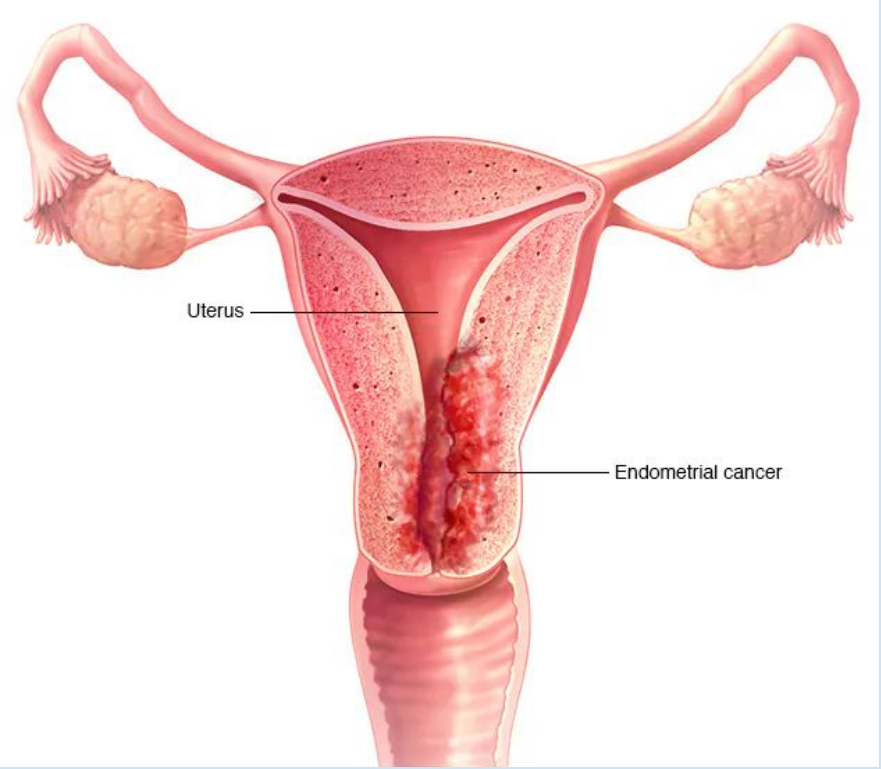
A Multi-Omic Analysis of Pregnancy Differences in Endometrial Carcinoma

Erika Li, Tomás Manea, Nathan Yoon

Background

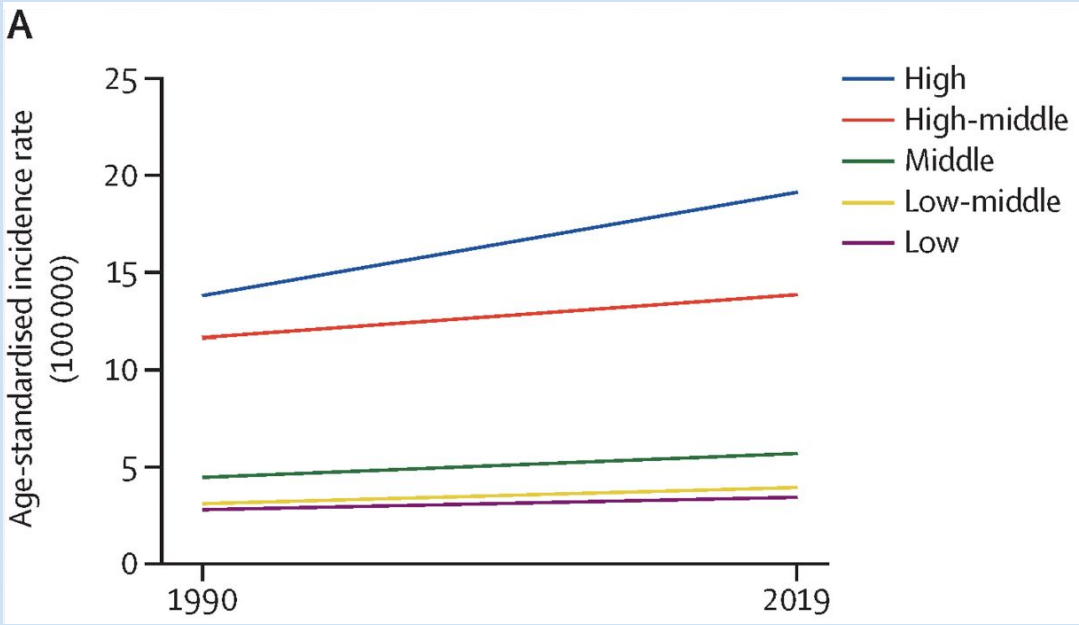
- Most common form of endometrial cancer
- Develops in uterine lining
- Symptomatology
- Treatment



Source: Mayo Clinic

Background

- 84% 5-year survival rate
- Over 400,000 new cases reported in 2020
    - Increasing incidence rate



Source: Crosbie et. al (2022)

Risk Factors

- Obesity
- Age
- Early menarche
- Late menopause
- Hormone treatment
- Nulliparity

Table 1
Risk Factors for Endometrial Carcinoma

Characteristic	No. of Times Risk Increased
Obesity	
30–49 lb	3.0
>50 lb	10.0
Nulliparity	2.0
Late menopause	2.4

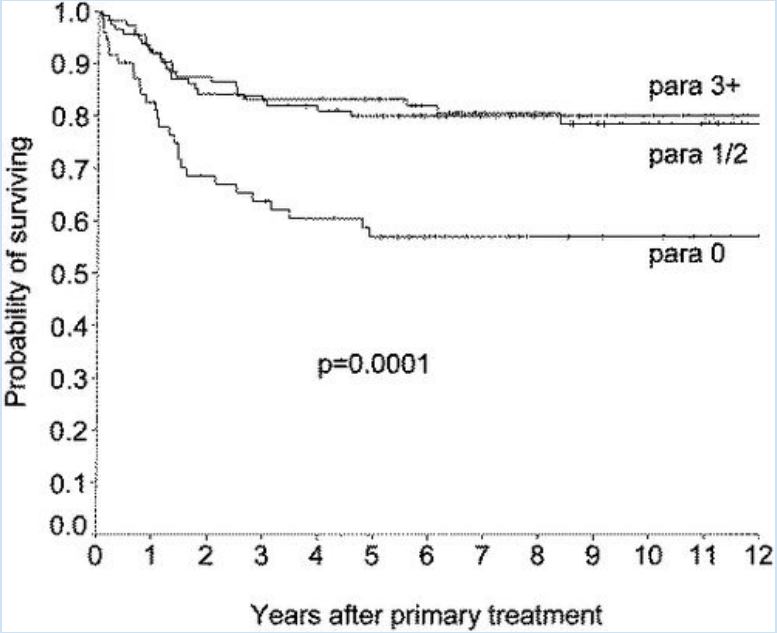
Source: Barakat et. al (1998)

Protective effects of pregnancy

- **Jordan et. al (2020)**: each full-term pregnancy associated with a 15% reduction in cancer risk
- **D'Urso et. al (2022)**: **3 live births** compared to none attributed to 50% decrease in cancer risk

Protective effects of pregnancy

- **Salvesen et. al (2000)**: nulliparous women had a poorer 5-year survival rate compared with patients who had had 1 or more deliveries
- **Hachisuga et. al (2002)**: highest survival in parity of **3 or more**



Aim to understand the variances between a **high pregnancy** group (three or more pregnancies) and a **low-medium pregnancy** group (less than three pregnancies), by exploring differences across **genomic**, **transcriptomic**, and **proteomic** landscapes in endometrial cancer.

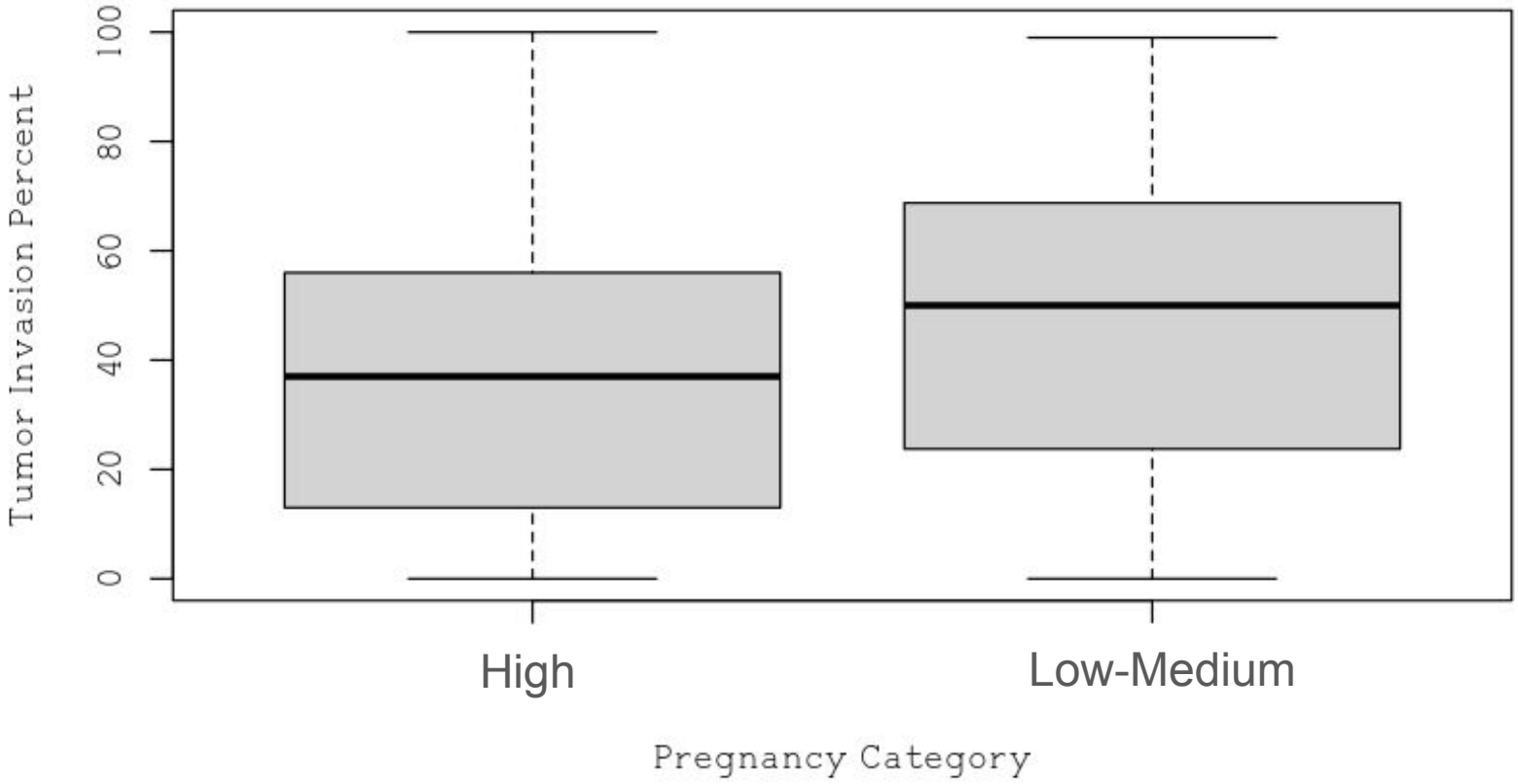
Introduction of Methods

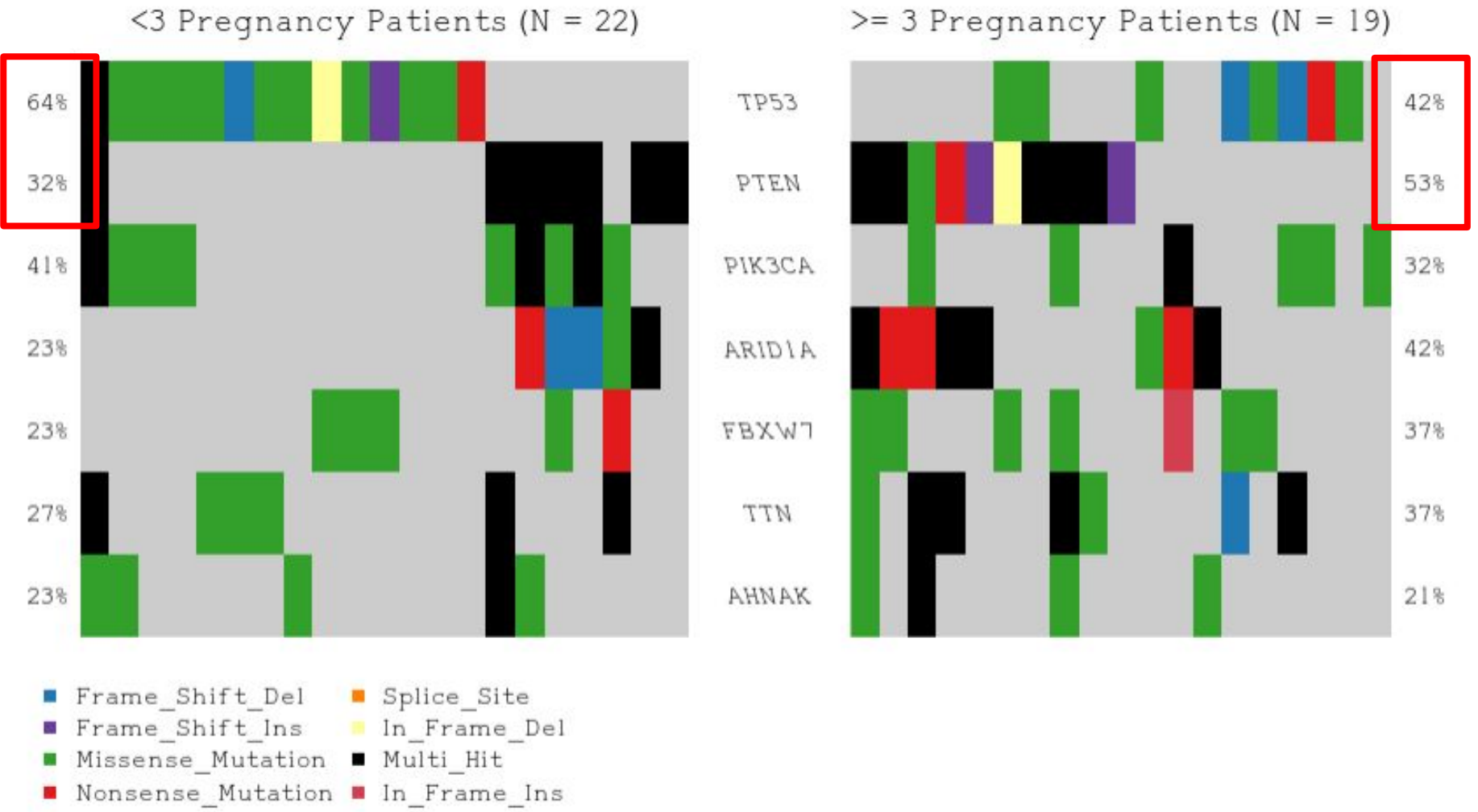
- The Cancer Genome Atlas **(TCGA)**
    - < 3 pregnancies: n = 22
    - ≥ 3 pregnancies: n = 19
- Clinical Proteomic Tumor Analysis Consortium **(CPTAC)**
    - < 3 pregnancies: n = 49
    - ≥ 3 pregnancies: n = 21

TCGA - Genomic and Transcriptomic Data Analysis in RStudio

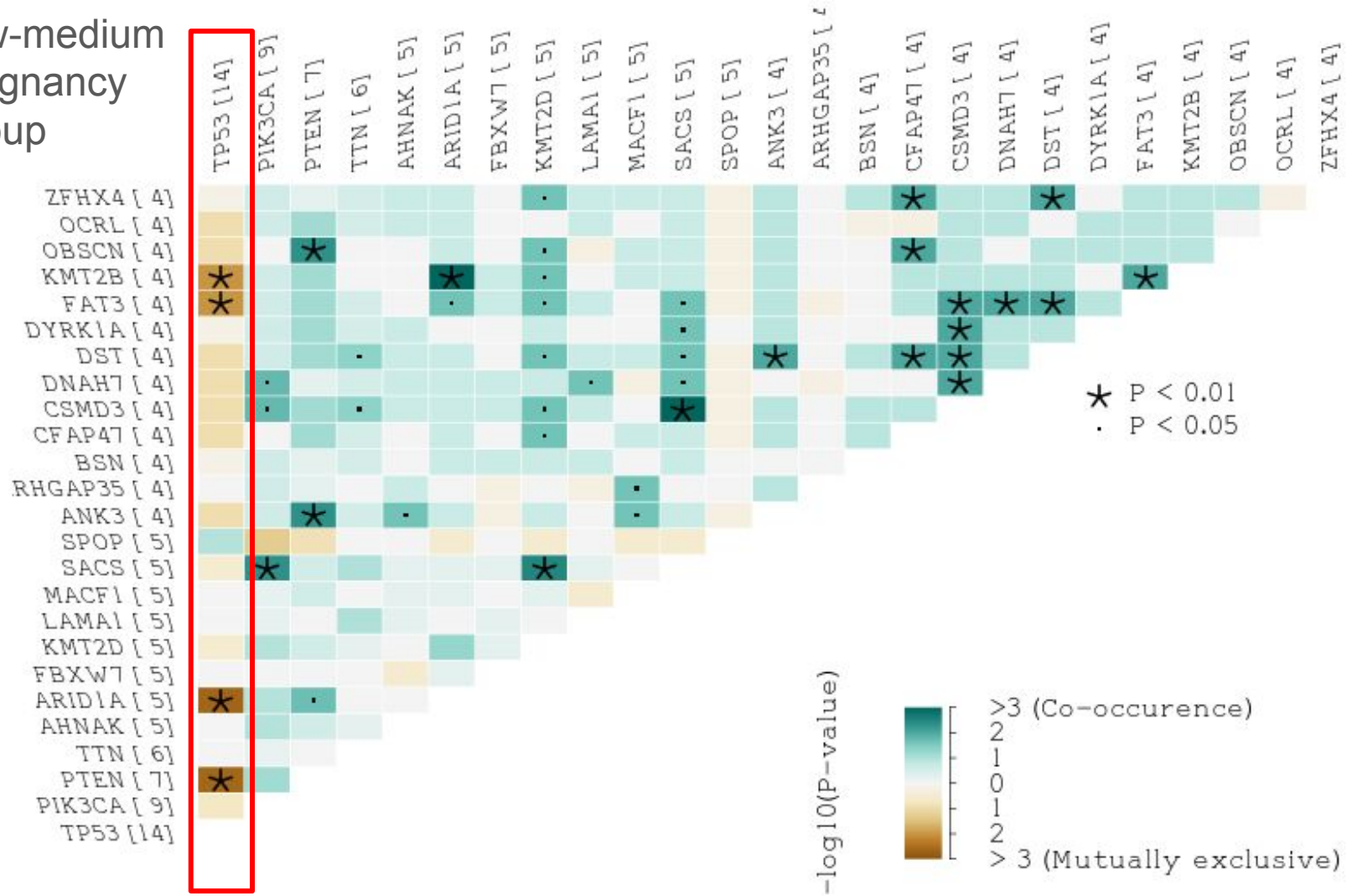
```
        Welch Two Sample t-test

data:  low_preg_pt$tumor_invasion_percent and high_preg_pt$tumor_invasion_percent
t = 1.3451, df = 35.48, p-value = 0.1871
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -6.446363 31.796522
sample estimates:
mean of x mean of y
 49.64286  36.96778
```

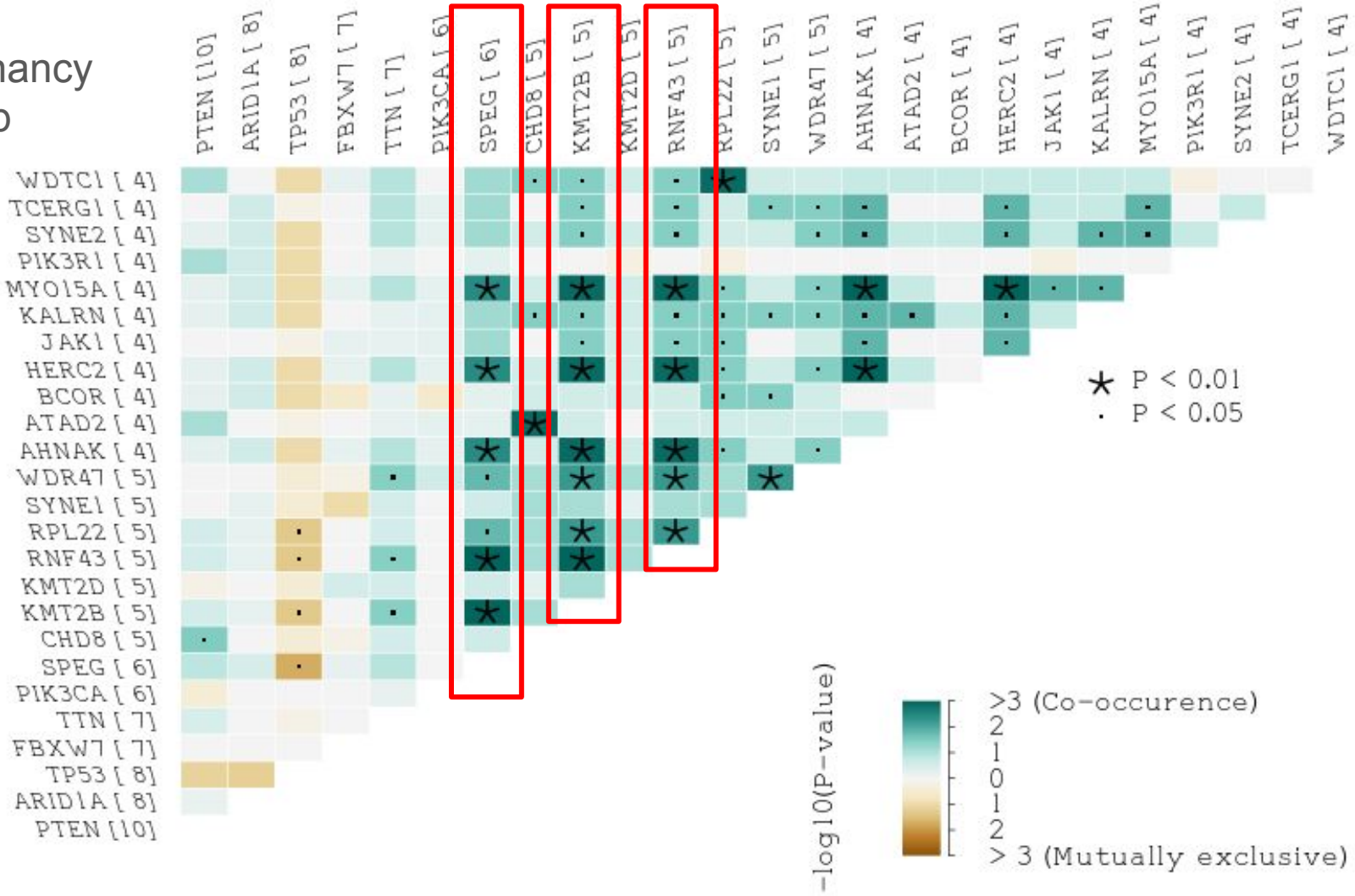


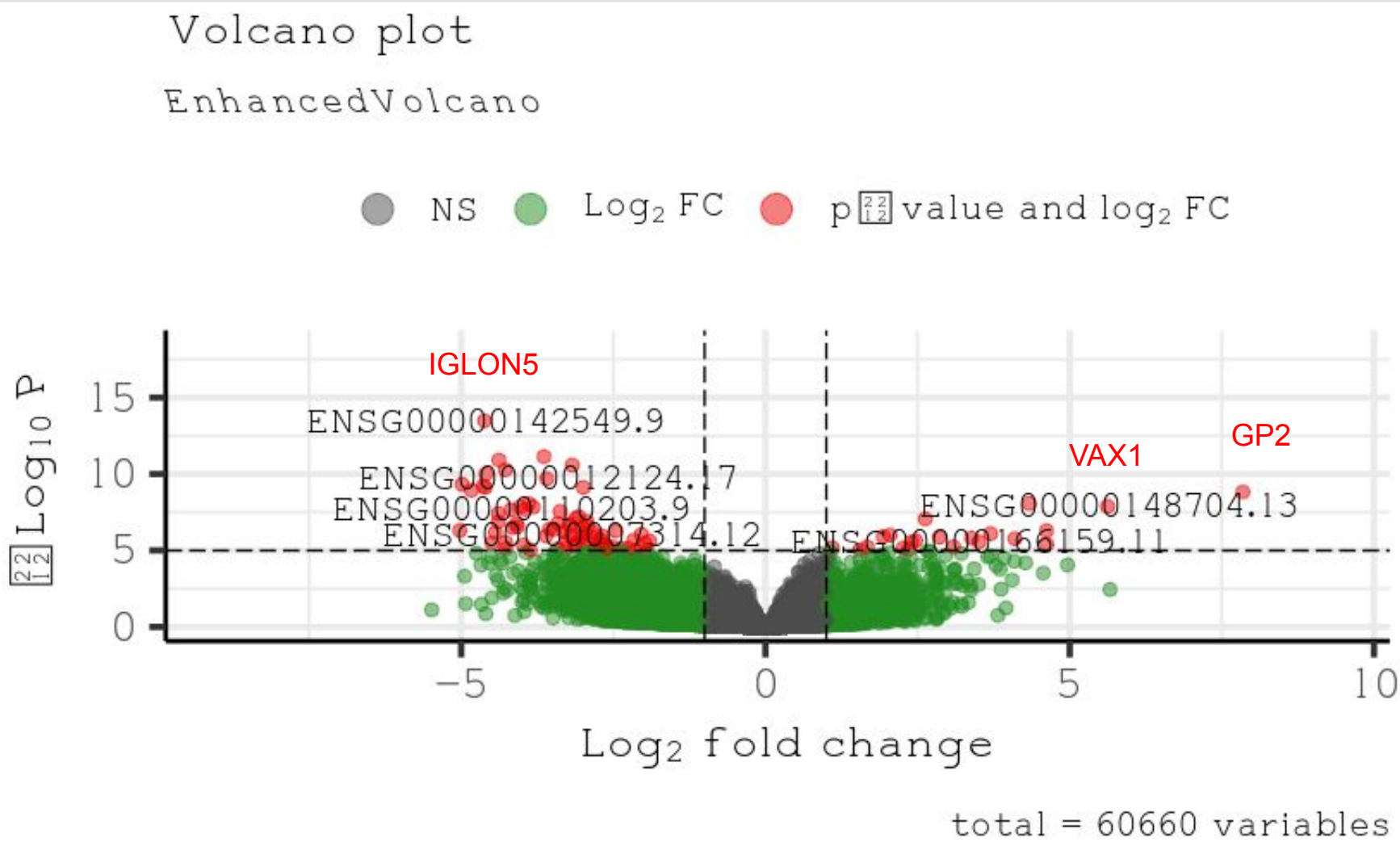

<3 Pregnancy Patients (N = 22)
>= 3 Pregnancy Patients (N = 19)
64%
32%
41%
23%
23%
27%
23%
TP53
PTEN
PIK3CA
ARID1A
FBXW7
TTN
AHNAK
42%
53%
32%
42%
37%
37%
21%
Frame_Shift_Del
Frame_Shift_Ins
Missense_Mutation
Nonsense_Mutation
Splice_Site
In_Frame_Del
Multi_Hit
In_Frame_Ins

Low-medium Pregnancy Group

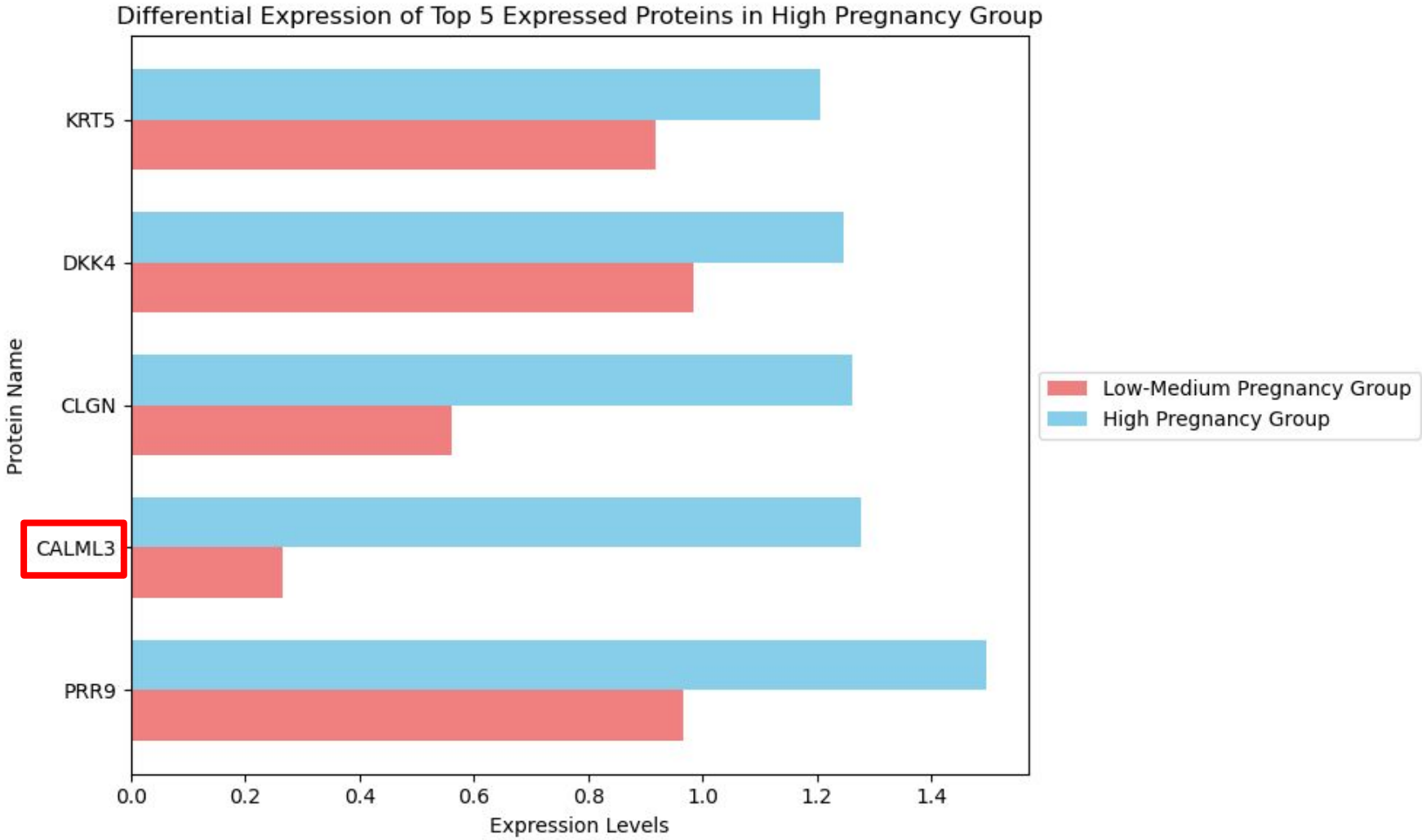


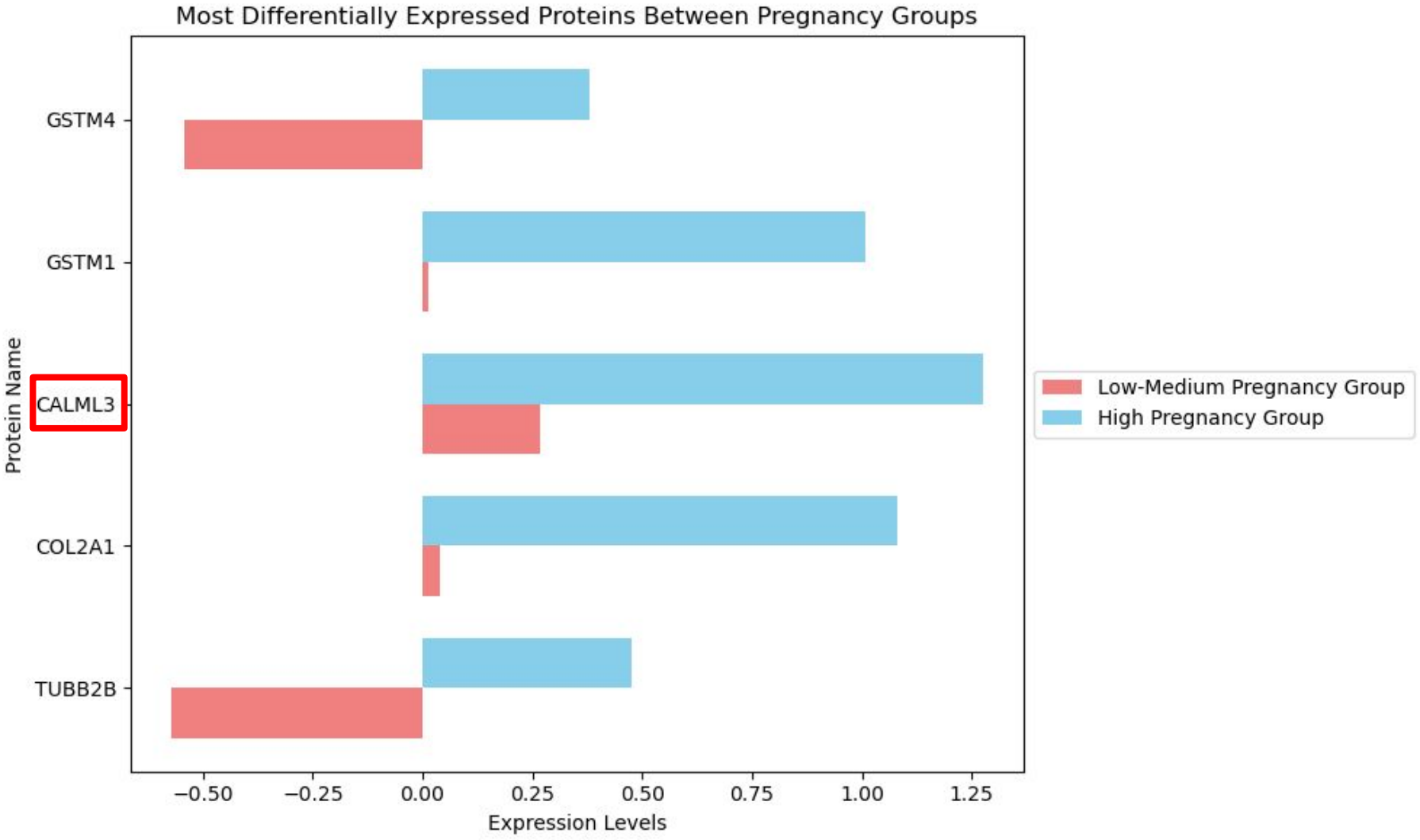
High Pregnancy Group




Volcano plot
EnhancedVolcano
NS
Log2 FC
p value and log2 FC
IGLON5
ENSG00000142549.9
ENSG00000012124.17
ENSG00000110203.9
ENSG00000007314.12
VAX1
GP2
ENSG00000148704.13
ENSG00000166159.11
Log10 P
15
10
5
0
−5
0
5
10
Log2 fold change
total = 60660 variables

CPTAC - Proteomic Data Analysis in Python


Differential Expression of Top 5 Expressed Proteins in High Pregnancy Group
KRT5
DKK4
CLGN
CALML3
PRR9
Protein Name
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
Expression Levels
Low-Medium Pregnancy Group
High Pregnancy Group


Most Differentially Expressed Proteins Between Pregnancy Groups
GSTM4
GSTM1
CALML3
COL2A1
TUBB2B
Protein Name
−0.50
−0.25
0.00
0.25
0.50
0.75
1.00
1.25
Expression Levels
Low-Medium Pregnancy Group
High Pregnancy Group

Discussion - TCGA

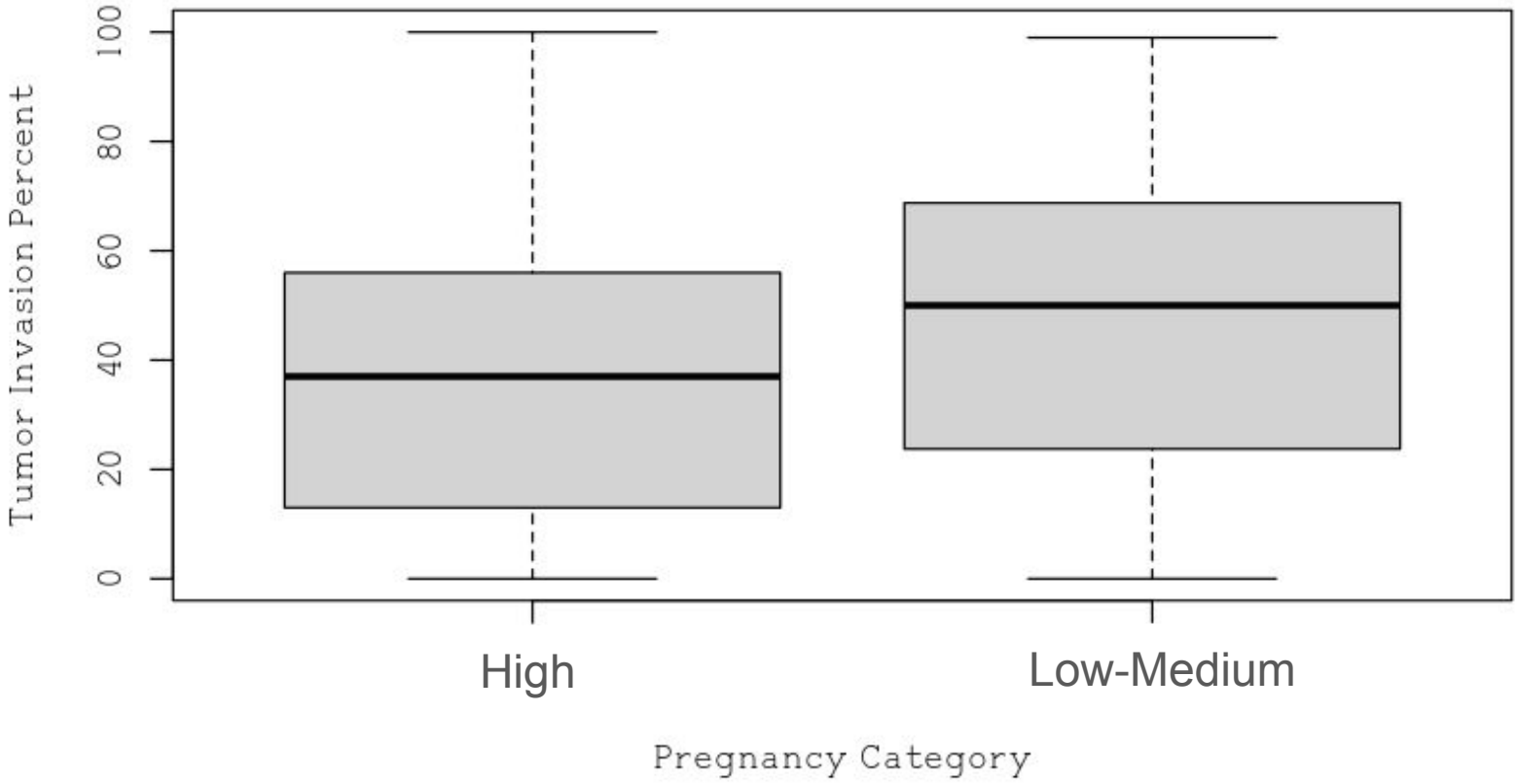
- **“High” pregnancy group**

- Genes, SPEG & RNF43, were ubiquitously co-occurrence

- Muscle Development - MYO15A & SPEG’s relation

```
        Welch Two Sample t-test

data:  low_preg_pt$tumor_invasion_percent and high_preg_pt$tumor_invasion_percent
t = 1.3451, df = 35.48, p-value = 0.1871
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -6.446363 31.796522
sample estimates:
mean of x mean of y
 49.64286  36.96778
```



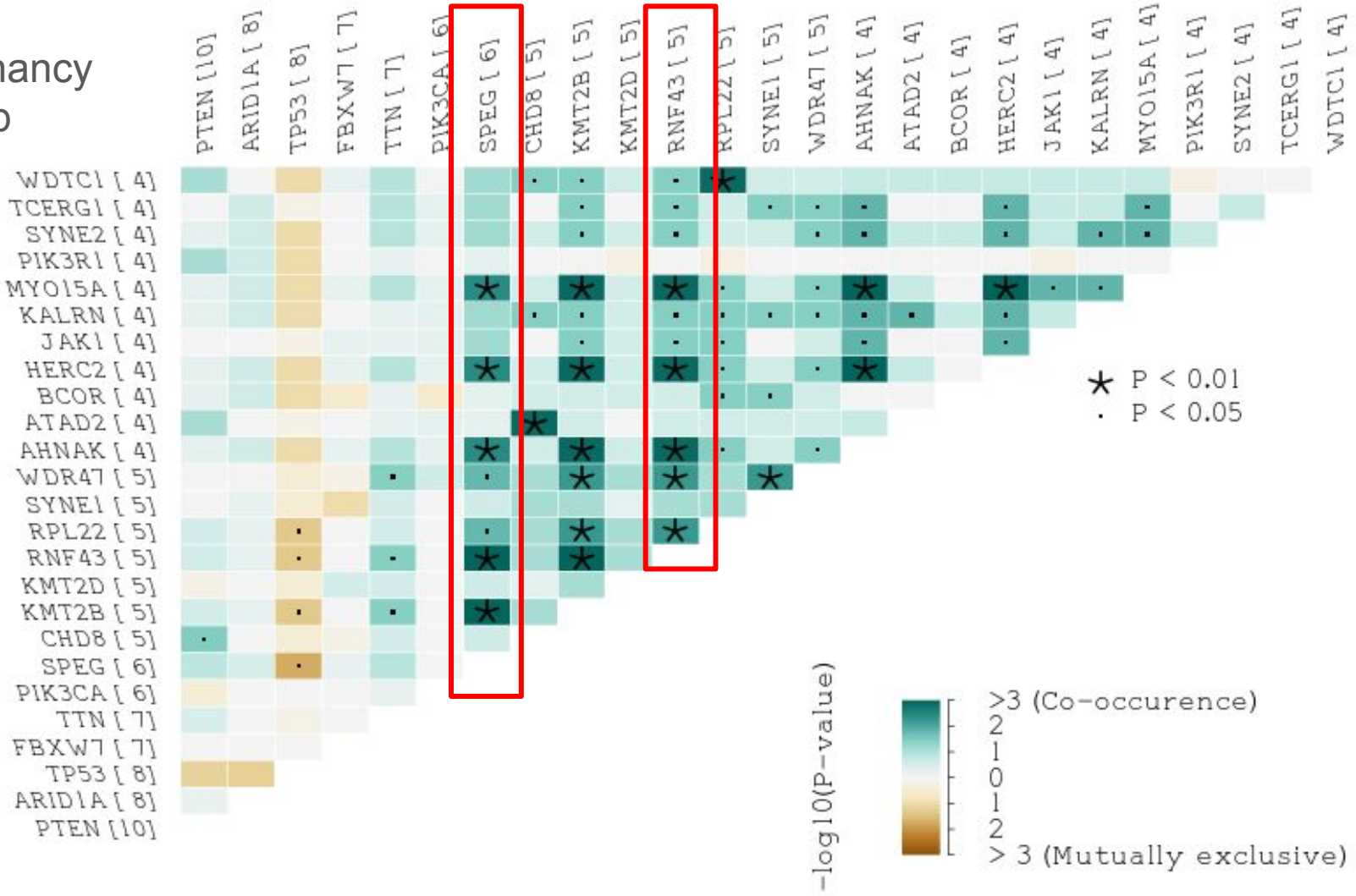
Discussion - TCGA

- “High” pregnancy group

- **Genes, SPEG & RNF43, were ubiquitously co-occurrence**

- **Muscle Development - MYO15A & SPEG’s relation**

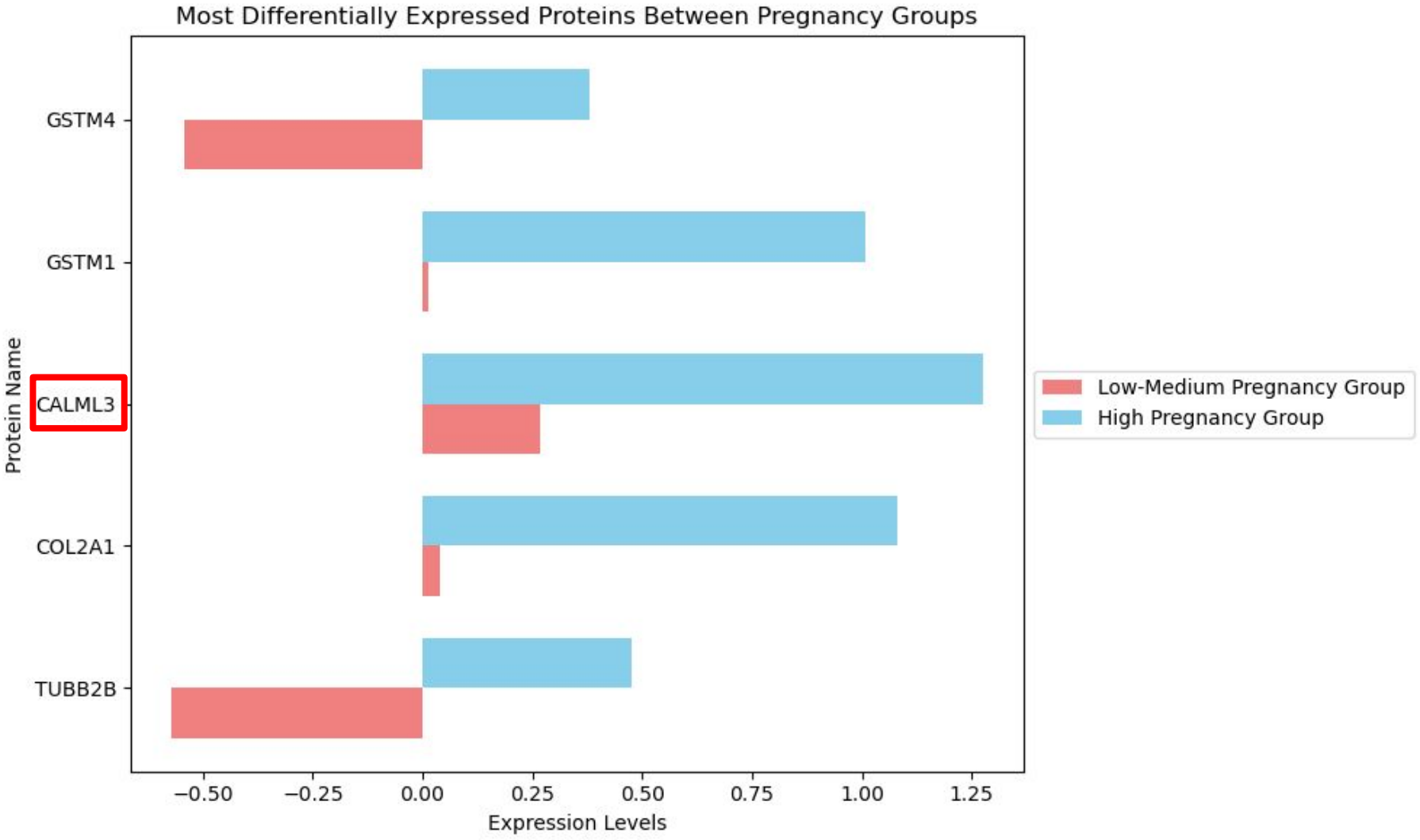
High Pregnancy Group



Discussion - CPTAC

- CALML3: Calcium ion binding activity

- Estrogen signaling & CALML3 upregulation


Most Differentially Expressed Proteins Between Pregnancy Groups
GSTM4
GSTM1
CALML3
COL2A1
TUBB2B
Protein Name
−0.50
−0.25
0.00
0.25
0.50
0.75
1.00
1.25
Expression Levels
Low-Medium Pregnancy Group
High Pregnancy Group

Discussion - CPTAC

- CALML3: Calcium ion binding activity

- Estrogen signaling & CALML3 upregulation

Limitations / Future Directions

- Stratifying parity through more factors

- Further contextualizing patient's data

- Honing in on myosin and estrogen-related protein pathways

Thank you for listening!
Questions?

References

Ali A. T. (2013). Risk factors for endometrial cancer. Ceska gynekologie, 78(5), 448–459.

Chavez, T. F., Snyder, R., Lee, R. K., et al. (2023). Rising endometrial cancer rates and potential for screening. International Journal of Gynecologic Cancer. https://doi.org/10.1136/ijgc-2023-004701.

Chen, Q., Tong, M., Guo, F., Lau, S., & Zhao, M. (2015). Parity Correlates with the Timing of Developing Endometrial Cancer, But Not Subtype of Endometrial Cancer. Journal of Cancer, 6(11), 1087–1092. https://doi.org/10.7150/jca.12736

Corpus uteri - International Agency for Research on Cancer. The Global Cancer Observatory. (2020). https://gco.iarc.fr/today/data/factsheets/cancers/24-Corpus-uteri-fact-sheet.pdf

Crosbie, E. J., Kitson, S. J., McAlpine, J. N., Mukhopadhyay, A., Powell, M. E., & Singh, N. (2022). Endometrial cancer. Lancet (London, England), 399(10333), 1412–1428. https://doi.org/10.1016/S0140-6736(22)00323-3

D'Urso, S., Arumugam, P., Weider, T., et al. (2022). Mendelian randomization analysis of factors related to ovulation and reproductive function and endometrial cancer risk. BMC Med, 20, 419. https://doi.org/10.1186/s12916-022-02585-w

Giannakis, M., Hodis, E., Jasmine Mu, X., Yamauchi, M., Rosenbluh, J., Cibulskis, K., Saksena, G., Lawrence, M. S., Qian, Z. R., Nishihara, R., Van Allen, E. M., Hahn, W. C., Gabriel, S. B., Lander, E. S., Getz, G., Ogino, S., Fuchs, C. S., & Garraway, L. A. (2014). RNF43 is frequently mutated in colorectal and endometrial cancers. Nature genetics, 46(12), 1264–1266. https://doi.org/10.1038/ng.3127

Hachisuga, T., Fukuda, K., Hirakawa, T., & Kawarabayashi, T. (2001). The Effect of Nulliparity on Survival in Endometrial Cancer at Different Ages. Gynecologic Oncology, 82(1), 122-126. https://doi.org/10.1006/gyno.2001.6220

Jordan, S. J., Na, R., Weiderpass, E., Adami, H. O., et al. (2021). Pregnancy outcomes and risk of endometrial cancer: A pooled analysis of individual participant data in the Epidemiology of Endometrial Cancer Consortium. International Journal of Cancer, 148(9), 2068–2078. https://doi.org/10.1002/ijc.33360

References (continued)

Main, C., Chen, X., Zhao, M., Chamley, L. W., Chen, Q. (2022). Understanding How Pregnancy Protects Against Ovarian and Endometrial Cancer Development: Fetal Antigens May Be Involved. Endocrinology, 163(11), bqac141. https://doi.org/10.1210/endocr/bqac141

Murali, R., Soslow, R. A., & Weigelt, B. (2014). Classification of endometrial carcinoma: more than two types. The Lancet. Oncology, 15(7), e268–e278. https://doi.org/10.1016/S1470-2045(13)70591-6

Novetsky, A. P., Zighelboim, I., Thompson, D. M., Jr, Powell, M. A., Mutch, D. G., & Goodfellow, P. J. (2013). Frequent mutations in the RPL22 gene and its clinical and functional implications. Gynecologic oncology, 128(3), 470–474. https://doi.org/10.1016/j.ygyno.2012.10.026

Salvesen, H. B., Akslen, L. A., Albrektsen, G., & Iversen, O. E. (1998). Poorer survival of nulliparous women with endometrial carcinoma. Cancer, 82(7), 1328-1333. https://doi.org/10.1002/(SICI)1097-0142(19980401)82:7<1328::AID-CNCR16>3.0.CO;2-8

Suda, K., Nakaoka, H., Yoshihara, K., Ishiguro, T., Tamura, R., Mori, Y., Yamawaki, K., Adachi, S., Takahashi, T., Kase, H., Tanaka, K., Yamamoto, T., Motoyama, T., Inoue, I., & Enomoto, T. (2018). Clonal Expansion and Diversification of Cancer-Associated Mutations in Endometriosis and Normal Endometrium. Cell reports, 24(7), 1777–1789. https://doi.org/10.1016/j.celrep.2018.07.037

Raglan, O., Kalliala, I., Markozannes, G., Cividini, S., Gunter, M. J., Nautiyal, J., Gabra, H., Paraskevaidis, E., Martin-Hirsch, P., Tsilidis, K. K., & Kyrgiou, M. (2019). Risk factors for endometrial cancer: An umbrella review of the literature. International Journal of Cancer, 145, 1719-1730. https://doi.org/10.1002/ijc.31961

Survival Rates for Endometrial Cancer. American Cancer Society. https://www.cancer.org/cancer/types/endometrial-cancer/detection-diagnosis-staging/survival-rates.html

Wu, Q. J., Li, Y. Y., Tu, C., et al. (2015). Parity and endometrial cancer risk: a meta-analysis of epidemiological studies. Sci Rep, 5, 14243. https://doi.org/10.1038/srep14243