COMPARATIVE GENOMIC PROFILING OF DIFFERENTIALLY EXPRESSED GENES AND PATHWAYS IN A CROSS-CANCER CONTEXT: BREAST CANCER, LUNG CANCER, LEUKEMIA AND SKIN CANCER

PRESENTED BY

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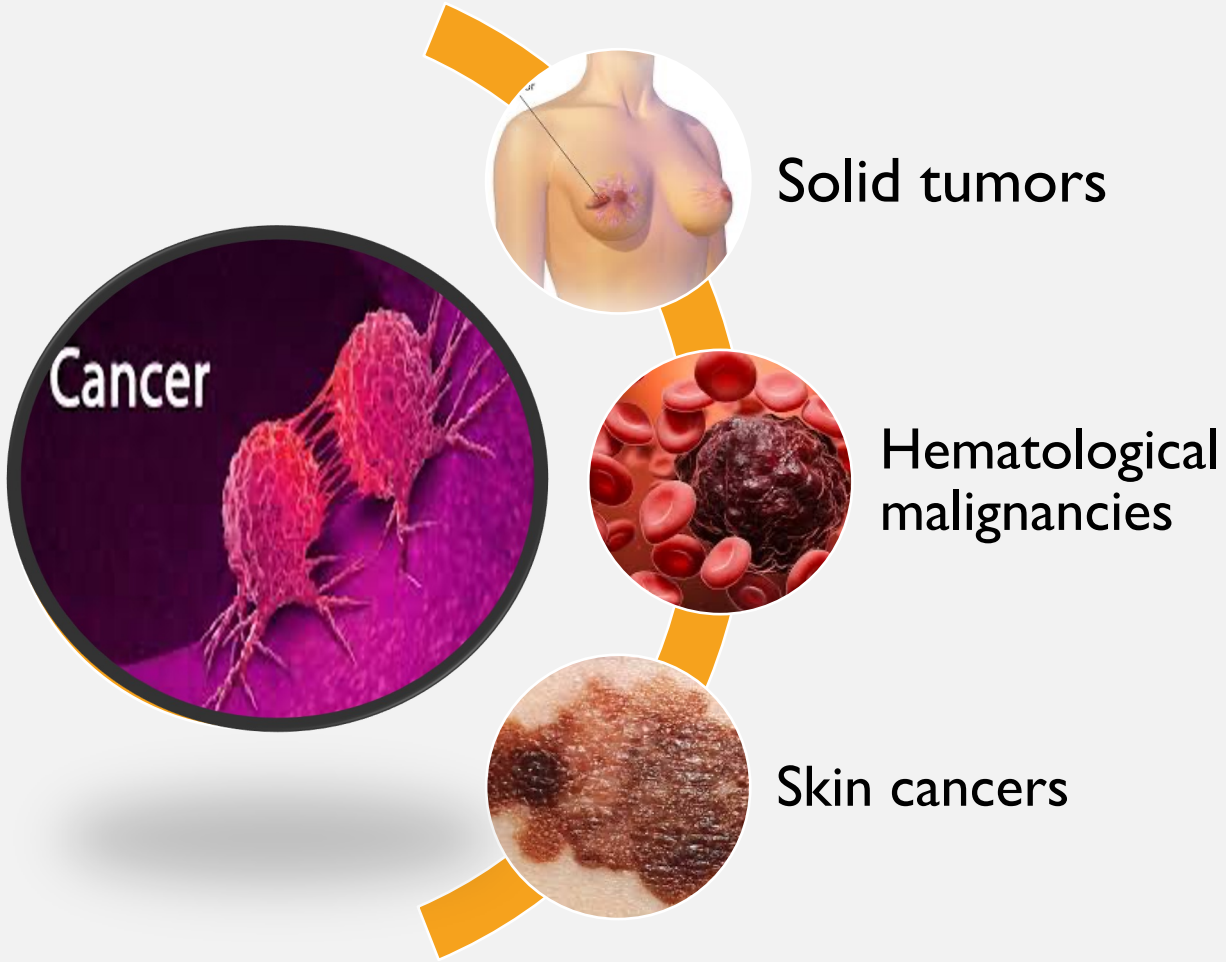
BACKGROUND: CANCER OVERVIEW

- Cancer is a major public health challenge in the 21st century.
- Cancer is characterized by the uncontrolled division of abnormal cells that can originate in almost any part of the body.
- In 2022, there were approximately 20 million new cancer cases and 9.7 million deaths globally.
- Cancers can be categorized into three, each with unique causes and characteristics.



BACKGROUND: PAN-CANCER RESEARCH

- A substantial number of studies have shown similarities between different cancers, such as key driver mutations, immune and microbial signatures.
- Many studies have identified cancer markers, but most focus on a single type of cancer.
- Pan-cancer analysis overcomes this limitation by increasing sample size, providing a powerful approach to studying cancer's heterogeneity.
- Pan-cancer research allows us to understand that the same cancer can differ at the molecular level, while diverse cancers may share molecular profiles.
- This shared etiology among cancers suggests the existence of pan-cancer biomarkers.

BACKGROUND: DEGS AND PATHWAYS

- With the progress of gene expression profiling methods such as RNA-seq, we have the ability to identify DEGs and shared signaling pathways.
- Differentially expressed genes (DEGs) are those whose expression levels differ significantly between cancerous and normal tissues.
- Each type of cancer is driven by unique regulatory circuits—signaling pathways and transcriptional regulators—that, when disrupted, contribute to the malignancy's progression.
- With such analyses, new potential biomarkers for developing broad spectrum anti-cancer treatment strategies can be discovered.

PROBLEM STATEMENT

- The heterogeneity of cancer, characterized by the diversity of molecular mechanisms across various types, poses a significant challenge to effective treatment and precision medicine.
- Each cancer types displays distinct genetic and epigenetic profiles that complicate their diagnosis and treatment.
- It is crucial to understand their distinct and shared molecular mechanisms to develop targeted therapies but also advance our understanding of cancer's underlying biology.
- While there are various treatment modalities tailored to specific cancers, the availability of broad-spectrum anti-cancer drugs remains limited, emphasizing the urgent need for discovery of more –such therapies.
- This potentiates the need to identify common DEGs and shared signaling pathways across diverse cancer types for the discovery of new pan-cancer biomarkers.
- Molecularly targeted therapies reduce costs and improve accessibility for early and accurate cancer diagnosis.

OBJECTIVES

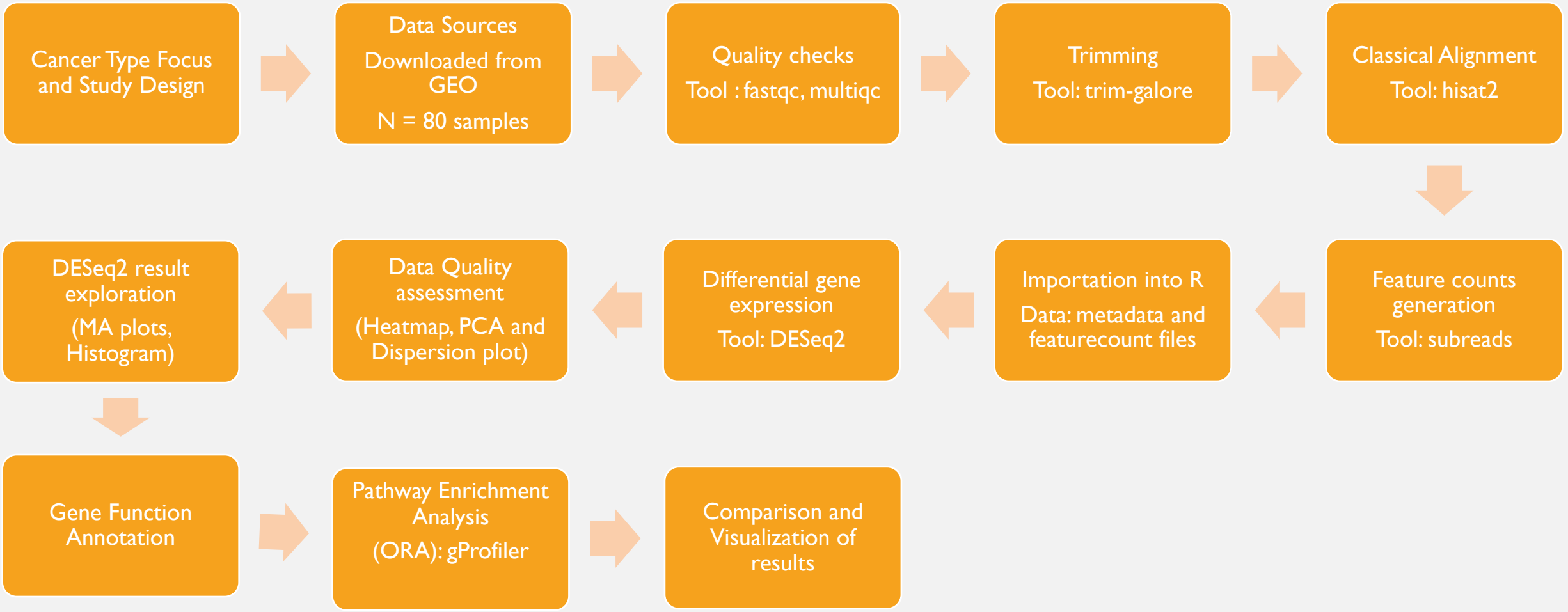
To identify common DEGs and shared signaling pathways across three cancer types.

1. **To identify and compare DEGs across solid tumors (breast cancer and lung cancer), hematological malignancies (leukemia), and skin cancers (Skin KS, GI KS, and Uveal Melanoma) using RNA-Seq data.**

2. **To perform pathway enrichment analysis to determine the biological pathways and biological terms significantly altered in each cancer type.**

3. **To compare and contrast the pathways and biological terms among the cancer types to identify common and unique molecular features.**

METHODOLOGY



IDENTIFICATION OF DEGS AMONG EACH CANCER TYPE

REGULATION	BREAST CANCER		LUNG CANCER		SKIN CANCERS			LEUKEMIA
	TNBC	HER2	KRAS	EGFR &MET	SKIN KS	GI-KS	UVEAL	
UPREGULATED	4	173	123	8	416	95	645	1273
DOWNREGULATED	11	4	6	12	142	2	1031	1171
TOTAL	**15**	**177**	**129**	**20**	**558**	**97**	**1676**	**2444**

IDENTIFICATION OF DEGS AMONG EACH CANCER TYPE

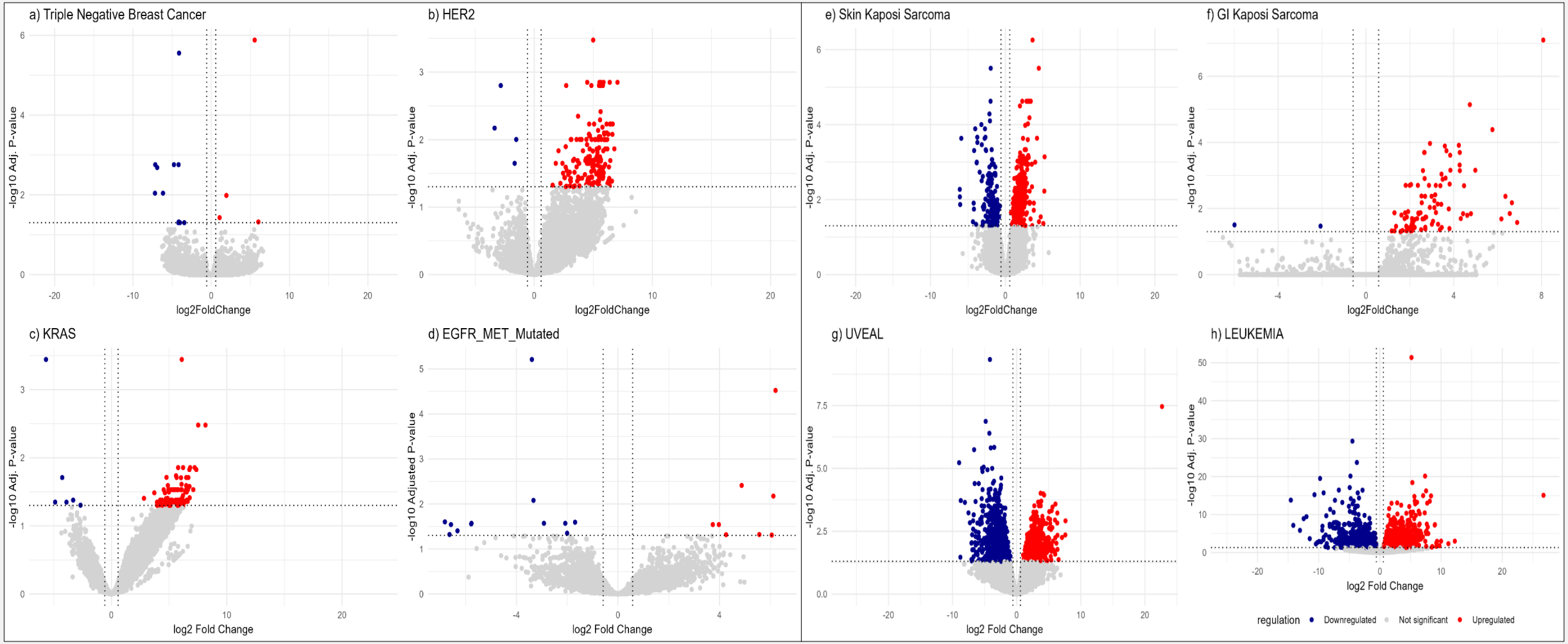


Figure 1:Volcano plots for each cancer type (a – h) showing the upregulated, downregulated and non-significant genes obtained after applying the selection criteria. Each dot represents one gene. The blue and red dots above and each side of the dotted line corresponds to those genes having p value ≤ 0.05 and log2fold change |0.58|. Blue dots are downregulated, and Red dots are upregulated genes.

DEGS ACROSS MULTIPLE CANCER TYPES

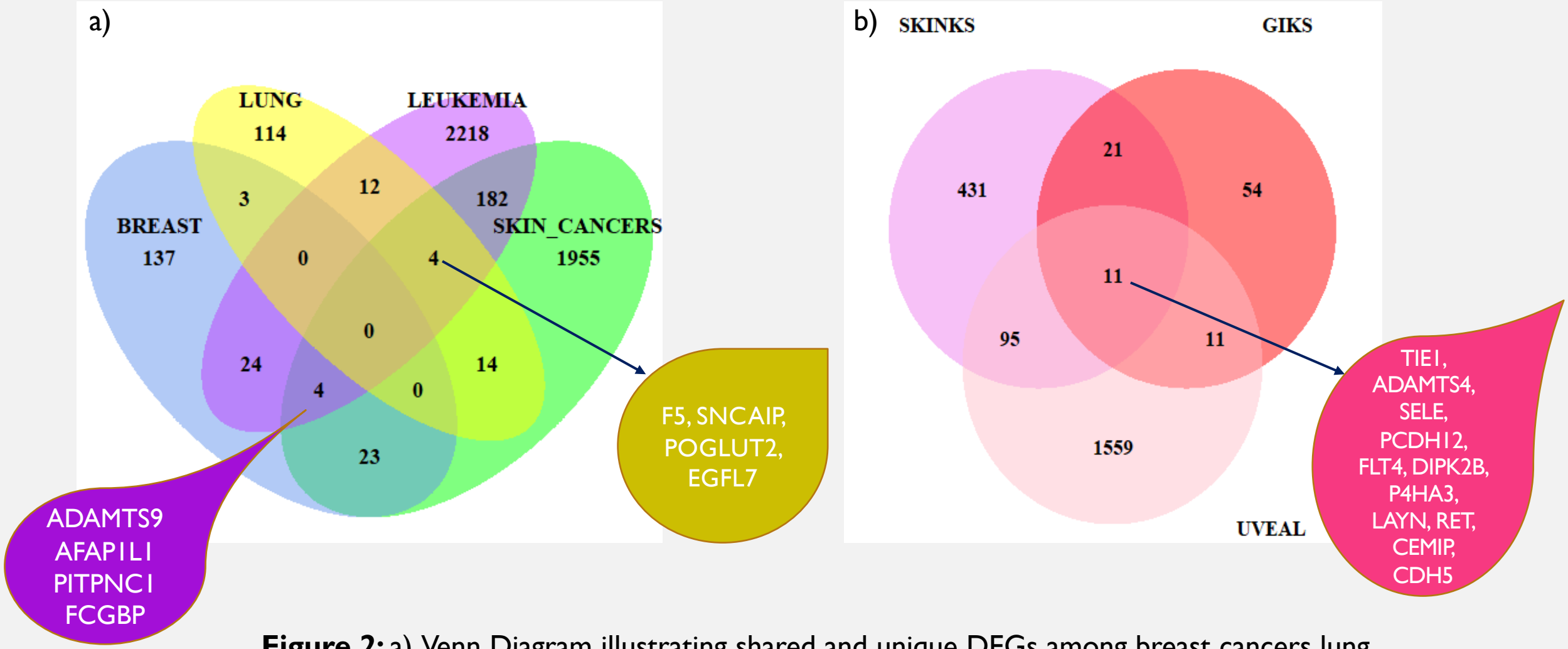


Figure 2: a) Venn Diagram illustrating shared and unique DEGs among breast cancers lung cancers, skin cancers and Leukemia. b) Venn Diagram depicting DEGs that are common among the skin cancers and those unique to each type.

DEGS ACROSS MULTIPLE CANCER TYPES

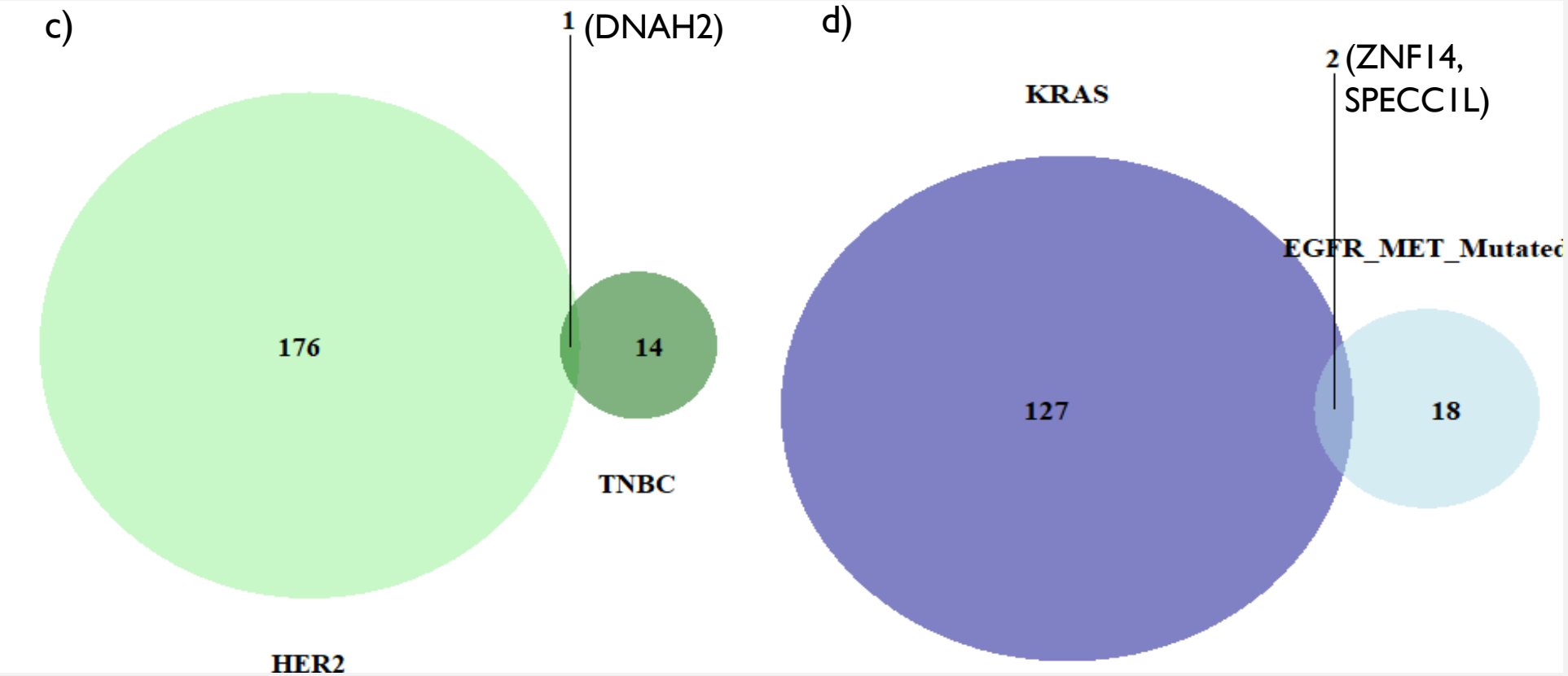


Figure 3: c) Venn Diagram showing DEGs that are shared between the breast cancers (TNBC and HER2) and those unique to each type. d) Venn Diagram indicating DEGs that are shared between the lung cancers (KRAS and EGFR_MET mutated) and those unique to each type.

UNIQUE AND SHARED DEGS ACROSS THE CANCER TYPES

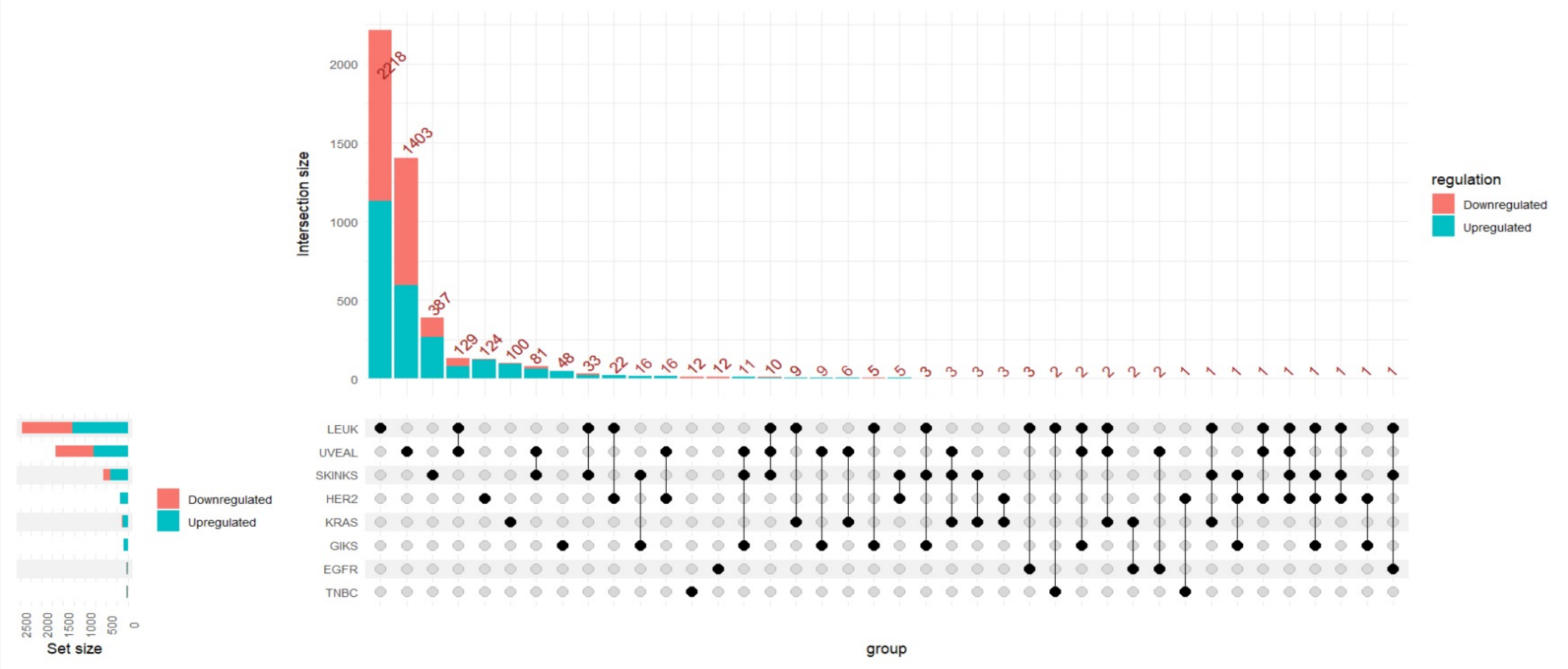
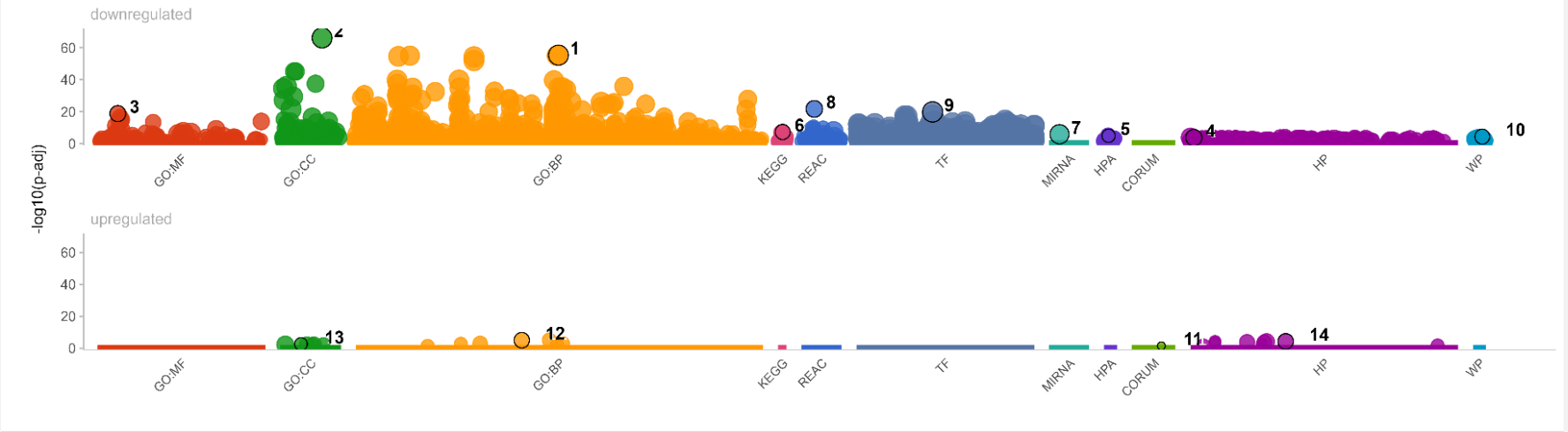


Figure 4: UpSet Plot Depicting the Exclusive Intersection of Differentially Expressed Genes Across the Eight Cancer Types: TNBC, HER2+, KRAS-mutated, EGFR-mutated, Skin-KS, GI-KS, Uveal melanoma, and Leukemia (LEUK).

ENRICHED PATHWAYS AND BIOLOGICAL FUNCTIONS



id	source	term_id	term_name	term_size	p_value downregulated	p_value upregulated
1	GO:BP	GO:0048856	anatomical structure development	5858	4.2e-56	NA
2	GO:CC	GO:0071944	cell periphery	6167	6.6e-67	NA
3	GO:MF	GO:0005201	extracellular matrix structural constituent	166	1.7e-19	NA
4	HP	HP:0000272	Malar flattening	208	1.8e-04	NA
5	HPA	HPA:0640693	endometrium; smooth muscle cells[High]	27	1.3e-05	NA
6	KEGG	KEGG:04512	ECM-receptor interaction	89	5.4e-08	NA
7	MIRNA	MIRNA:hsa-miR-335-5p	hsa-miR-335-5p	2532	1.4e-06	NA
8	REAC	REAC:R-HSA-1474244	Extracellular matrix organization	297	1.9e-22	NA
9	TF	TF:M13128_1	Factor: MED8; motif: CYYNSCYYCCTSCNCC; match class: 1	7806	1.5e-20	NA
10	WP	WP:WP5055	Burn wound healing	75	4.4e-05	NA
11	CORUM	CORUM:6203	TFAP2C-Myc-KDM5B complex	3	NA	3.5e-02
12	GO:BP	GO:0043473	pigmentation	114	NA	9.9e-06
13	GO:CC	GO:0033162	melanosome membrane	21	NA	2.7e-03
14	HP	HP:0009887	Abnormality of hair pigmentation	123	NA	5.8e-05

g:Profiler (biit.cs.ut.ee/gprofiler)

Figure 5: Manhattan plot and table showing significantly enriched terms from the analysis of downregulated and upregulated genes in UVEAL Ocular cancer. The top panel of the plot represents downregulated genes, while the bottom panel represents upregulated genes.

SHARED PATHWAYS AND BIOLOGICAL TERMS

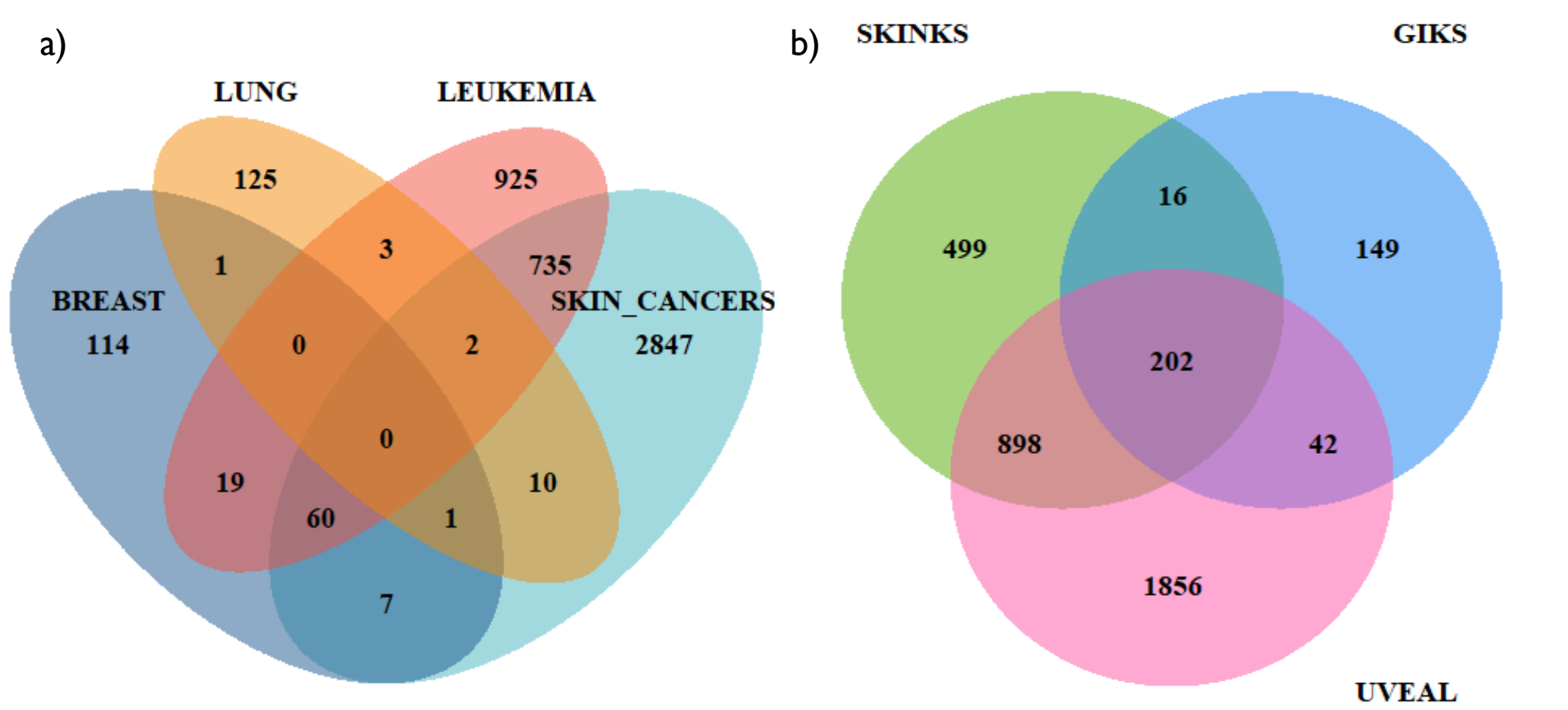


Figure 6: a) Venn Diagram illustrating shared and unique enriched pathways and biological functions among breast cancers (TNBC and HER2), lung cancers (KRAS and EGFR_MET mutated), melanomas (Skin-KS, GI-KS, and Uveal), and Leukemia. **b)** Venn Diagram depicting enriched pathways that are common among the melanomas (Skin-KS, GI-KS, and Uveal) and those unique to each type.

ENRICHED TERMS ACROSS THE SPECIFIC CANCER TYPES

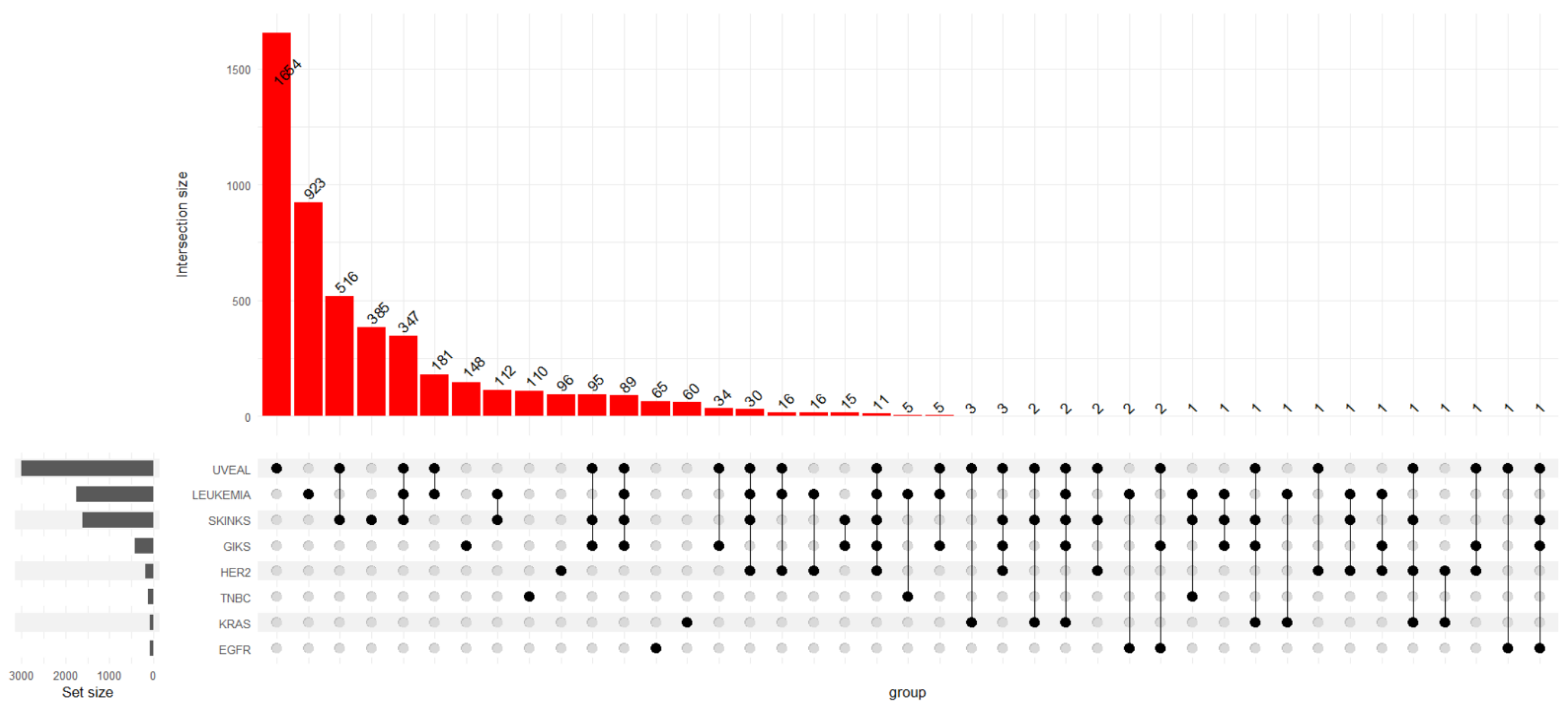


Figure 7: UpSet Plot Depicting the Exclusive Intersection of Enriched Terms Across the Eight Cancer Types: TNBC, HER2+, KRAS, EGFR, SKINKS, GI-KS, Uveal melanoma, and Leukemia (LEUK).

DISCUSSION

- The absence of cross-DEGs in our analysis may possibly reflect the unique molecular signatures specific to the cancer types we studied.
- Differences in sample size, methodology, or the specific biological contexts of the cancers might have influenced our ability to detect shared DEGs.
- 11 genes were shared across skin cancers. These genes were consistently downregulated in Uveal Melanoma but upregulated in Kaposi sarcomas.
- For instance, P4HA3 has previously been reported to be significantly overexpressed in skin cancers, where it promotes tumor proliferation and evasion (Gu *et al.*, 2020).

DISCUSSION

- A single gene, DNAH2, was found to be upregulated in both breast cancer subtypes in and this concurs with previous findings which report its potential as a valuable biomarker.

- Two DEGs shared were shared between lung cancers, of significance was SPECC1L which has emerged as a potential novel tumor driver gene in lung cancer patients(Ma *et al.*, 2020).

- We identified three genes shared between breast and lung cancers, highlighting potential molecular connections between these solid tumors.

- Among these are two lncRNAs which are reported to be overexpressed in lung cancer tissues and this underscores a possible interplay between the molecular mechanisms driving breast and lung cancers.

DISCUSSION

- Another shared gene, USP29 has been implicated in promoting tumor progression in TNBC as well as its enhancement of chemotherapy-induced stemness in NSCLC suggesting its potential as valuable therapeutic target for both breast and lung cancers.

- Our analysis revealed notable shared gene expression patterns between lung cancers, skin cancers and leukemia.

- Of importance is EGFL7 which has been reported to control proliferation in melanoma, hepatocellular carcinoma, and clear cell renal cell carcinoma.

- EGF17 stands out due to its critical role in the metastatic program, inhibition of anti-cancer immune response, and contribution to drug resistance (Tang *et al.*, 2019; Zhai *et al.*, 2019).

DISCUSSION

- Four genes, including ADAMTS9, AFAP1L1, PITPNC1, and FCGBP, were shared among breast cancer, leukemia, and skin cancers.

- Of significant importance was PITPNC1 where its overexpression has been studied particularly in metastatic contexts of breast, colon, and melanoma cancers(Halberg *et al.*, 2016).

- This suggests that this shared gene expression patterns across diverse cancer types points to common molecular pathways that could be pivotal in tumor progression and metastasis.

DISCUSSION

- Upregulated DEGs were particularly enriched in pathways such as the PI3K/AKT/mTOR signaling pathway, neutrophil degranulation, and sphingolipid dysregulation.
- Downregulated DEGs were significantly enriched in pathways such as bile secretion, burn wound healing, and cancer immunotherapy via PD-1 blockade.
- This overall downregulation points to a possible suppression of pro-tumor pathways and immune evasion mechanisms, which could be leveraged.
- Certain pathways were unique to specific cancers, while others were shared among multiple cancer types.

DISCUSSION

- No single pathway was shared across all eight cancer types, but skin cancers had the highest number of unique pathways.
- Notably, 202 pathways were shared between skin cancer types.
- Among these, the ECM (ExtraCellularMatrix)-receptor interaction pathway was enriched with the downregulated DEGs of Uveal Melanoma but enriched with the upregulated genes of KS.
- Our study also identified quite a number of regulatory motifs and microRNAs enriched in various cancer types, underscoring their general importance in tumor progression.

STUDY LIMITATIONS

- The sample size, particularly for certain cancer types, was relatively small, which may limit the generalizability of our findings.
- While we identified several DEGs and pathways, further experimental validation is necessary to confirm their functional roles in cancer progression.
- Future research should also explore the potential of these DEGs as biomarkers for early cancer detection and their utility in precision oncology.

CONCLUSION

- Our study provides valuable insights into the shared molecular mechanisms of breast cancer, lung cancer, leukemia, and melanoma.
- We identified a set of biomarkers that were differentially expressed in multiple types of cancers, and these biomarkers can be potentially used for diagnosis and used as therapeutic targets.
- More research therefore needs to be done to understand the mechanisms of how these various DEGs and pathways contribute to tumor progression.
- Our findings provide new clues for pan-cancer classification in complex cancer biology and facilitate early diagnosis and precise treatment of cancer.

THANK YOU FOR LISTENING!