

# Risk of cognitive impairment in prostate cancer patients undergoing androgen deprivation therapy

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## ABSTRACT

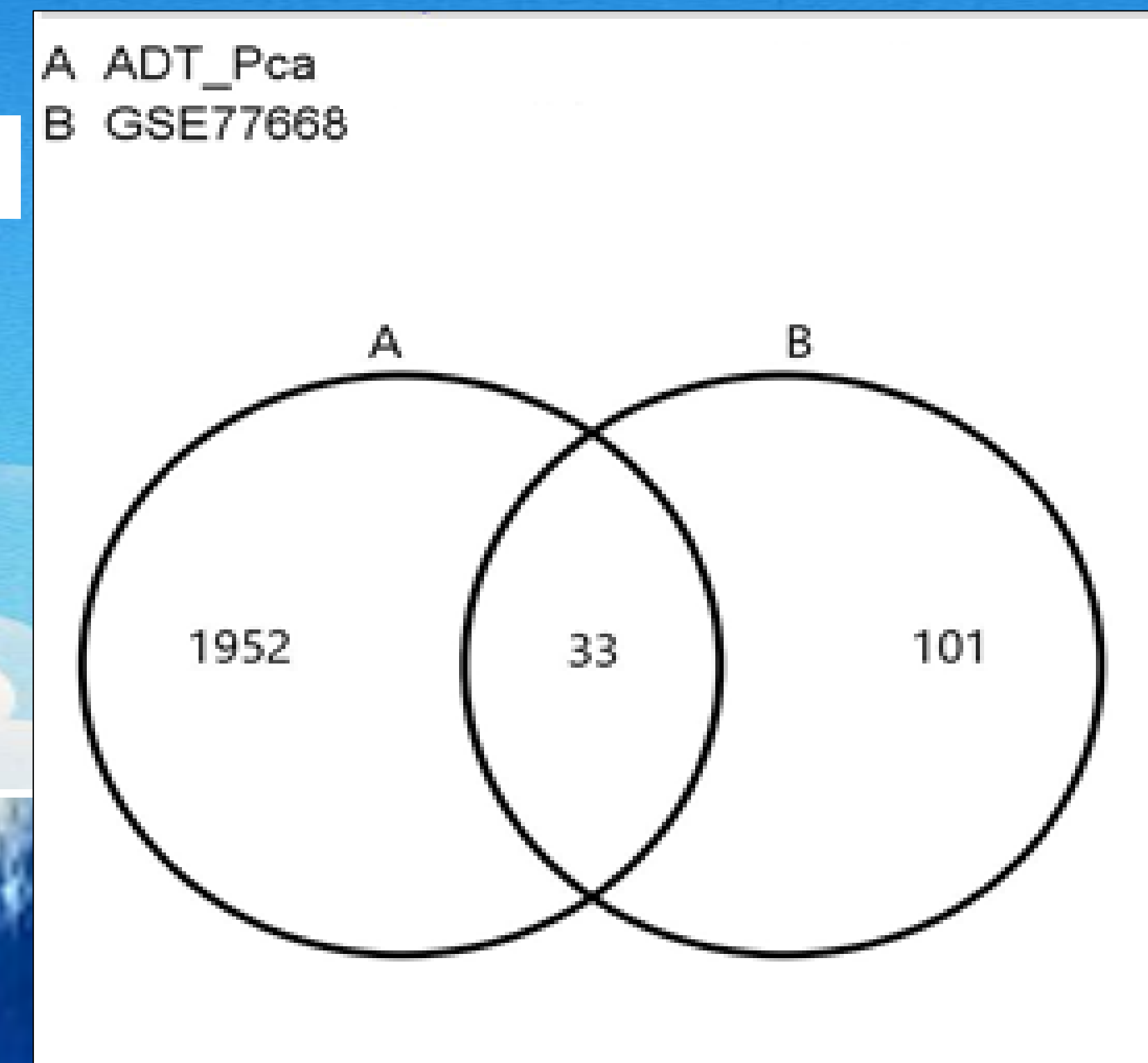
Androgen deprivation therapy (ADT) is a commonly used clinical treatment for non-metastatic and metastatic hormone-sensitive prostate cancer. Long-term ADT treatment results in adverse side-effects in patients including depression, cognitive impairment and dementia. Studies have reported increased levels of pro-inflammatory cytokines and inflammatory markers in older cancer patients, however, the relationship between inflammatory biomarkers and severity of cognition in prostate cancer patients under ADT has not been investigated. We sought to identify peripheral biomarkers that could provide links between the mental changes and major pathological mechanisms responsible for the development of cognition in patients. Gene expression data (GSE69223) of 30 matched malignant and non-malignant prostate tissue samples from 15 prostate cancer patients receiving neoadjuvant antiandrogen therapy before prostatectomy, were compared in parallel with postmortem brain tissue samples of Parkinson's and Alzheimer patients as additional neurological diagnosis. Validation was performed in BT142-neural cells and M059K-glia cells by qRT-PCR with and without antiandrogen (enzalutamide) treatment. Total of 1952 DEGs were identified in postmortem brain tissue specimens, and 101 DEGs were identified in prostate cancer patients receiving ADT before surgery. IPA analysis revealed 33 commonly expressed genes with changes in cytokine-cytokine signaling network overlapped in both patient cohorts. Pathway analysis showed that IL17 signaling pathway, regulation of cytokine production and changes in T-cell subsets by IL-17A and IL-17F were overrepresented. Furthermore, lipopolysaccharide (LPS), TNF and toll-like receptors were identified as upstream transcriptional regulators of these signaling pathways. Gene expression of pro-inflammatory cytokines viz. LIFR, IL1RN, IL6, IL10 and LIF were increased in both neural and glial cells treated with enzalutamide, compared to non-enzalutamide treated cells. Our results suggest that changes in cytokine signaling under the influence of ADT in prostate cancer patients may linked with cognitive impairment presenting new areas for diagnostic and therapeutic development in combating brain deficits.

**Objective:** inflammation-induced in response to ADT therapy secretes pro-inflammatory cytokines which induce adaptive-immune cells and stimulates neuro-pathological injury to glial and neuronal cells may cause aging related disease.

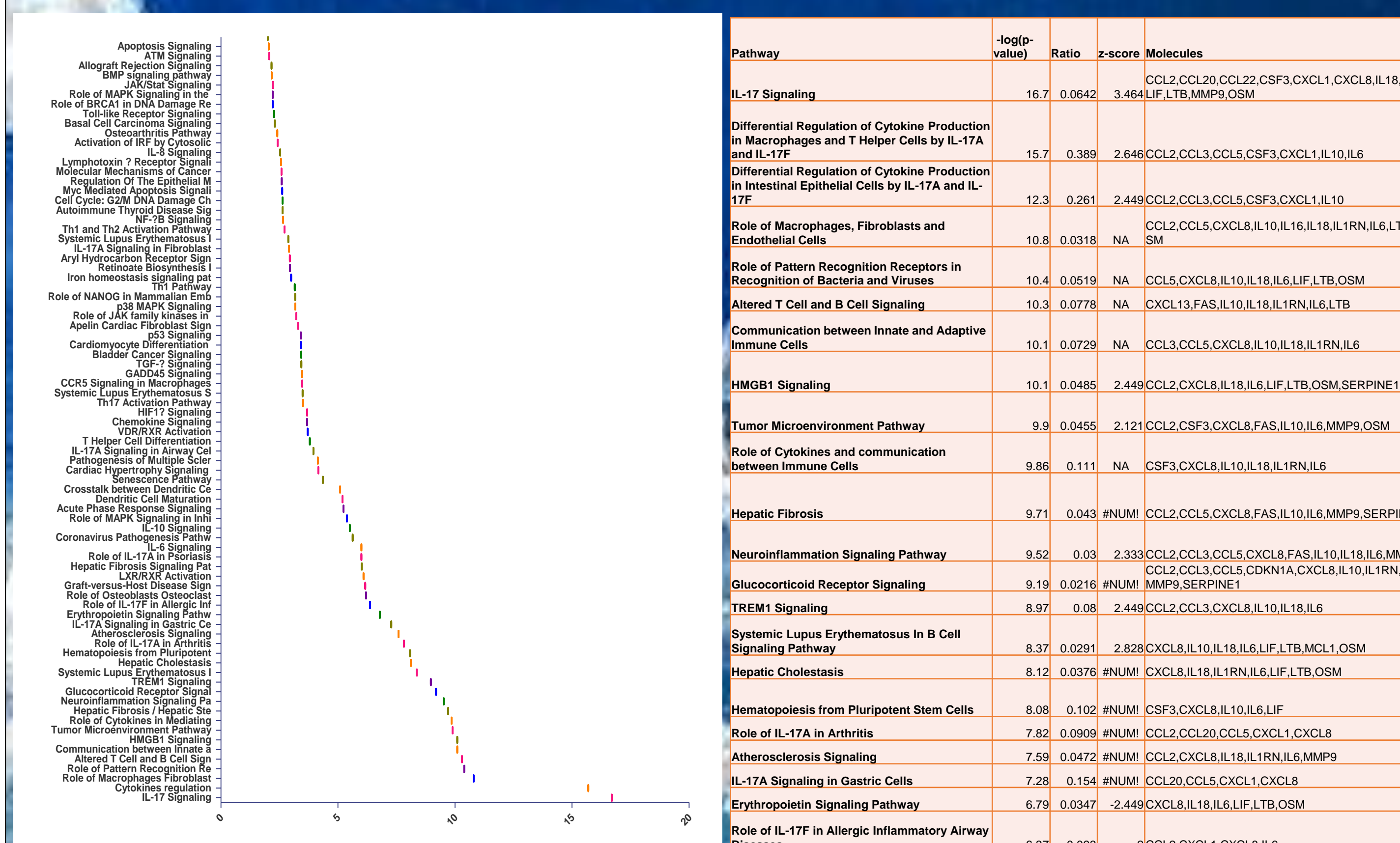
## MATERIALS & METHODS

- ❖ Alzheimer and ADT treated prostate cancer patient databases were downloaded from NCBI-GEO and analyzed using GEO2-R program. Data was analyzed using Ingenuity Pathway Analysis (IPA) (Figure 1, Figure 2, and Figure 4).
- ❖ The gene expression . CCL2, IL10, IL-6, IL1RN, LIF/LIFR and others were derived from RNA seq data brain-map (<http://aging.brain-map.org>). (Figure 3)
- ❖ Metascape was used to analyze enrichment and overrepresented pathway (Figure 5)
- ❖ Cell lines and qRT-PCR. Two cell lines of brain M059K (glial cell, malignant glioblastoma) and BT142 (neural cell, oligoastrocytoma; Grade III) were treated with enzalutamide, RNA was isolated from the cells and cDNA was synthesized and used in qRT-PCR.

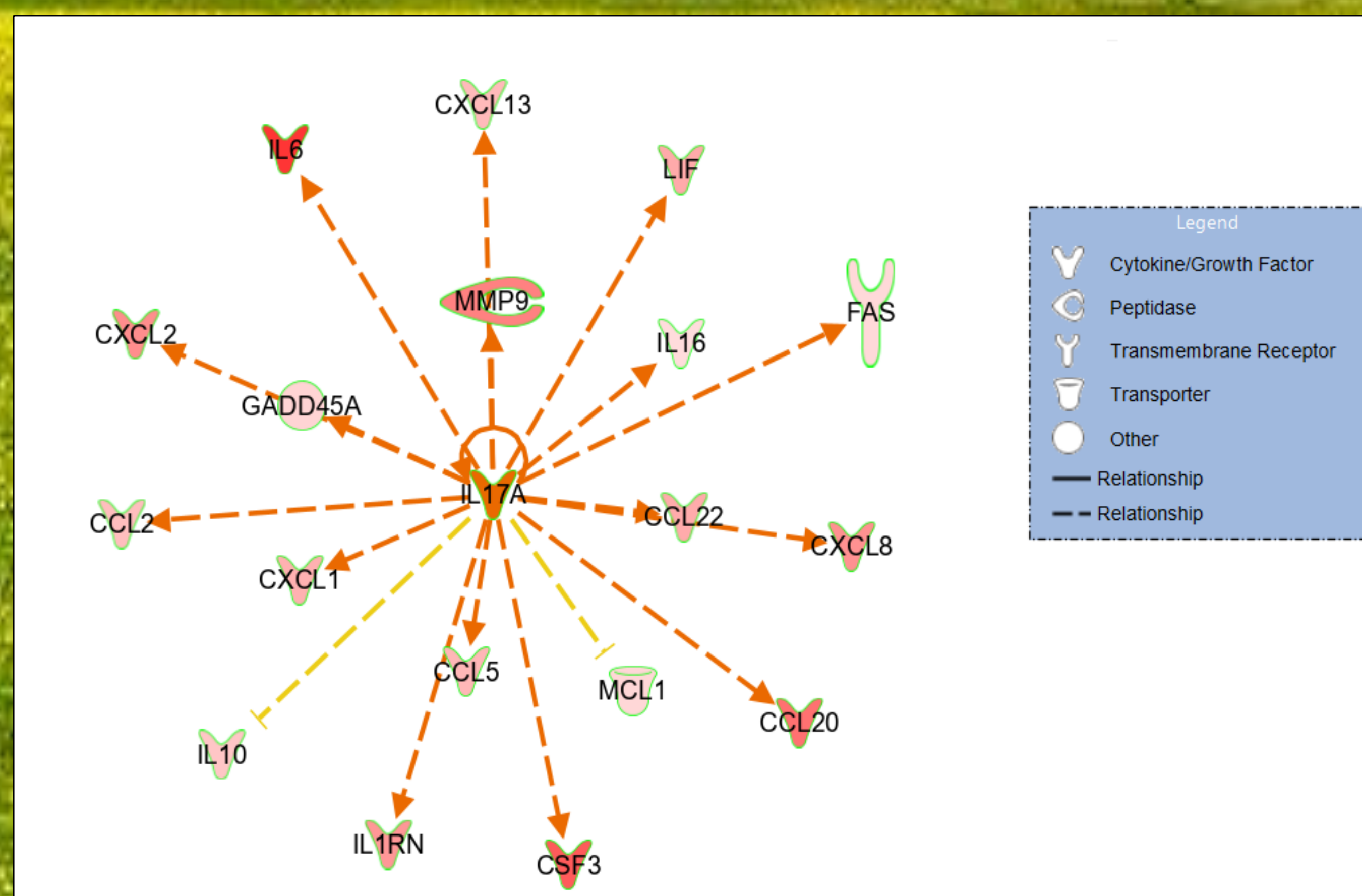
## RESULTS



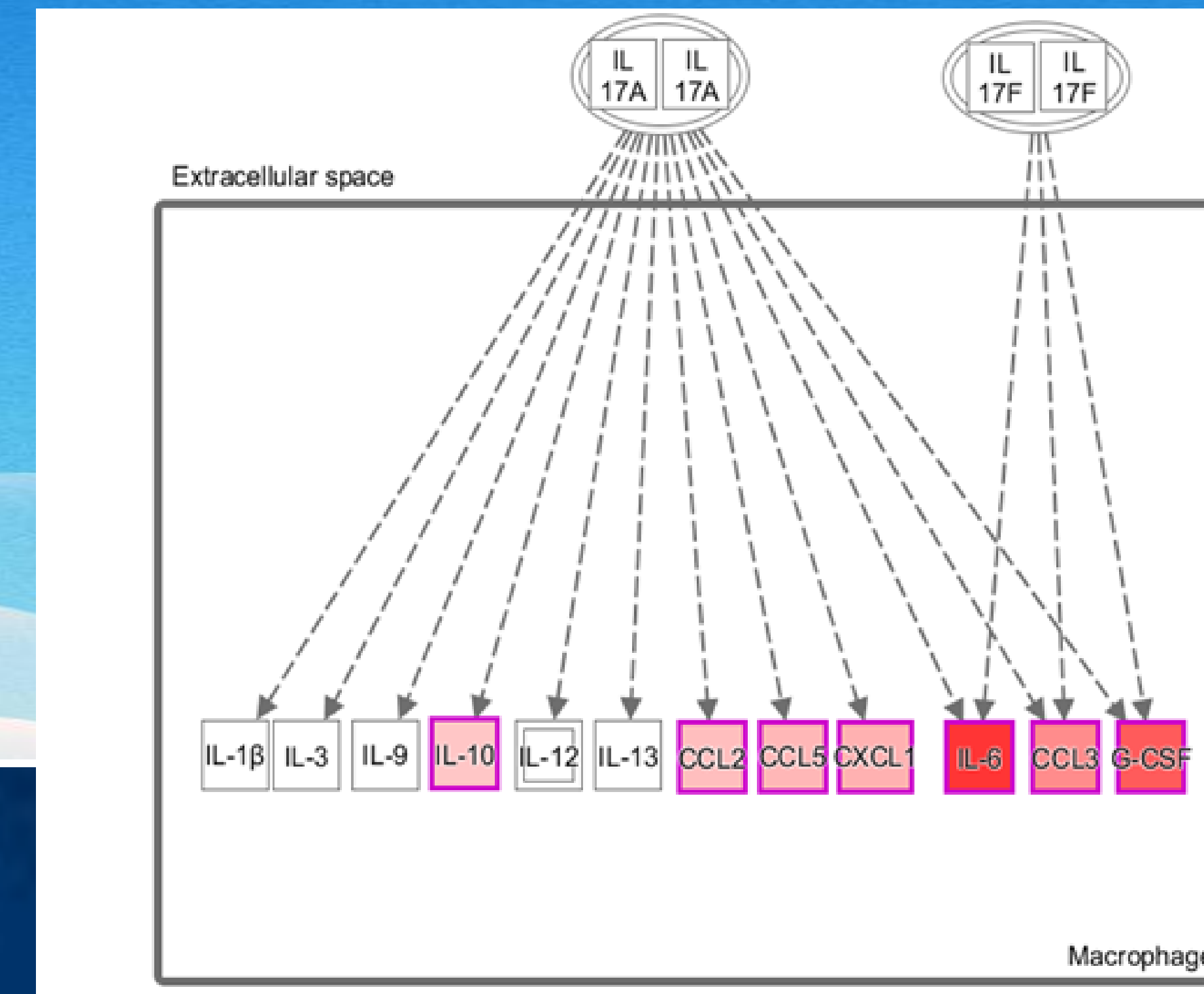
**Figure 1.** DEGs of ADT-prostate cancer patients overlaid with Alzheimer database, and 33 common gene found to be differentially expressed in both dataset..



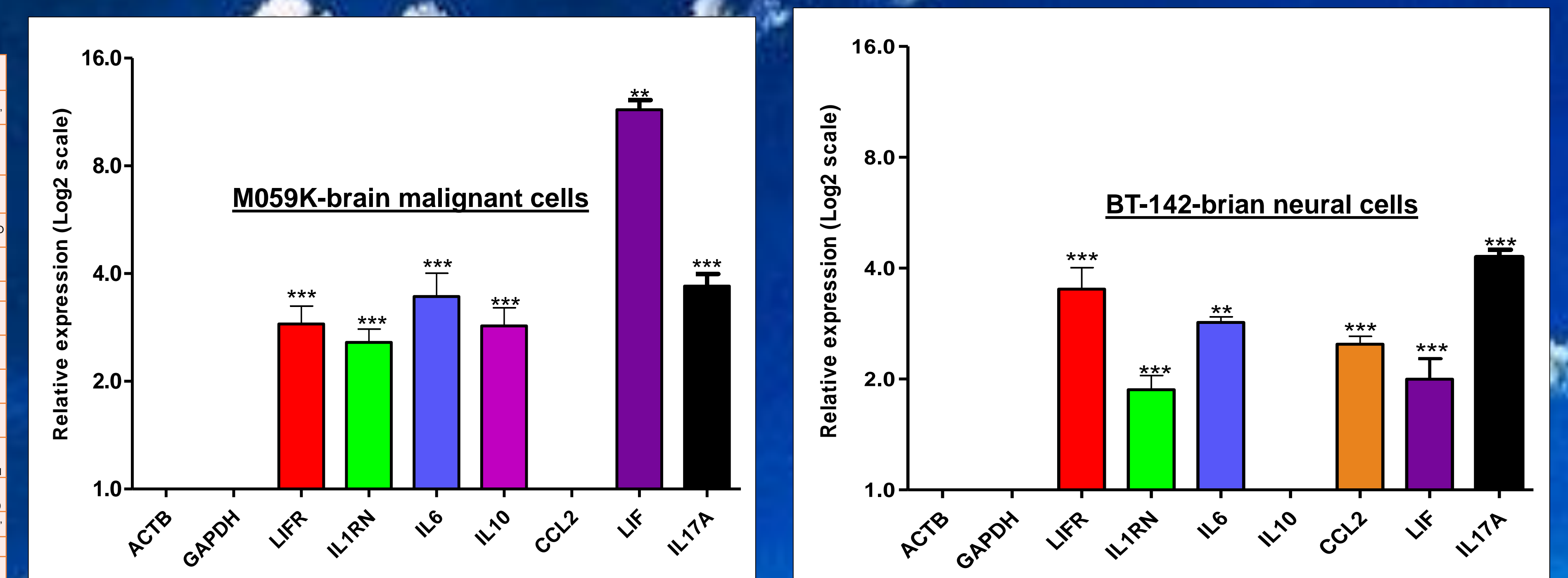
**Figure 2.** IPA analysis revealed the signaling pathways associated with common DEGs.



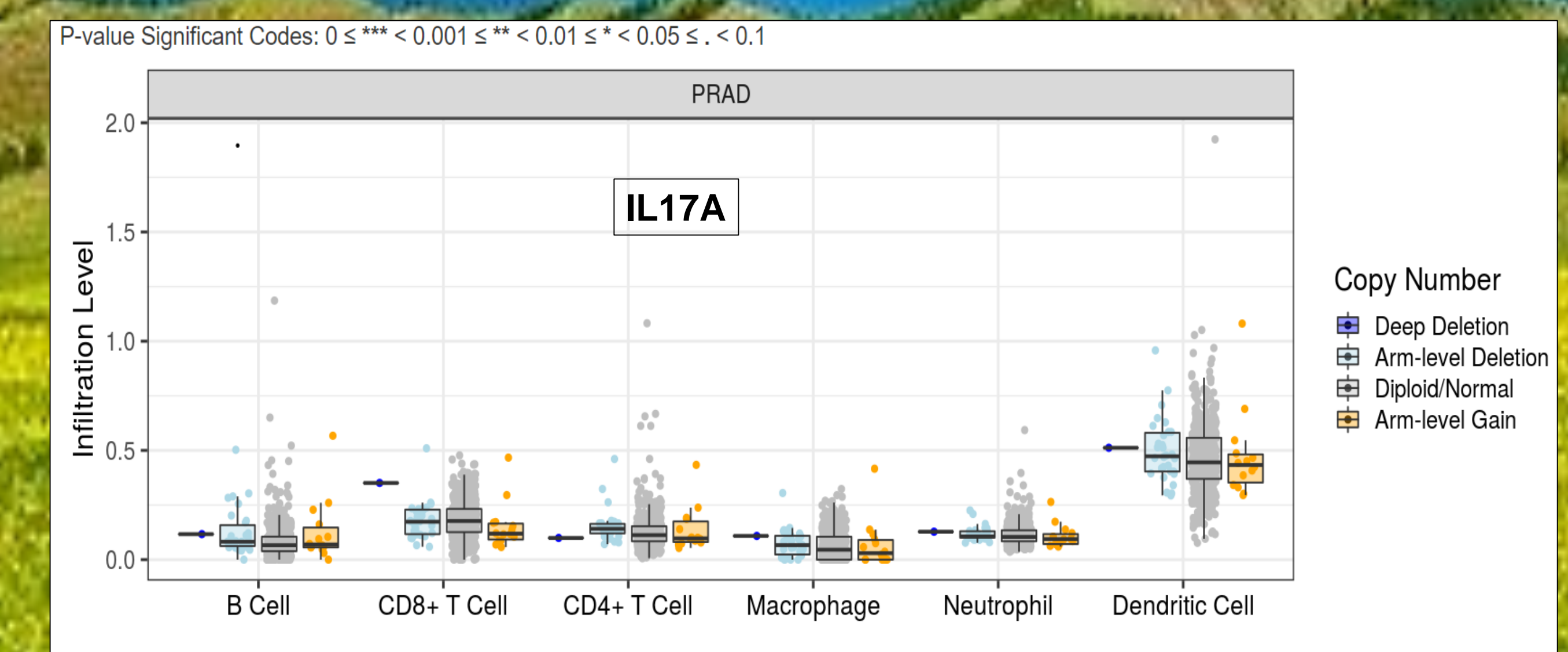
**Figure 3.** IL17A and its down stream target gene analysis



**Figure 4.** Differential regulation of cytokine production in Macrophage and T-helper cells by IL17A and IL-17F.



**Figure 5.** qRT-PCR of common genes differentially expressed in neural (BT-142) and malignant (M059K) brain cells after enzalutamide treatment.



**Figure 6.** IL17A and immune cell regulation in PRAD

## CONCLUSIONS

Our results here suggest clinicians need to raise their alertness about potential long-term effects of ADT and discuss these risks in the perspectives of aging related disorder with their patients.

## ACKNOWLEDGEMENTS

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