

BACKGROUND

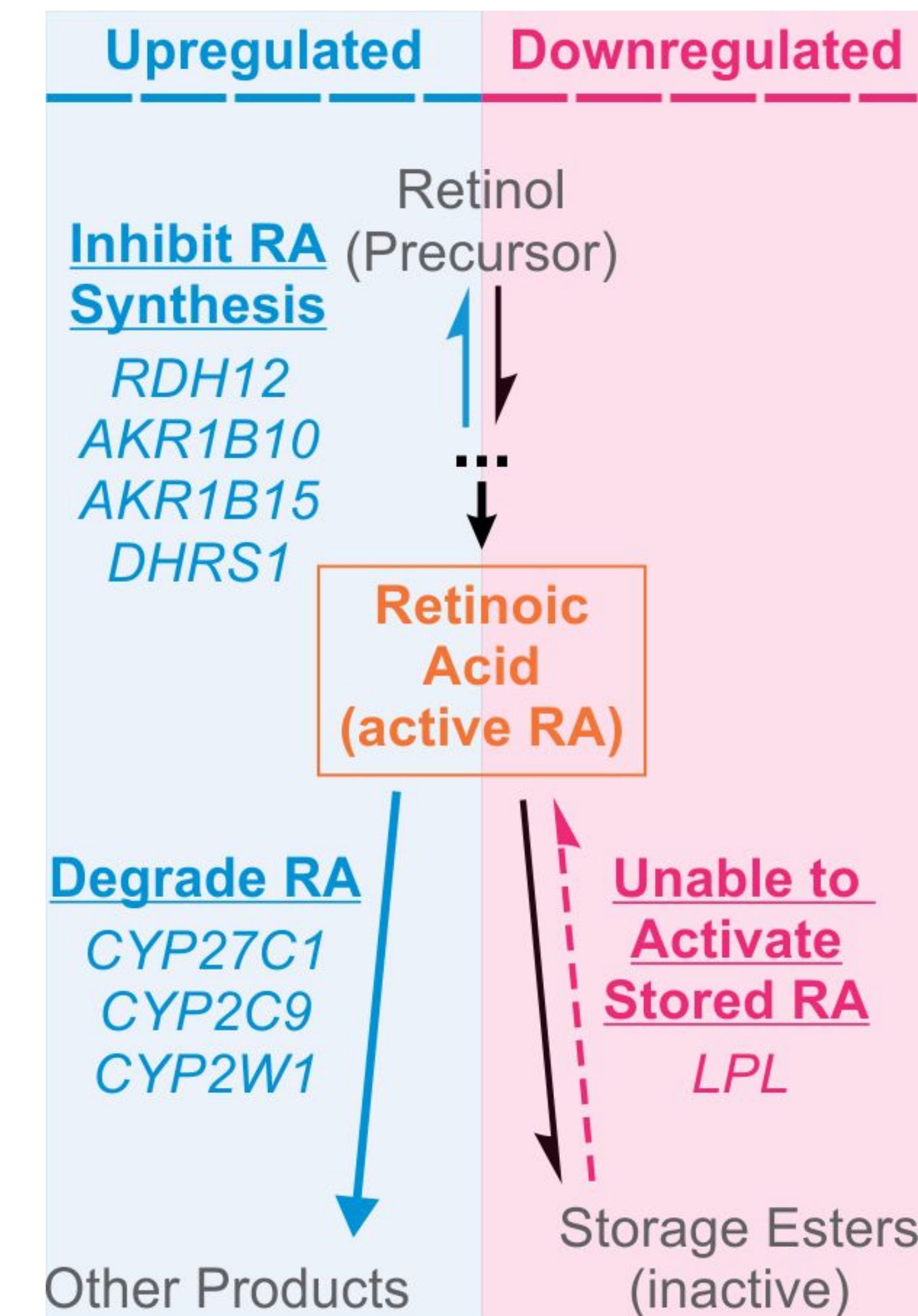
- Tracheal stenosis (TS) is progressive occlusion of the airway
 - Standard of care revolves around endoscopic interventions
 - Carbon dioxide laser, cryoablation, balloon dilation [1]
 - Significant (~15%) of patients exhibit recalcitrant disease course and need repeated procedures
- Need to develop pharmacological adjunct to consolidate interventional management
 - TS known to involve epithelial hyperkeratinization, hyperproliferation, and granulation tissue accumulation [2]
 - Retinoic acid known to favorably regulate these pathways
- Utilize next-gen sequencing to elucidate nature of retinoid dysfunction in TS

METHODS

- Design:** adult patients with severe, recalcitrant TS (IRB approval ID: 2019-19, Nuvance Health)
- Setting:** single center, JFK University Medical Center outpatient facility
- Intervention:** tracheal granulation tissue biopsies collected at time of endoscopic intervention
- Main outcome measures:** next-gen sequencing (RNAseq)
- Analysis:** differential gene expression between diseased tissue and normal control data (from public databases), functional interaction network

RESULTS

Dysregulated Retinoid Metabolism Pathway



Dysregulated Retinoid Metabolism Gene Expression

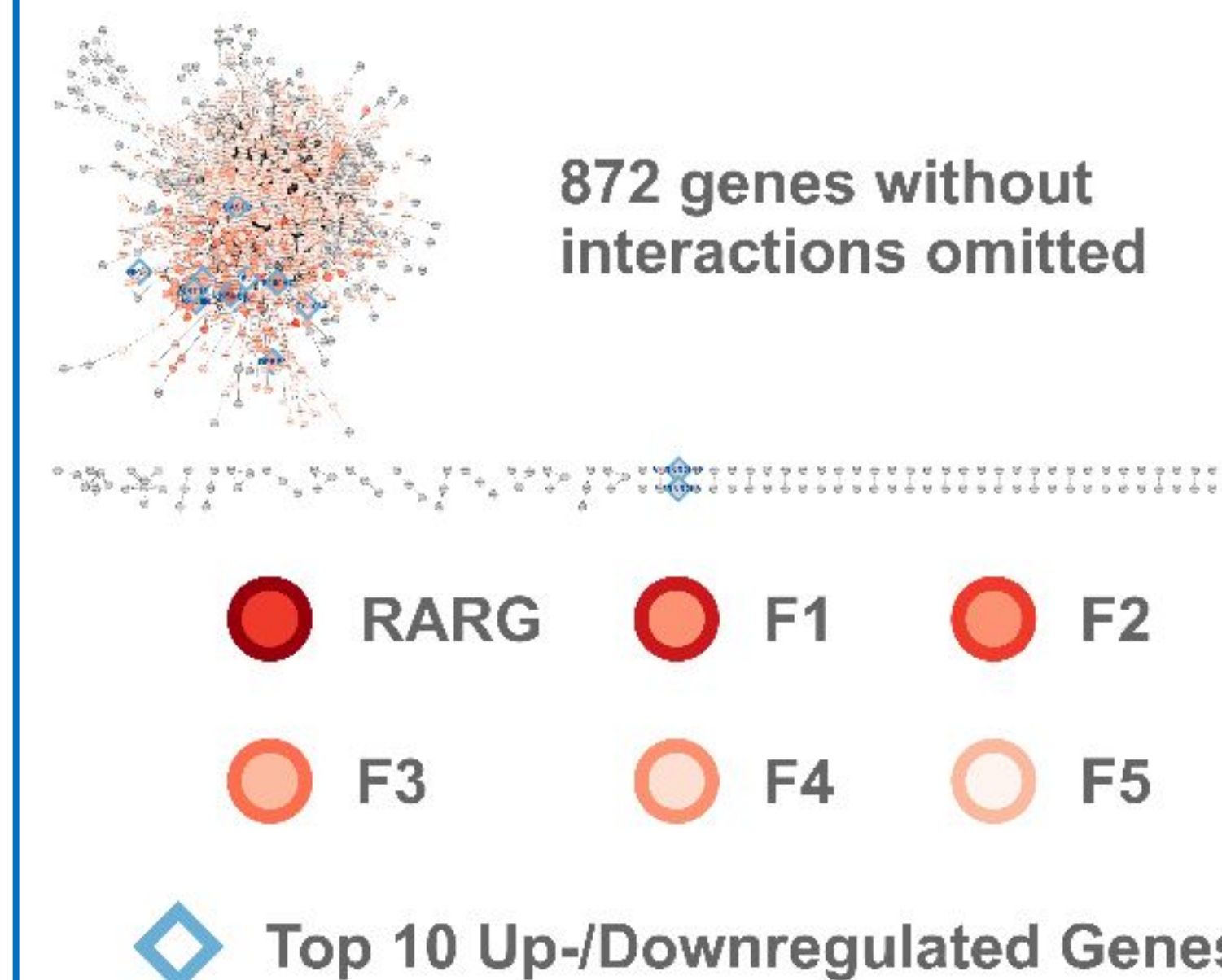
Name	Fold change	FDR p-value
RDH12	26.68	6.53E-03
AKR1B10	30.48	1.74E-06
AKR1B15	105.83	1.94E-03
DHRS1	3.72	0.01
CYP27C1	16.38	4.58E-07
CYP2C9	17.5	3.33E-03
CYP2W1	13.54	0.02
LPL	-16.61	7.21E-04

RDH12- retinol dehydrogenase 12, AKR1B10- aldo-keto reductase family 1 member B10, AKR1B15- aldo-keto reductase family 1 member B15, DHRS1- dehydrogenase/reductase 1, CYP27C1- cytochrome P450 family 27 subfamily C member 1, CYP2C9- cytochrome P450 family 2 subfamily C member 9, CYP2W1- cytochrome P450 family 2 subfamily W member 1, LPL- lipoprotein lipase

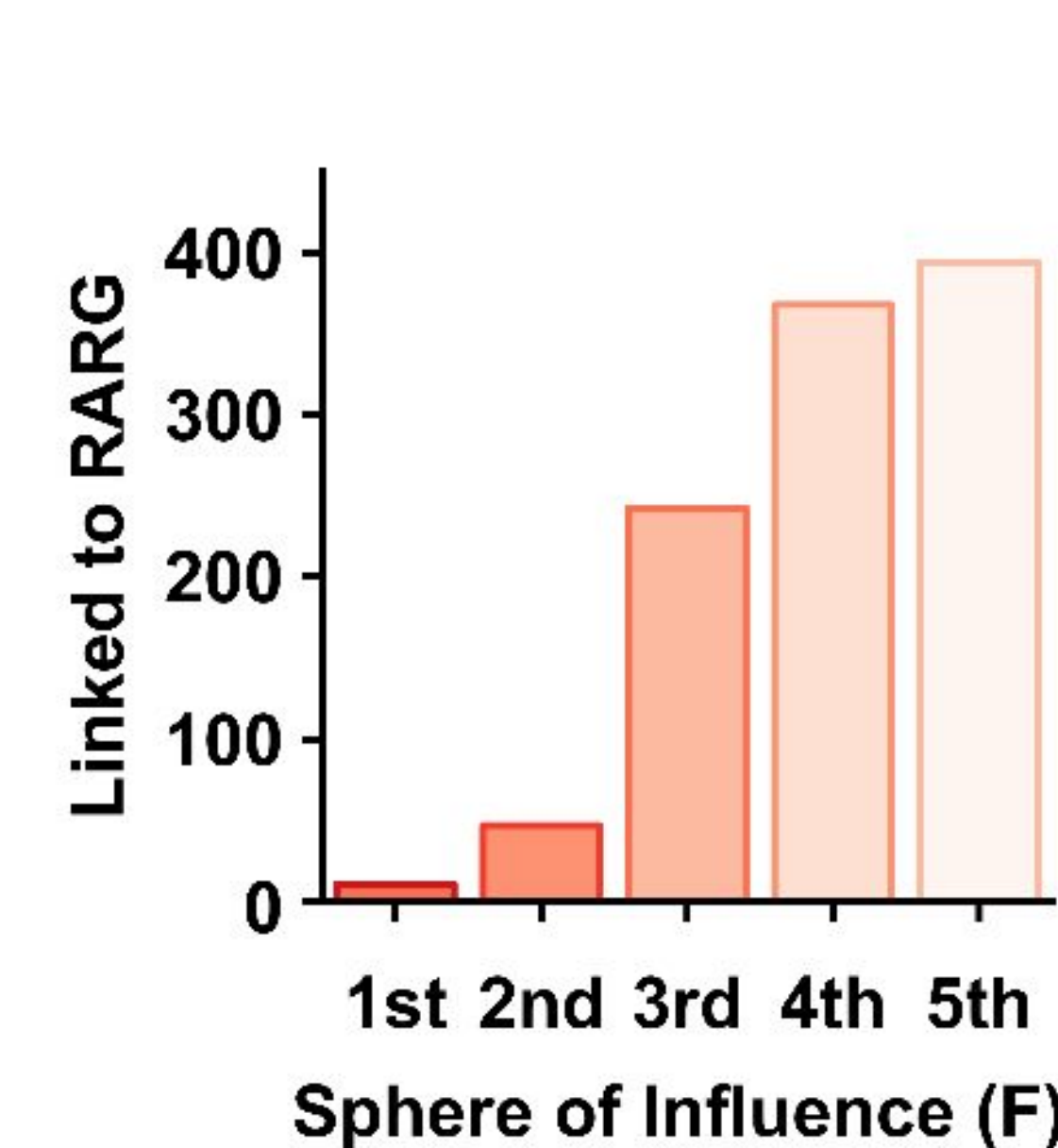
Blue - downregulated, red - upregulated

Genes Affected by Retinoid Deficiency (Retinoic Acid Receptor- γ , RARG)

a) Functional Interaction Network

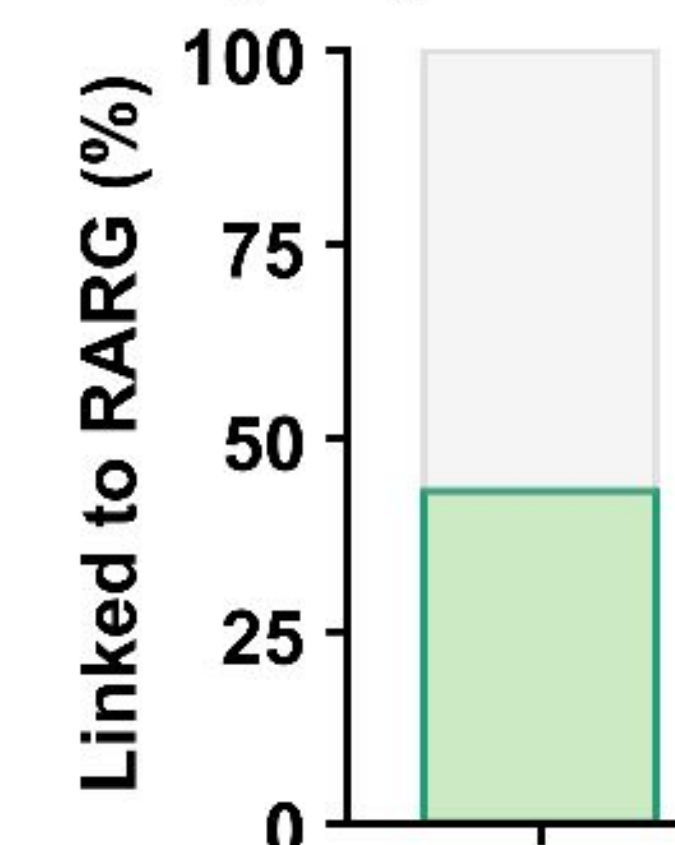


b) Number of RARG-Linked Genes

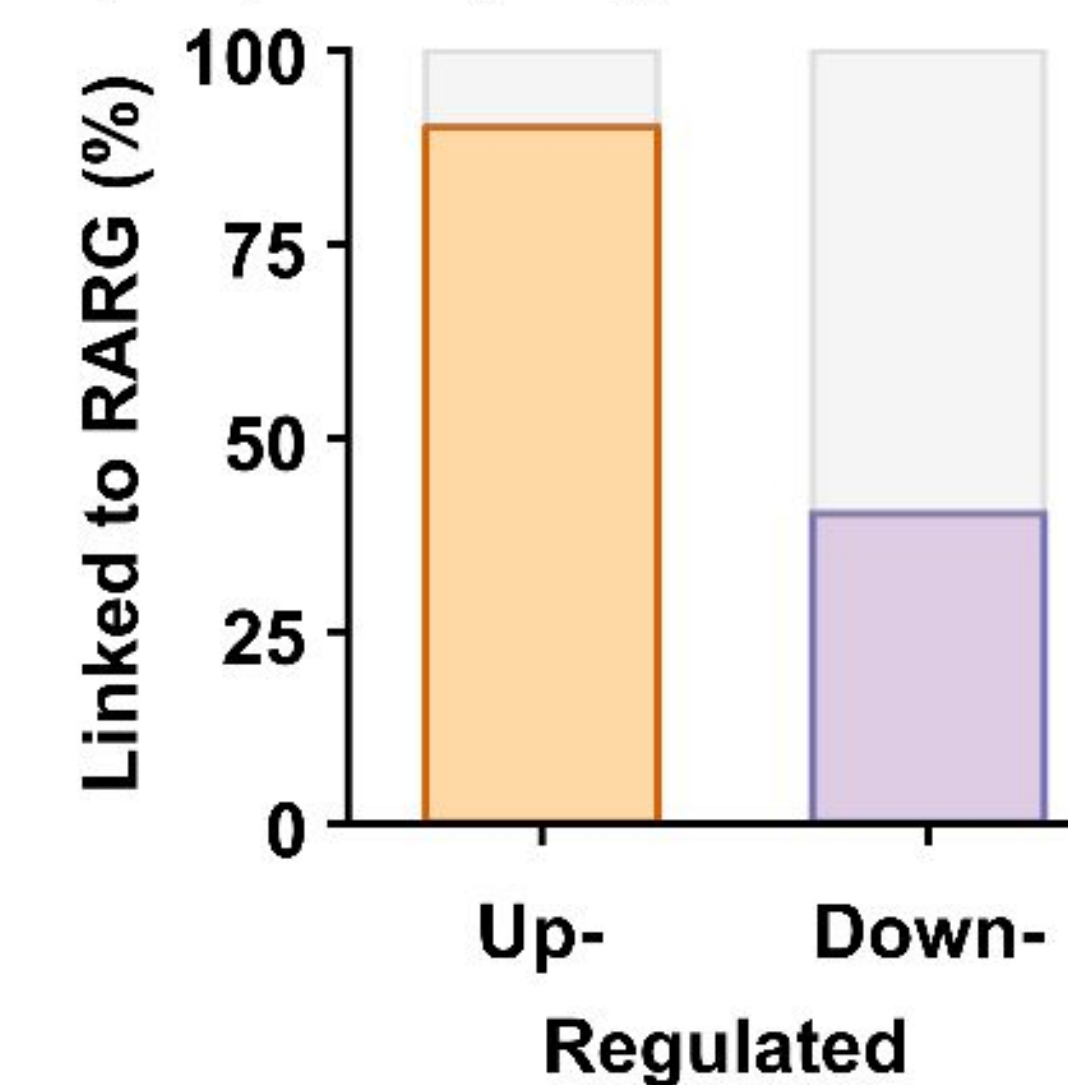


c) Proportion of RARG-Linked Genes

i) Total Dysregulated Genes



ii) Top 10 Dysregulated Genes



LIMITATIONS

- Limited number of patients (n = 11)
- Complementary proteomics and histopathological analysis ideal to support transcriptomic data
- In vitro/in vivo experiments necessary to confirm biological efficacy of retinoic acid/retinoid therapy

CONCLUSIONS

- Severe, recalcitrant TS associated with decreased RA synthesis, increased RA degradation, and reduced RA activity in the cell
- Administration of pre-formed RA may alleviate key genetic dysregulations in TS

NEXT STEPS

- Examine differences between recalcitrant vs non-recalcitrant TS gene expression
- Verify local RA depletion in TS granulation tissue biopsies
- Pre-clinical animal models: RA administration as prophylactic and curative treatment

REFERENCES

- [1] Almanzar A, Danckers M. Laryngotracheal Stenosis. StatPearls [Internet]: StatPearls Publishing; 2022
- [2] Carpenter DJ, Hamdi OA, Finberg AM, Daniero JJ. Laryngotracheal stenosis: Mechanistic review. Head Neck. 2022 Aug;44(8):1948-1960. doi: 10.1002/hed.27079. Epub 2022 Apr 30. PMID: PMC9543412.