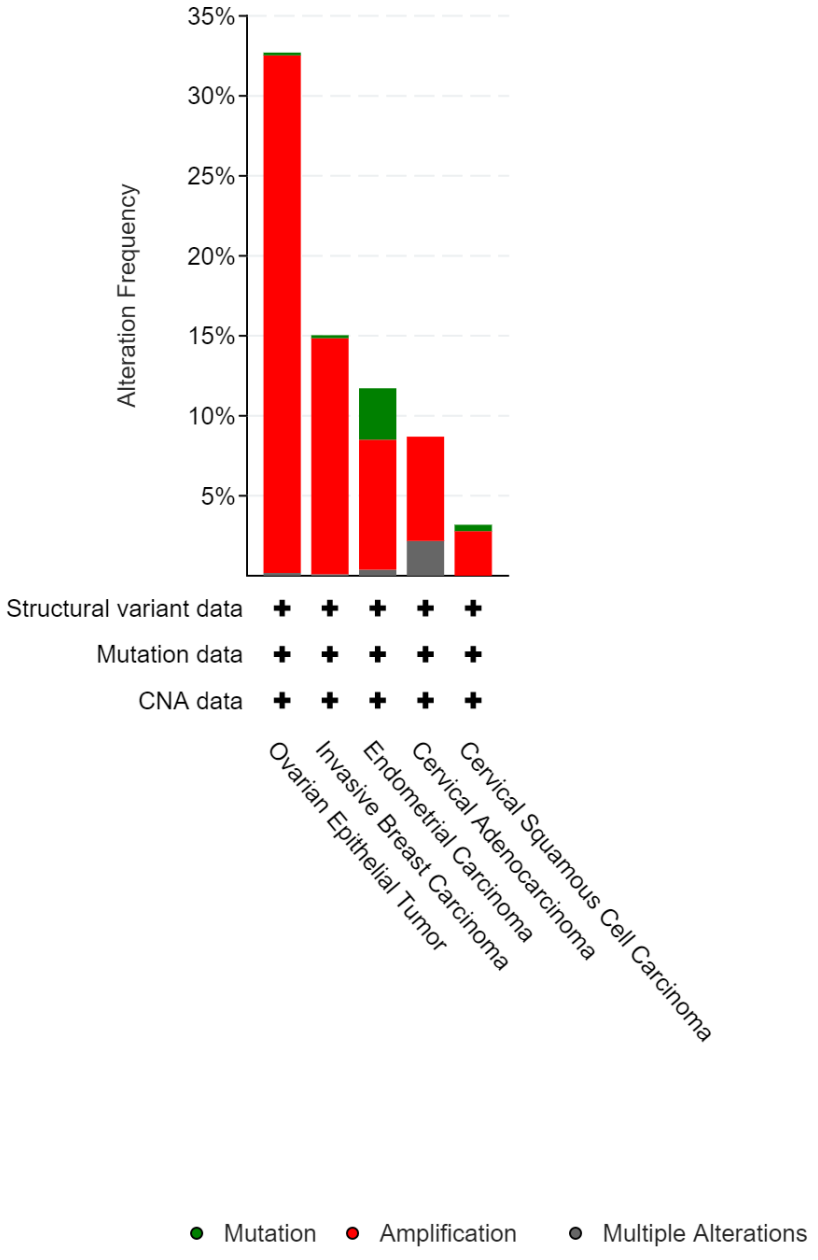


graph D:



1.6:

As we can see the most abundant genetic alteration in this gene is amplification - in red.



Question 2:

2.1:
Let-7g is affiliated with the miRNA class. MiRNAs are short (20-24 nt) non-coding RNAs that are involved in post-transcriptional regulation of gene expression in multicellular organisms by affecting both the stability and translation of mRNAs. MiRNAs are transcribed by RNA polymerase II as part of capped and polyadenylated primary transcripts (pri-miRNAs) that can be either protein-coding or non-coding.

Function of let-7g: according to the article “Folate deficiency disturbs hsa-let-7 g level through methylation regulation in neural tube defects” - hsa-let-7g plays important roles in the prevention of NTDs by folic acid.

In addition, MicroRNA let-7g acts as tumor suppressor and predictive biomarker for chemoresistance in human epithelial ovarian cancer and might be used to disable EOC tumor progression and chemoresistance to cis-platinum-based chemotherapy. Furthermore, we propose that decreased expression of let-7g could serve as a tissue and serum biomarker able to predict the chemo-resistant features of EOC patients.

(Biamonte, F., Santamaria, G., Sacco, A. et al. MicroRNA let-7g acts as tumor suppressor and predictive biomarker for chemoresistance in human epithelial ovarian cancer. Sci Rep 9, 5668 (2019). https://doi.org/10.1038/s41598-019-42221-x)

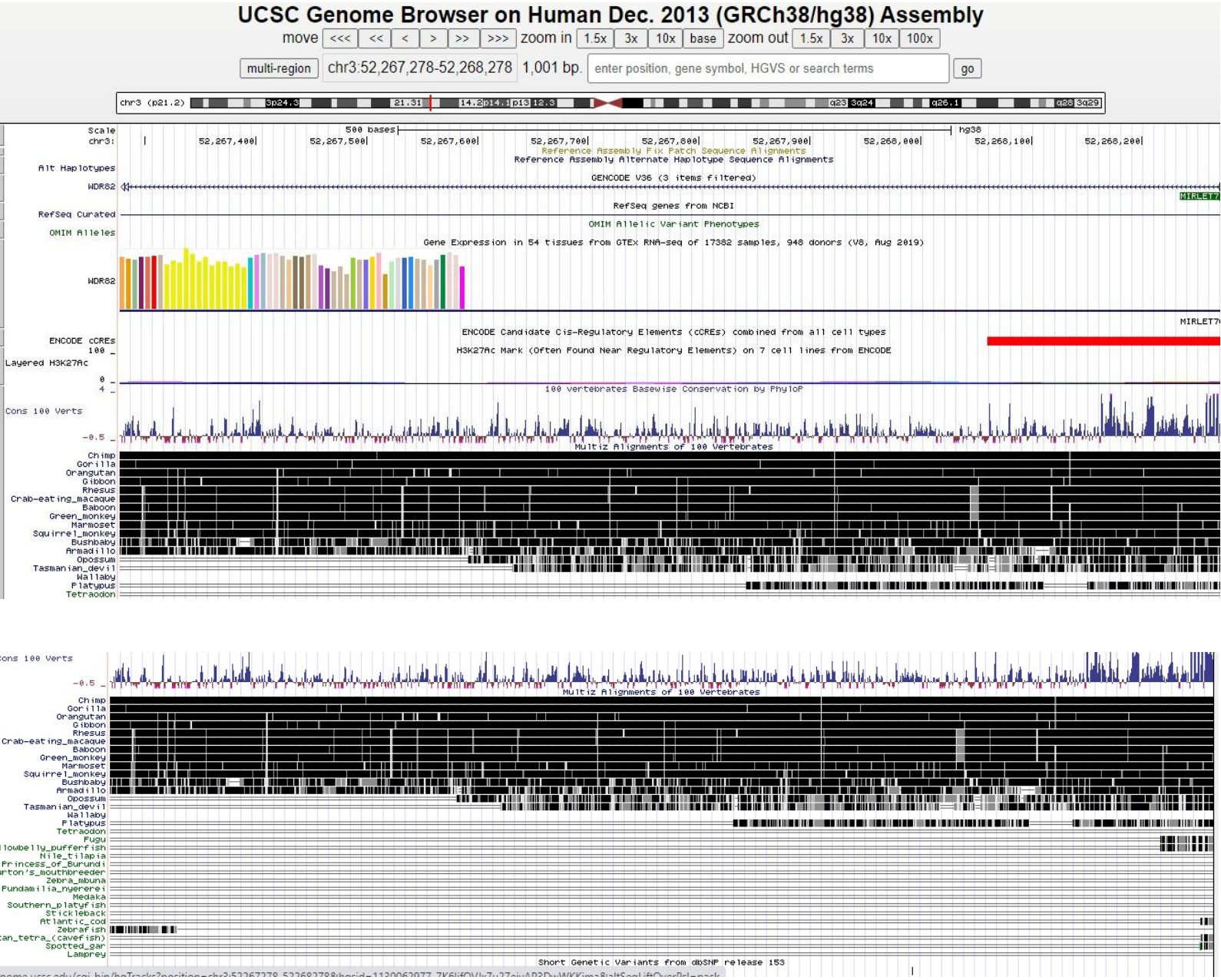
Diseases associated with let-7g include Ovarian Cancer and Lung Cancer. Among its related pathways are Metastatic brain tumors and MicroRNAs in cancer.

(https://www.genecards.org/cgi-bin/carddisp.pl?gene=MIRLET7G)

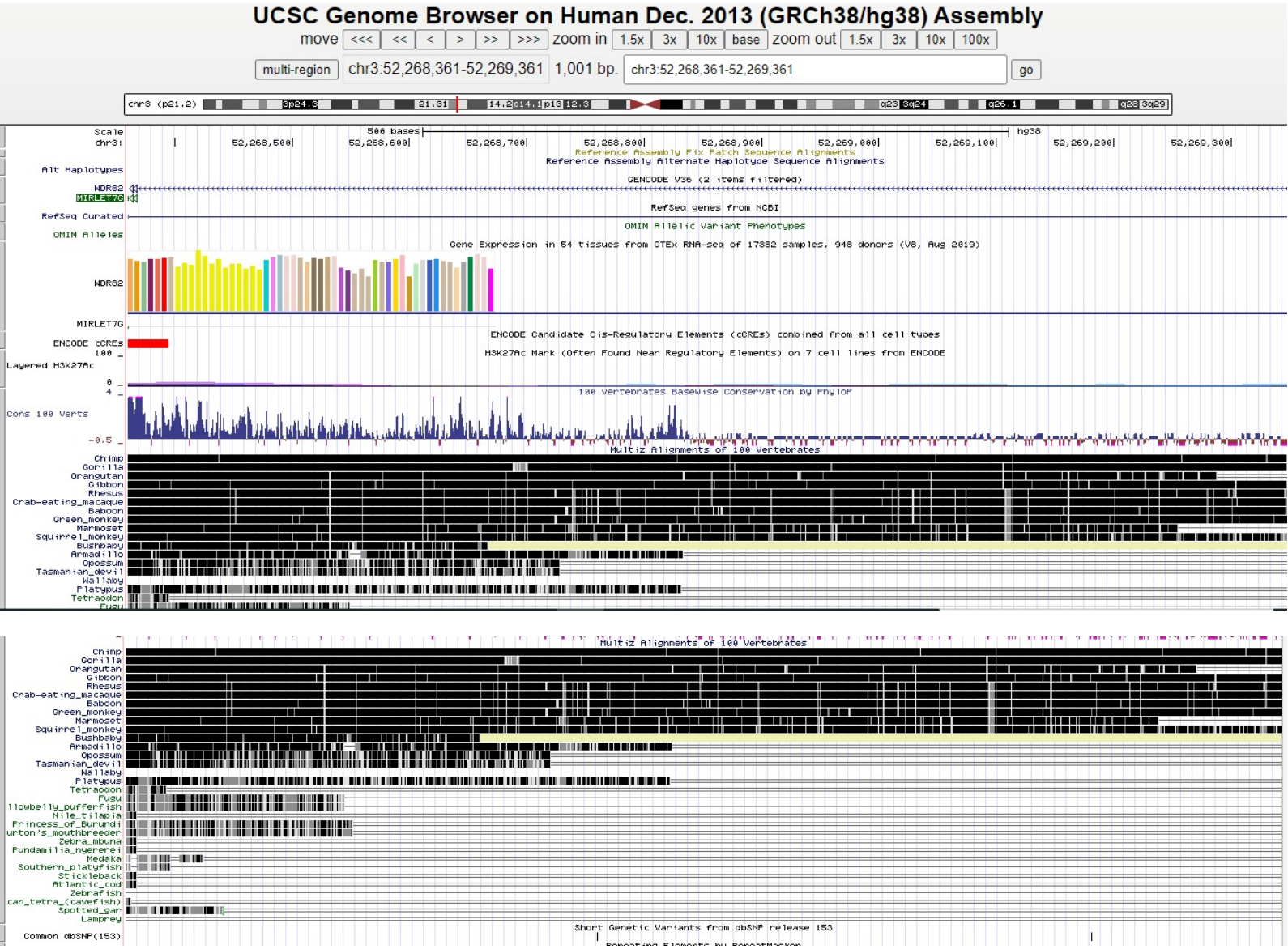
2.2.1
WDR82

2.2.2
Our gene is located at “chr3:52,268,278-52,268,361”.
we will show the conservation of the area at +- 1,000 bp from both sides of let-7g:

- Left side:


UCSC Genome Browser on Human Dec. 2013 (GRCh38/hg38) Assembly
move <<< << < > >> >>> zoom in 1.5x 3x 10x base zoom out 1.5x 3x 10x 100x
multi-region chr3:52,267,278-52,268,278 1,001 bp. enter position, gene symbol, HGVS or search terms go
chr3 (p21.2)
Scale
chr3:
500 bases
hg38
52,267,400 52,267,500 52,267,600 52,267,700 52,267,800 52,267,900 52,268,000 52,268,100 52,268,200
Reference Assembly Fix Patch Sequence Alignments
Reference Assembly Alternate Haplotype Sequence Alignments
Alt Haplotypes
GENCODE V36 (3 items filtered)
WDR82
MIRLET7
RefSeq Curated
RefSeq genes from NCBI
OMIM Alleles
OMIM Allelic Variant Phenotypes
Gene Expression in 54 tissues from GTEx RNA-seq of 17382 samples, 948 donors (V8, Aug 2019)
WDR82
ENCODE cCREs
ENCODE Candidate Cis-Regulatory Elements (cCREs) combined from all cell types
H3K27Ac Mark (Often Found Near Regulatory Elements) on 7 cell lines from ENCODE
Layered H3K27Ac
100 vertebrates Basewise Conservation by PhyloP
Cons 100 Verts
Multiz Alignments of 100 Vertebrates
Chimp
Gorilla
Orangutan
Gibbon
Rhesus
Crab-eating_macaque
Baboon
Green_monkey
Marmoset
Squirrel_monkey
Bushbaby
Armadillo
Opossum
Tasmanian_devil
Wallaby
Platypus
Tetraodon
Fugu
Nile_tilapia
Zebra_mbuna
Medaka
Southern_platyfish
Stickleback
Atlantic_cod
Zebrafish
Spotted_gar
Lamprey
Short Genetic Variants from dbSNP release 153

- Right side



We can say regarding the conservation of let-7g versus conservation of the area adjacent +-1000 bps to it, that the conservation of let-7g is identical in all verts almost completely. In contrast to the conservation of the area adjacent +-1000 bps to it which varies and is not permanent.

2.3:

A	B	Neither	A Not B	B Not A	Both	Log2 Odds Ratio ▼	p-Value	q-Value	Tendency
MIR-34/34A	TP53	1416	8	920	17	1.710	0.004	**0.006**	**Co-occurrence**
TP53	AGO2	1275	727	149	210	1.306	<0.001	**<0.001**	**Co-occurrence**
MIR-34/34A	AGO2	1984	18	352	7	1.132	0.073	0.073	Co-occurrence

Showing 1-3 of 3

2.3.1:
MIR-34A and TP53 , TP53 and AGO2, and MIR-34A and AGO2 all tend to co-occur.

2.3.2:
we can see that MIR-34A and TP53 have the highest value of log2 odds ratio,(positive-co occurrence and negative-mutually exclusive), therefore it's the most significant pair.
A study supporting the tendency described-Okada N, Lin CP, Ribeiro MC, et al. A positive feedback between p53 and miR-34 miRNAs mediates tumor suppression. Genes Dev. 2014;28(5):438-450. doi:10.1101/gad.233585.113.

2.3.3:
“miR-34a, one of the best described p53-regulated miRNA, contributes to tumor suppression by inhibiting cellular proliferation and survival; down-regulation of let-7a, let-7e, let-7f, some of let-7 family members, is associated with aggressive behaviour of tumor and represents potential markers of invasion and metastasis in EOC”
from-
Biamonte, F., Santamaria, G., Sacco, A. et al. MicroRNA let-7g acts as tumor suppressor and predictive biomarker for chemoresistance in human epithelial ovarian cancer. Sci Rep 9, 5668 (2019). https://doi.org/10.1038/s41598-019-42221-x.