

Sex Differences in Resilience to Alzheimer's Disease Pathology: Preliminary Results of a CSF Proteomics study

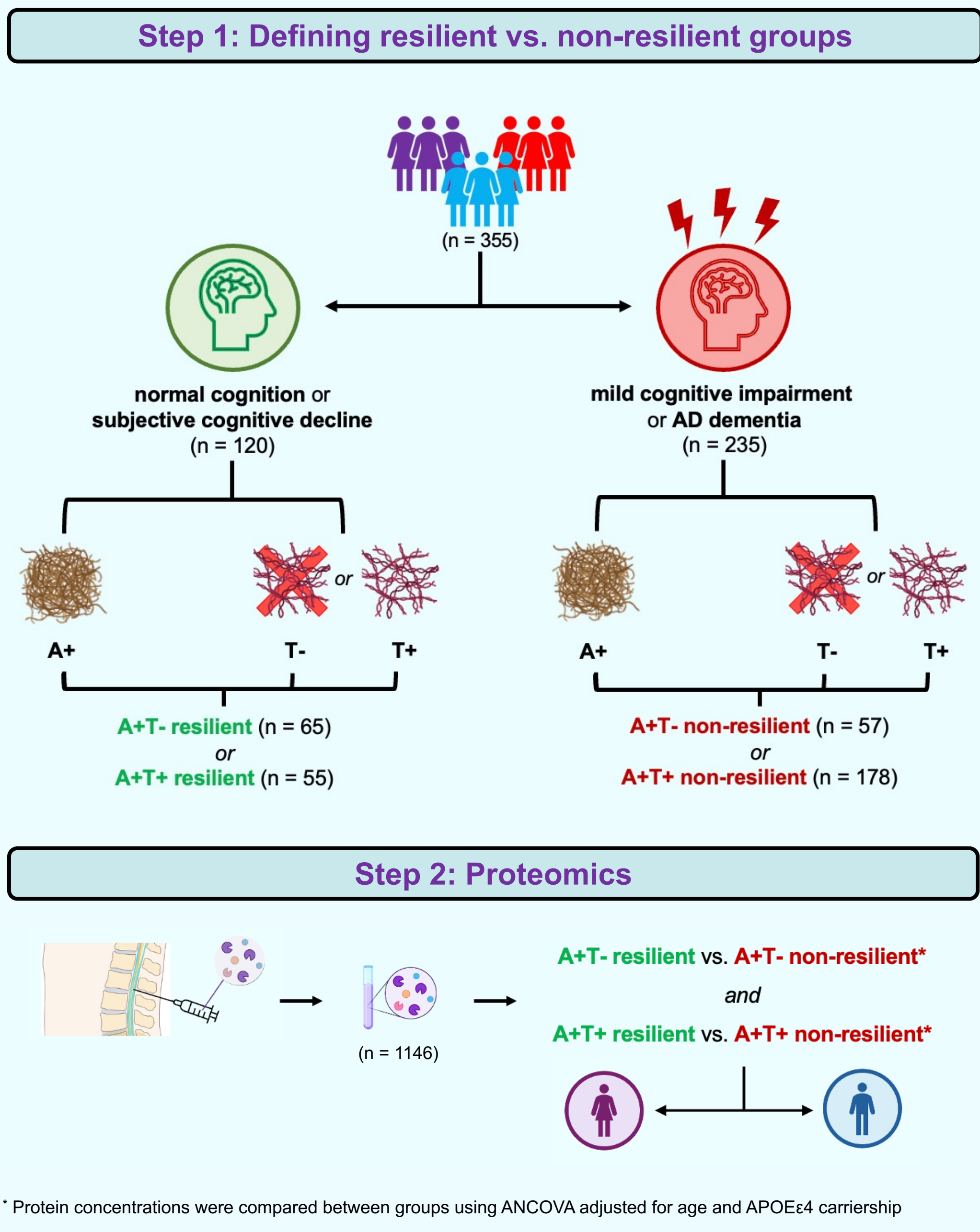
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Background

- Up to **25%** of individuals with AD pathology, amyloid- β deposition (A) and tau tangle formation (T), remain cognitively healthy throughout life,¹ showing **resilience to AD pathology**.
- There seem to be **sex differences** in resilience to AD pathology,² though the underlying pathophysiology remains relatively unknown.
- The aim is to investigate **sex differences in underlying pathophysiology** of resilience to AD pathology, using cerebrospinal fluid (CSF) proteomics.

Methods



Conclusion

Resilience to AD is associated with sex-specific proteomic signatures and underlying biological pathways, which are more pronounced in the presence of tau pathology.

- A+T- resilient females and males show **partially overlapping** upregulated proteins, associated with neuronal and synaptic pathways.
- A+T+ resilient females and males show **distinct dysregulated** proteins and pathways.

Female A+T- resilient vs. Female A+T- non-resilient

A+T- resilient females (Figure 1A):

- 134 upregulated proteins**, associated with **nervous system development** and **synaptic processes**.
- 44 downregulated proteins** associated with **innate immune system**, **hemostasis** and **metabolic processes**.

Male A+T- resilient vs. Male A+T- non-resilient

A+T- resilient males (Figure 1B):

- 86 upregulated proteins**, associated with **nervous system development**, **synaptic processes**, and **angiogenesis**.
- 30 downregulated proteins**, **unrelated to any biological pathway**.

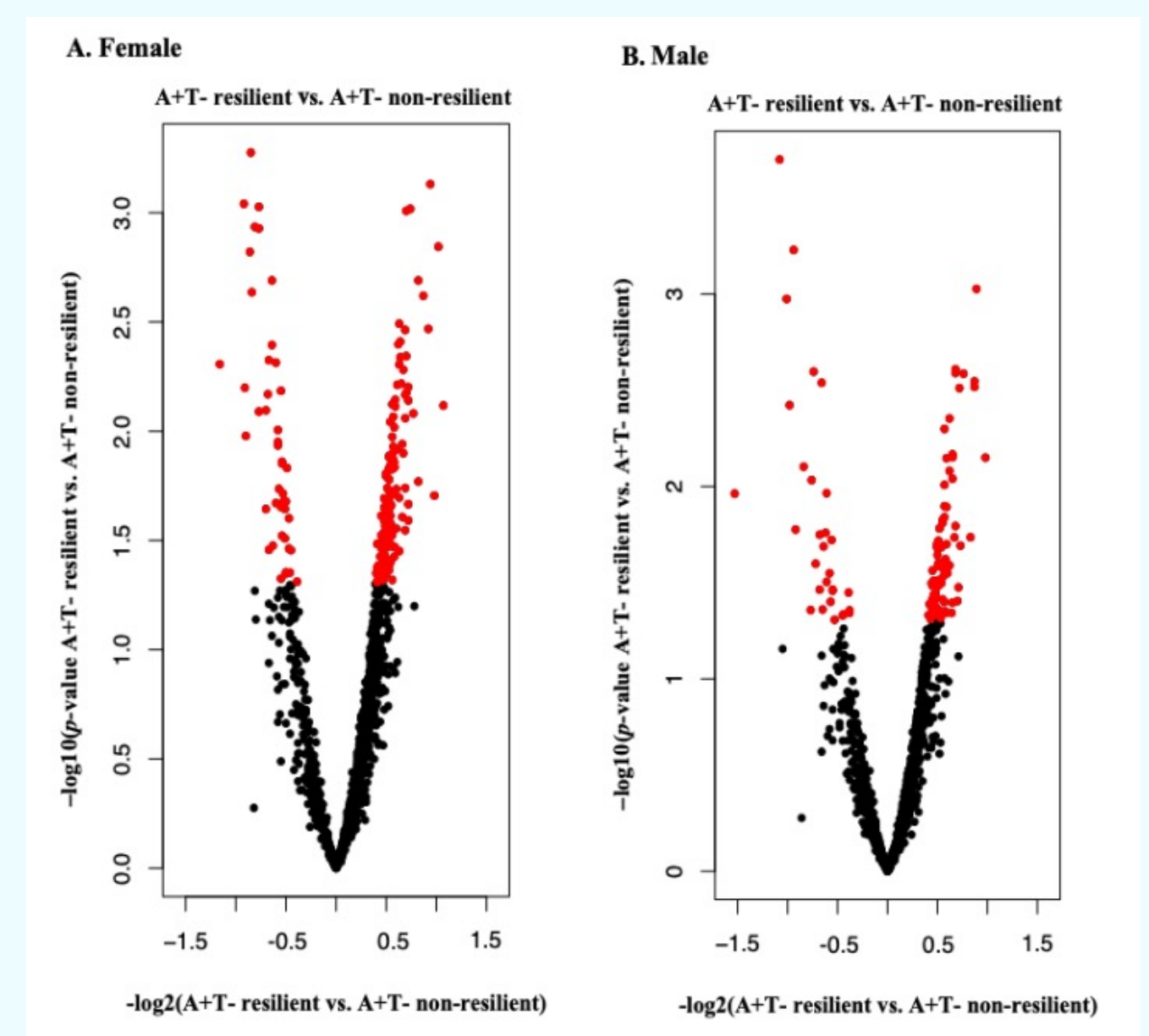


Figure 1. Volcano plots of comparisons between **A.** A+T- resilient females vs. A+T- non-resilient females, **B.** A+T- resilient males vs. A+T- non-resilient males. Volcano plots displaying the log2 fold-change against the $-\log_{10}$ statistical p-value for the comparison of A+T- resilient vs. A+T- non-resilient. Significantly different proteins are red ($p < 0.05$).

Results

Female A+T+ resilient vs. Female A+T+ non-resilient

A+T+ resilient females (Figure 2A):

- 45 upregulated proteins**, associated with **synaptic processes** and **innate immune system**.
- 19 downregulated proteins**, **unrelated to any biological pathway**.

Male A+T+ resilient vs. Male A+T+ non-resilient

A+T+ resilient males (Figure 2B):

- 16 upregulated proteins**, **unrelated to any biological pathway**.
- 24 downregulated proteins**, **unrelated to any biological pathway**.

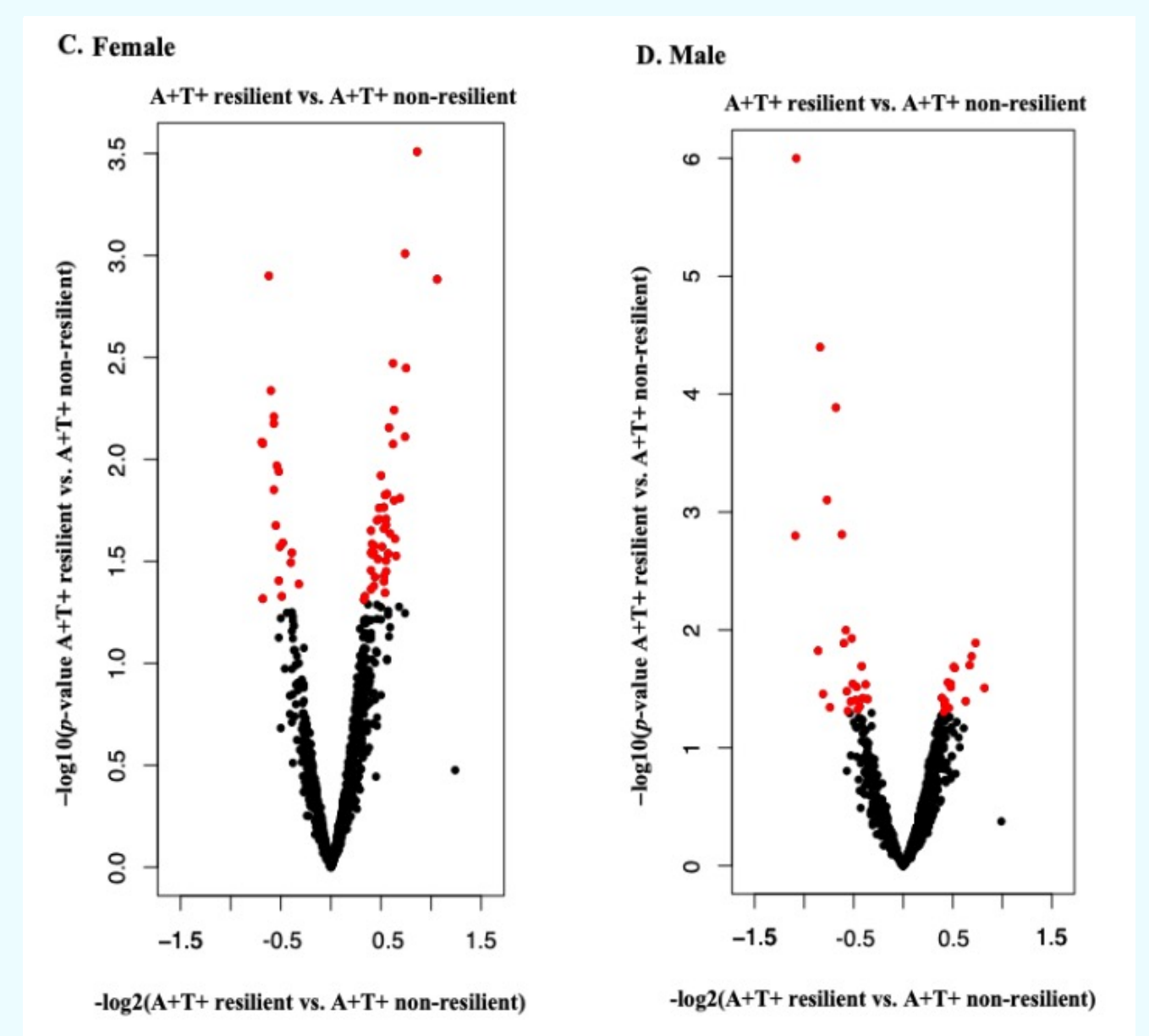


Figure 2. Volcano plots of comparisons between **A.** A+T+ resilient females vs. A+T+ non-resilient females, **B.** A+T+ resilient males vs. A+T+ non-resilient males. Volcano plots displaying the log2 fold-change against the $-\log_{10}$ statistical p-value for the comparison of A+T+ resilient vs. A+T+ non-resilient. Significantly different proteins are red ($p < 0.05$).

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Female A+T- resilient vs. Male A+T- resilient

A+T- resilient females and **males** showed overlap in **40 upregulated proteins**, associated with **neuronal** and **synaptic plasticity**.

A+T- resilient females and **males** showed **no overlap** in downregulated proteins.

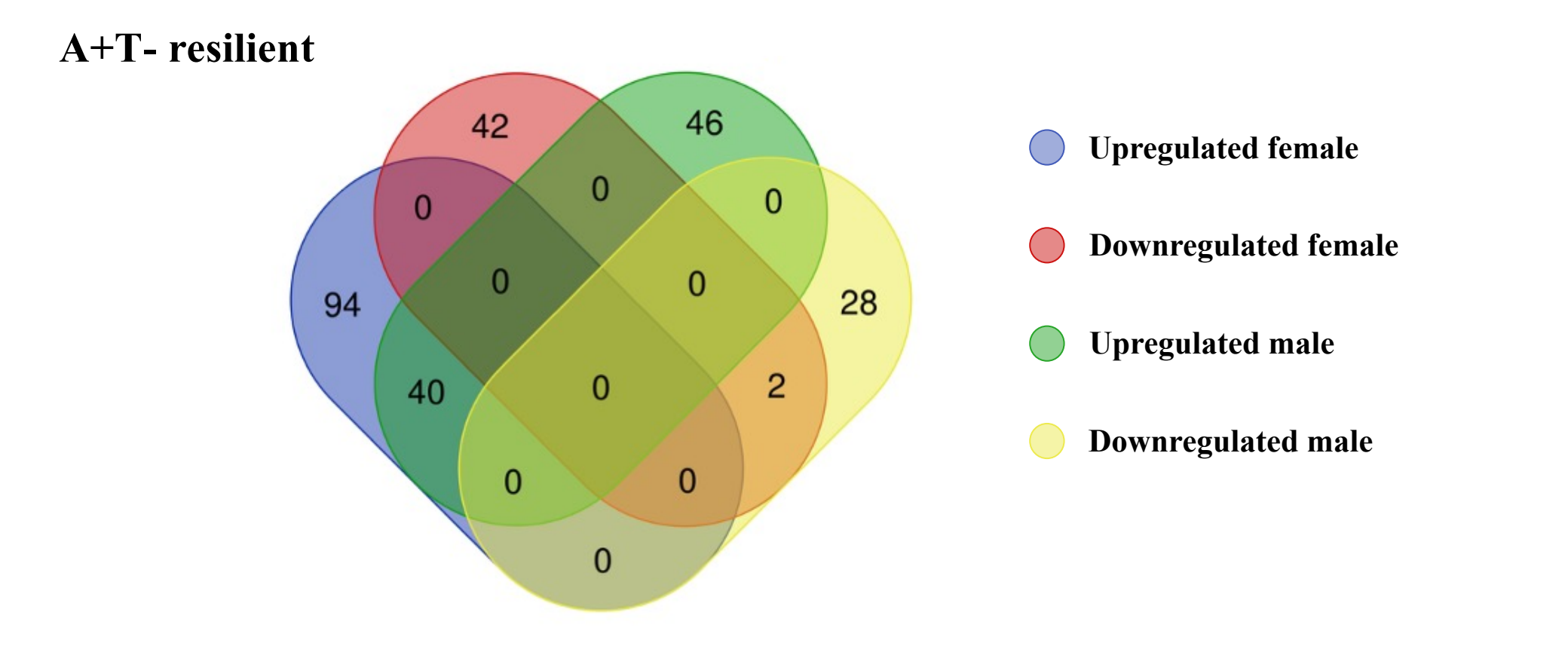


Figure 3. Venn diagram of up- and downregulated proteins in A+T- resilient females and males.

Female A+T+ resilient vs. Male A+T+ resilient

A+T+ resilient females and **males** showed overlap in **2 upregulated proteins**, **unrelated to any biological pathway**.

A+T+ resilient females and **males** showed **no overlap** in downregulated proteins.

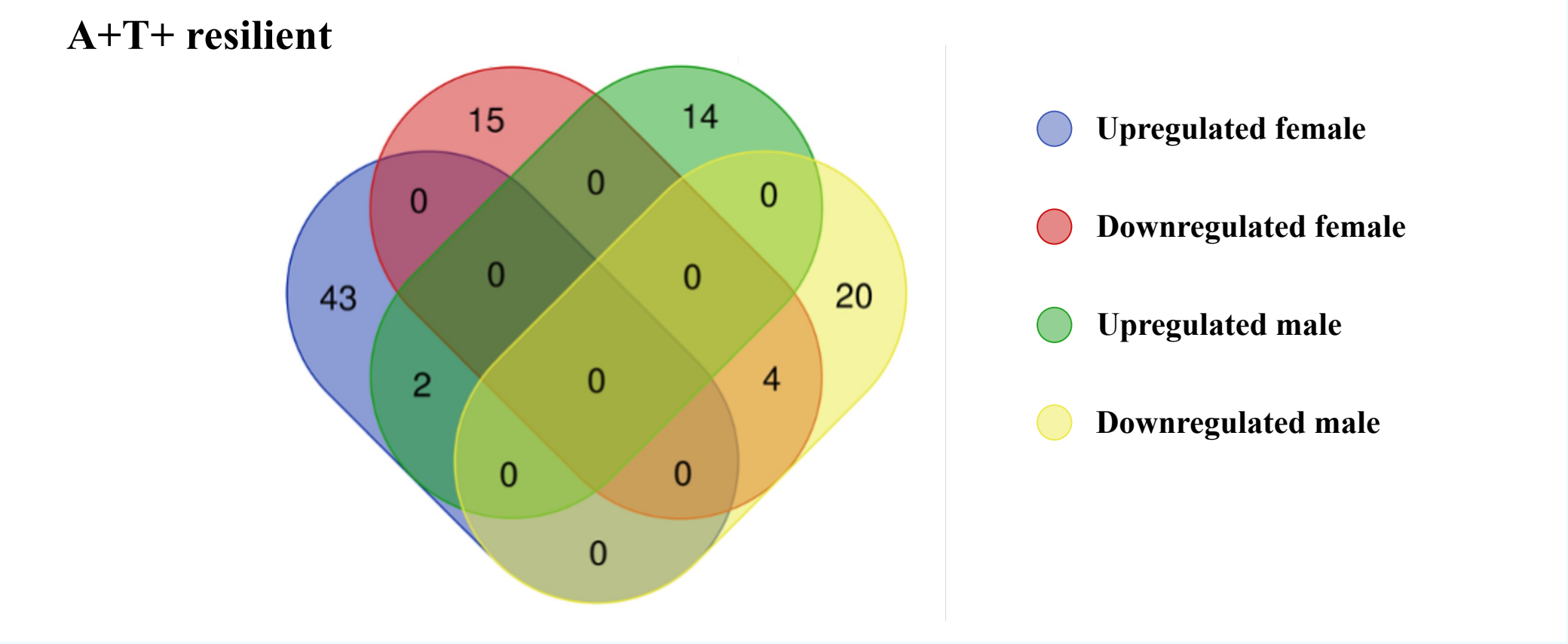


Figure 4. Venn diagram of up- and downregulated proteins in A+T+ resilient females and males.

References

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