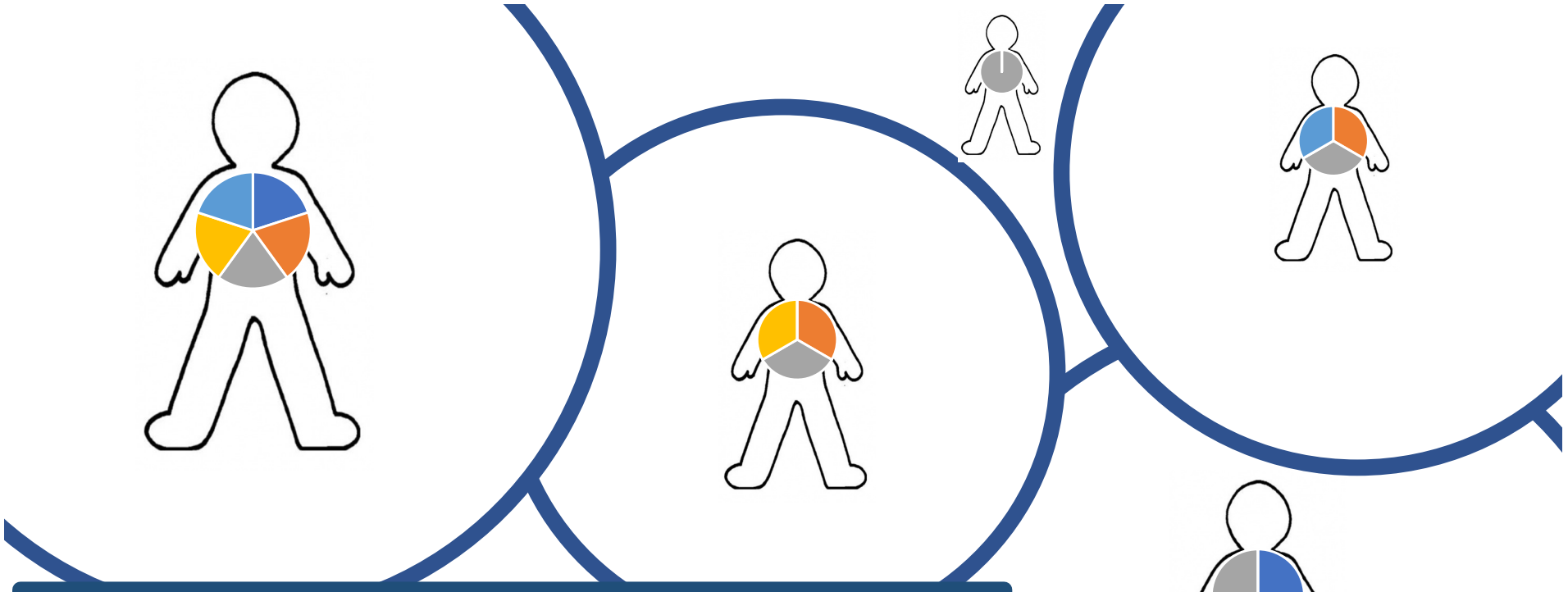
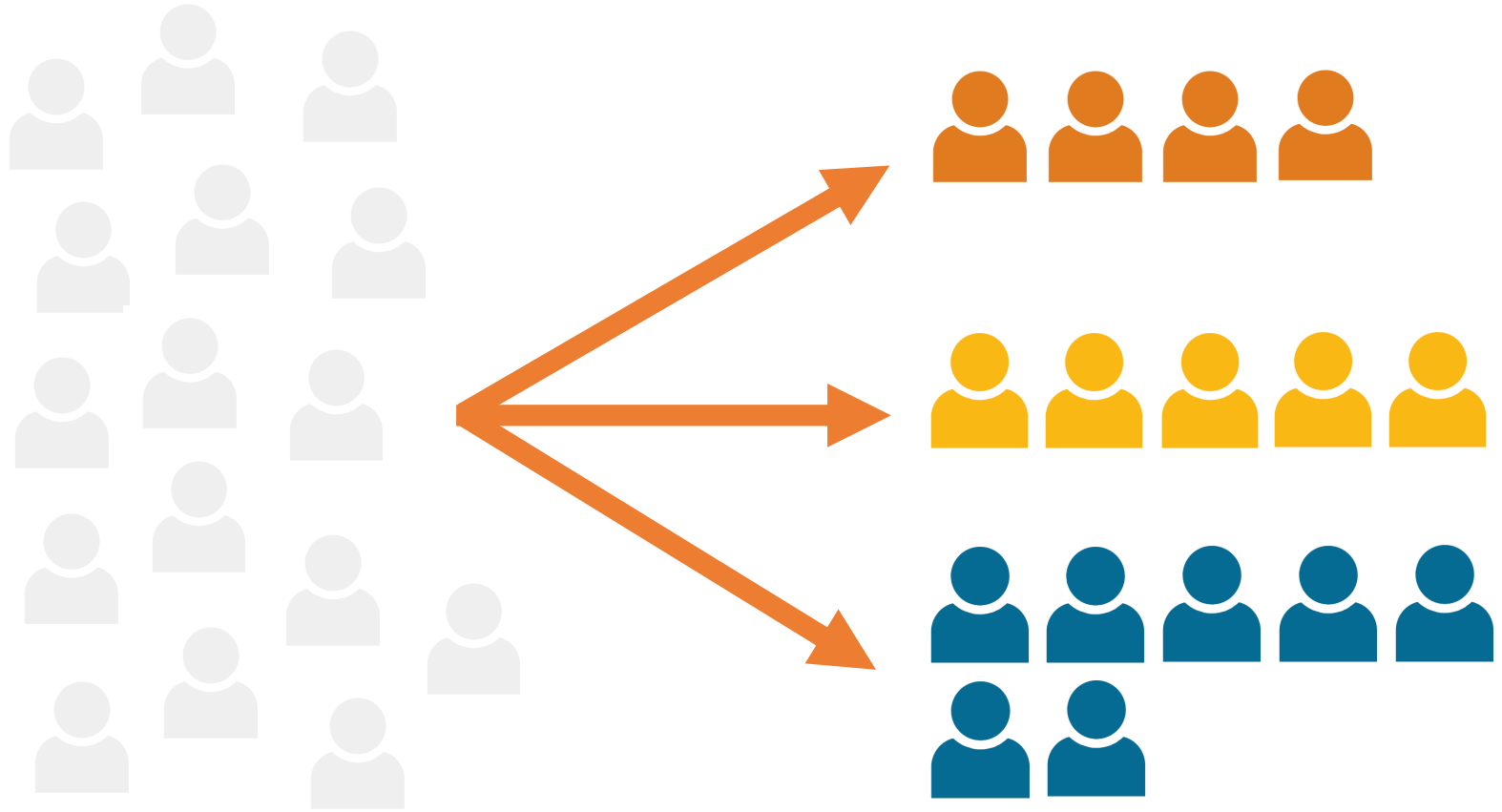
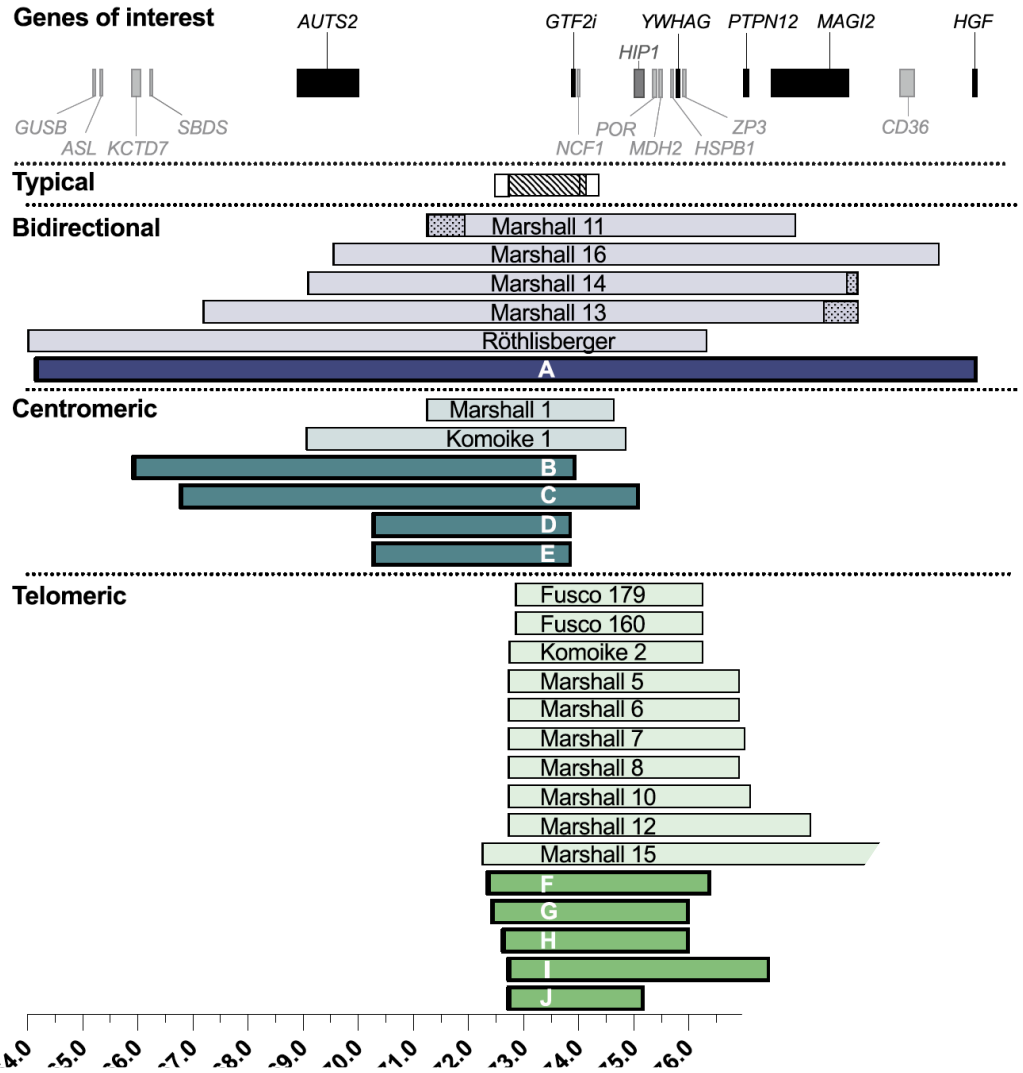


Genes modifying cardiovascular disease outcomes in Williams syndrome

Beth A. Kozel, MD, PhD
National Heart, Lung, and Blood Institute

Understanding variability in outcome for people with WS



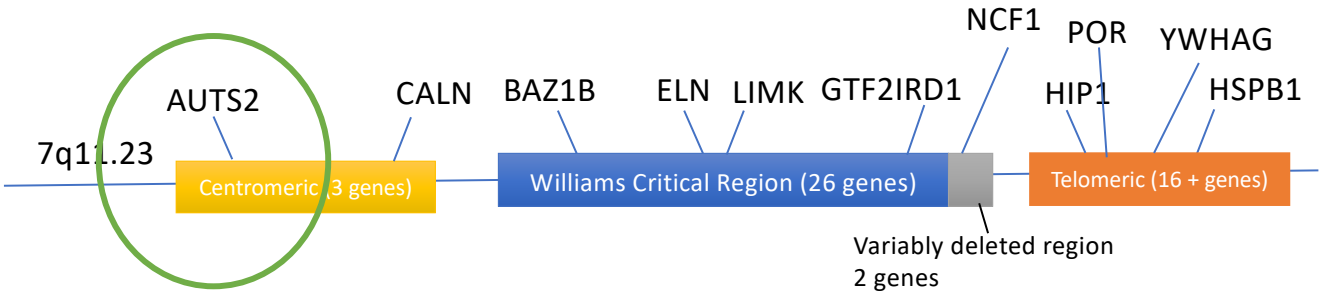


Atypical WS Deletions and second genetic events explain many “rare-rares”

* 95% of people with WS have a 1.5-1.8 MB deletion at 7q11.23
* ~5% have atypical deletions

Lugo et al, AJMG 2020

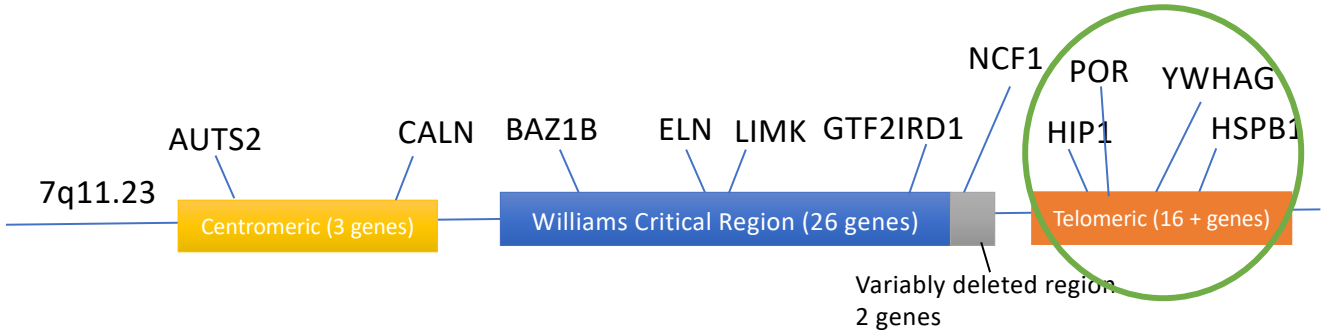
WSCR flanking genes impact phenotypic outcomes



Smaller than typical head size
Decreased speech, autism
Spasticity
Severe reflux in deletions extending even further centromeric

Adapted from Lugo et al, *AJMG* 2020

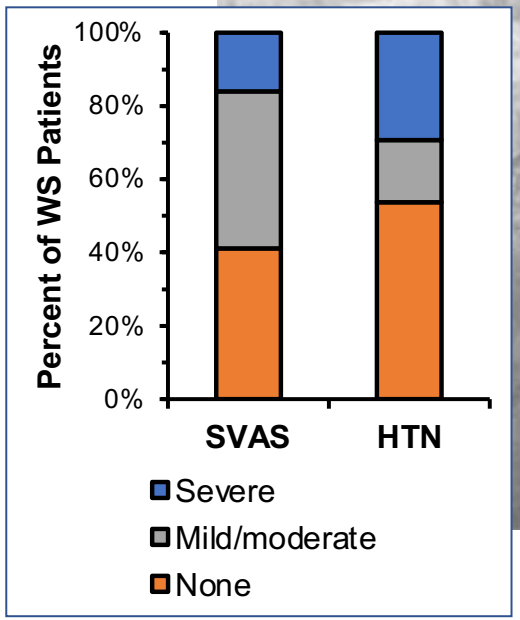
WSCR flanking genes impact phenotypic outcomes

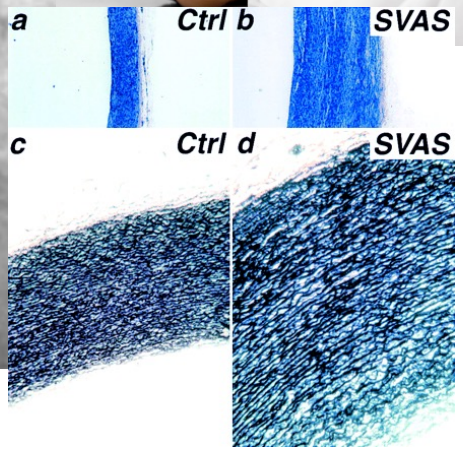


Autism
Seizures (MAGI2)
Other heart anomalies
Genital anomalies (possibly related to hormone function-POR)

Adapted from Lugo et al, *AJMG* 2020

Elastin mediated vascular disease





Li et al, Nature, 1998

WS arises due to misalignment of flanking low copy number repeats

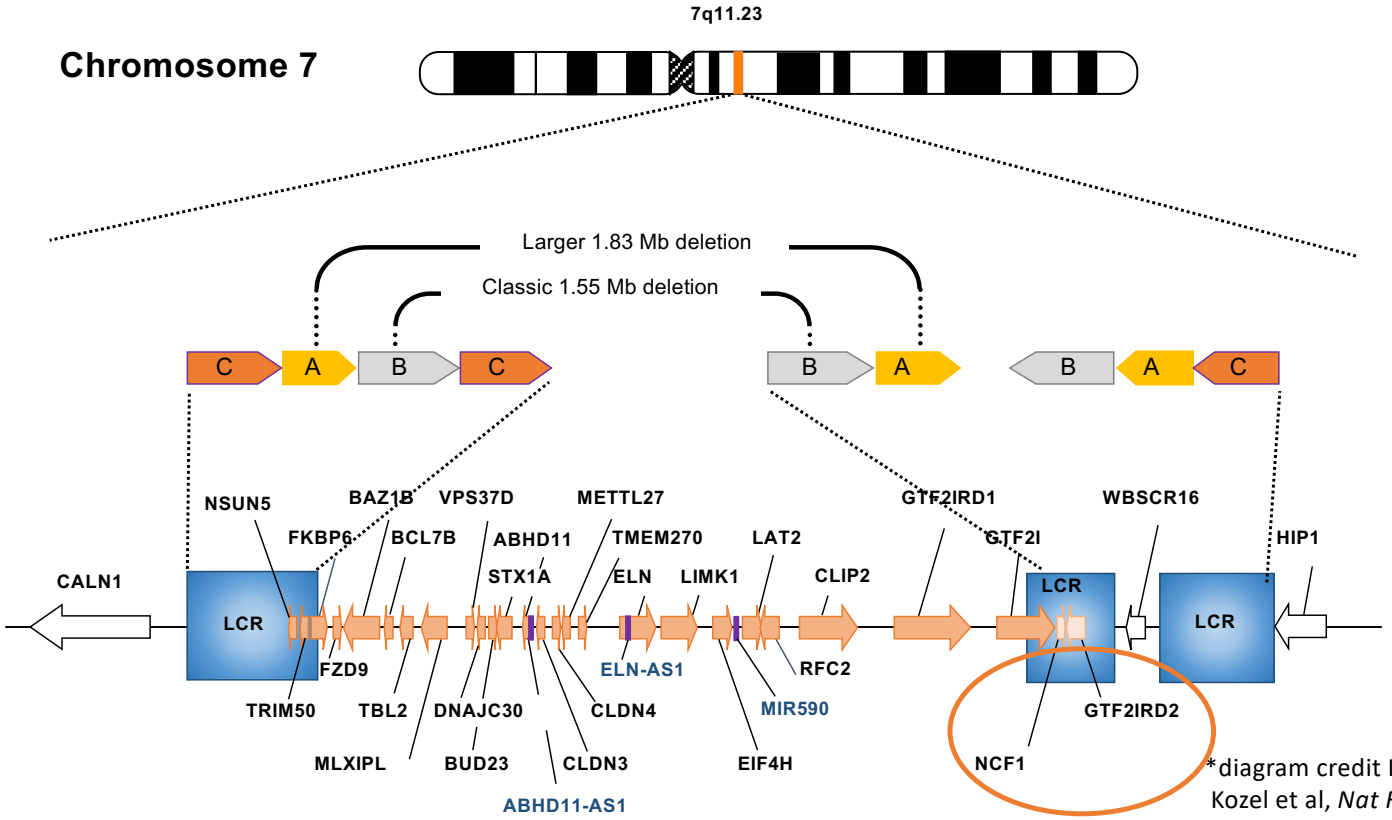
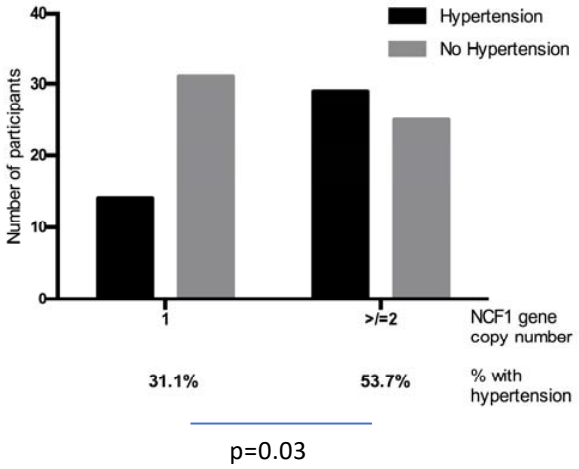
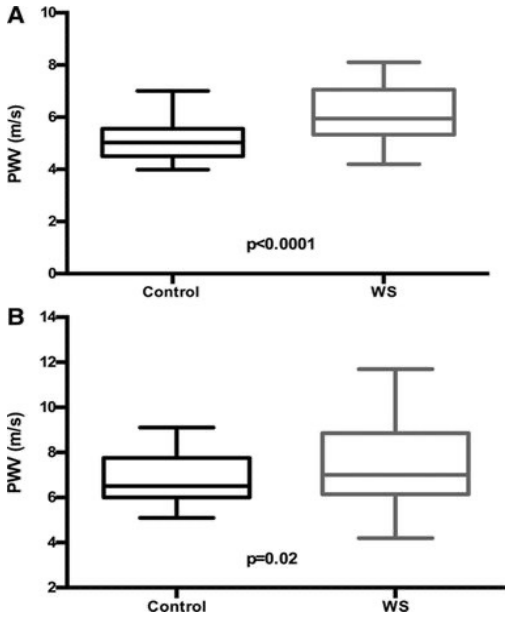
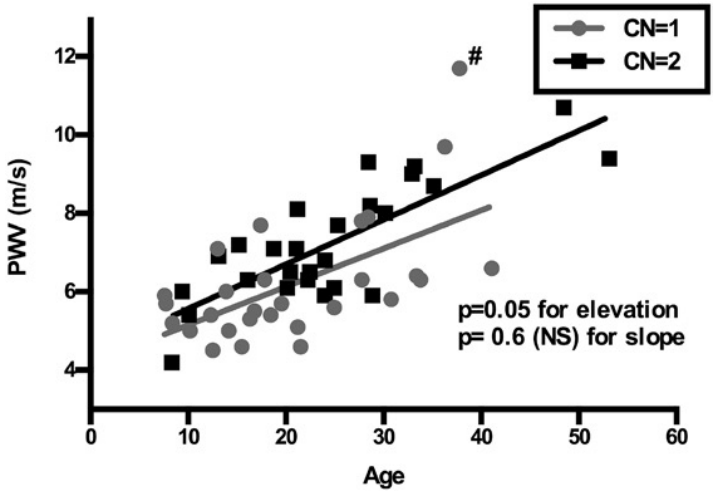


*diagram credit L Osborne for Kozel et al, *Nat Rev Primers* on WS

Dosage of *NCF1,* the regulatory component of NADPH oxidase (NOX), is associated with risk of hypertension and vascular stiffness in WS

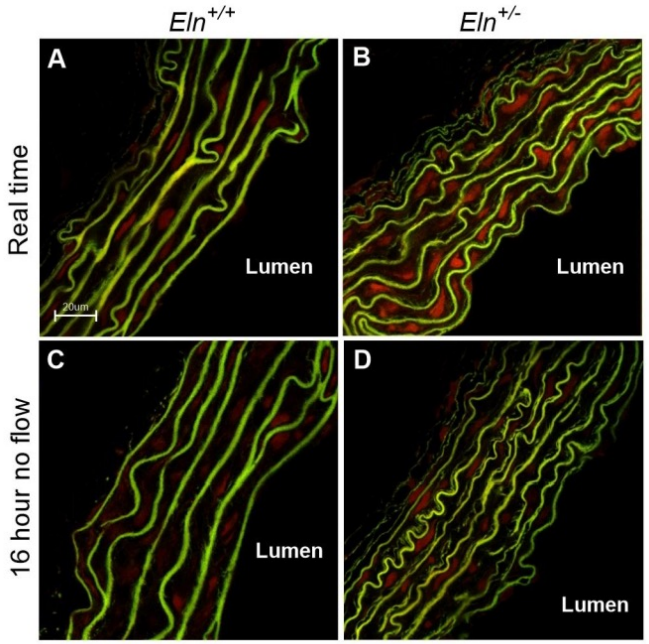


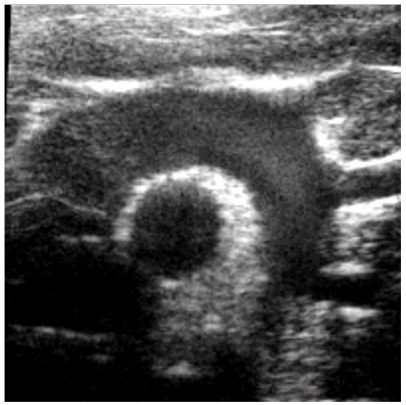




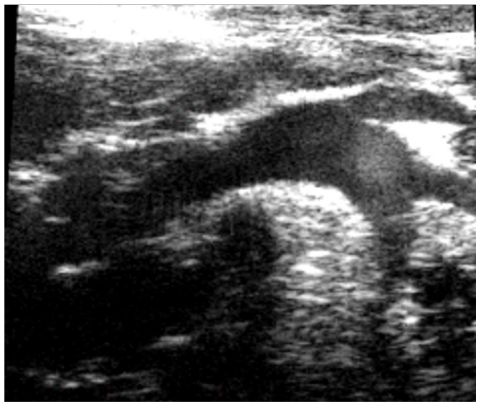
Kozel et al, *Hypertension*, 2014

Altered anatomy produces turbulent (oscillatory) flow and increased reactive oxygen species (ROS) in *Eln*$^{+/-}$





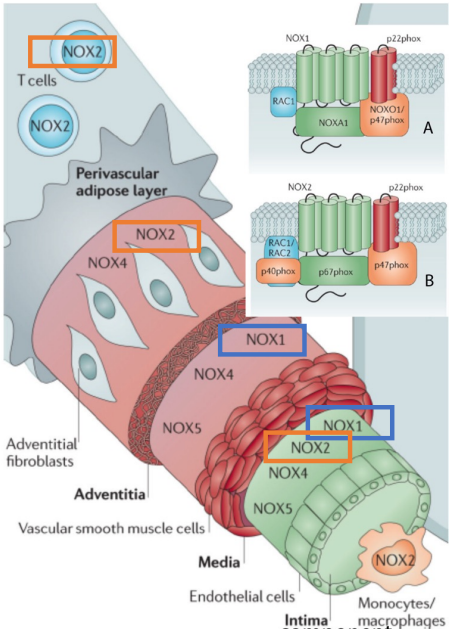
Eln$^{+/+}$



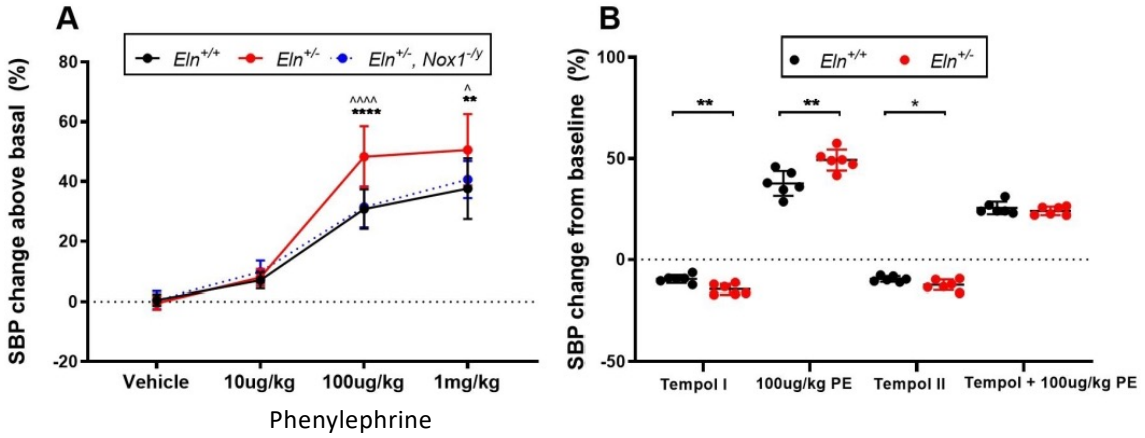
Eln$^{+/-}$

Troia et al (Kozel lab), *Function* 2021

Nox1 mediates blood pressure change in *Eln*$^{+/-}$ mice

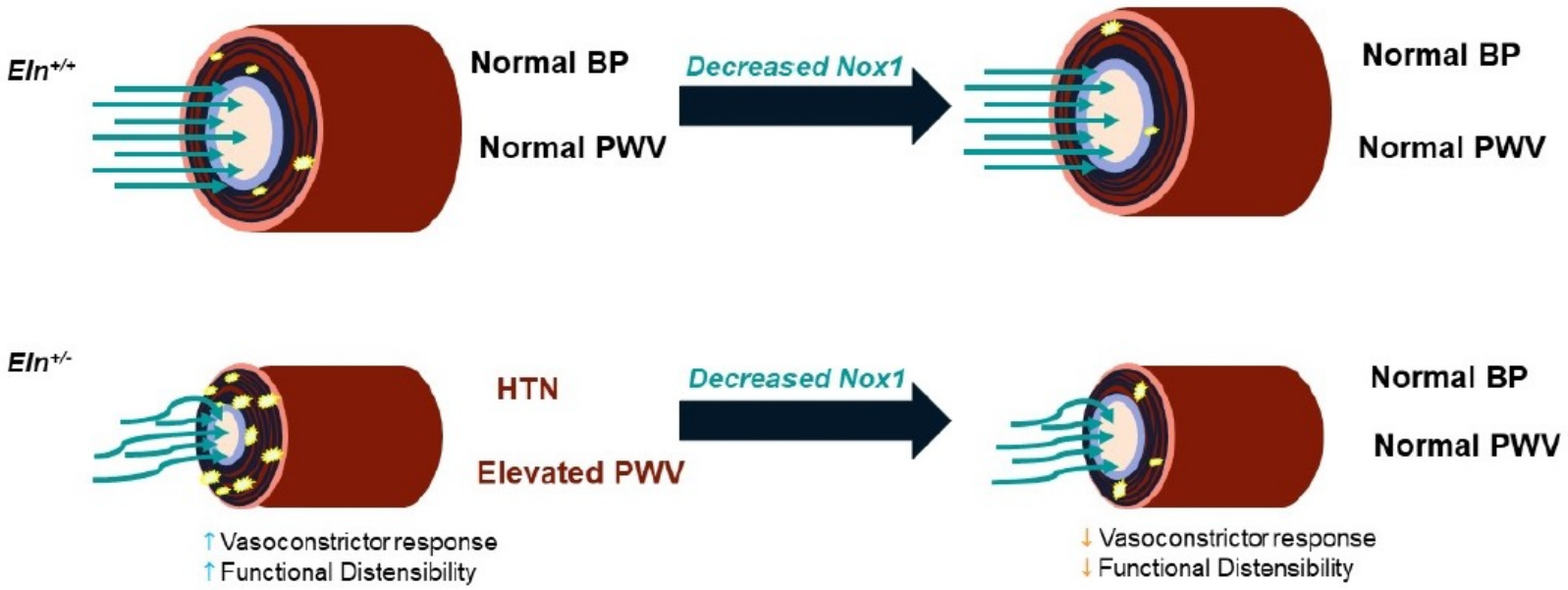


Adapted from Drummond et al, Nat Rev Drug Discovery, 2011



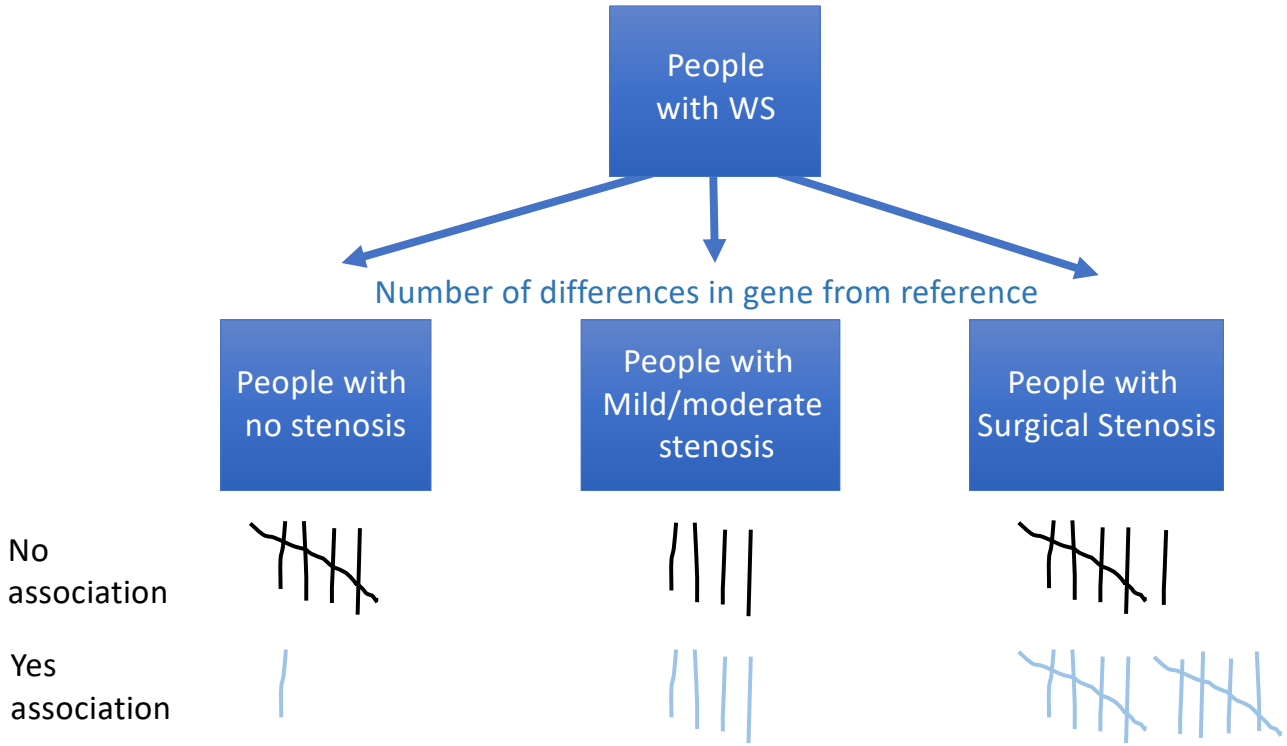
Troia et al (Kozel lab), *Function* 2021

Decreased Nox dosage is associated with lower blood pressure and decreased stiffness in $Eln^{+/-}$

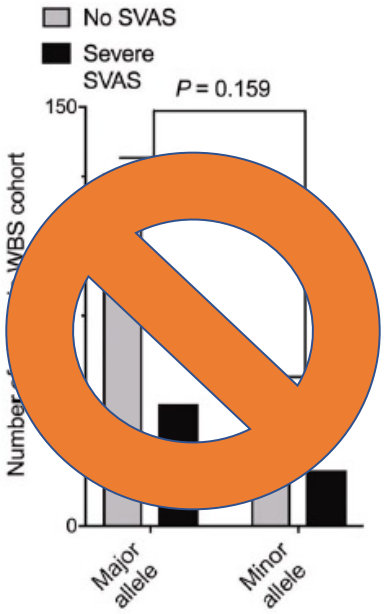


Troia et al (Kozel lab), *Function* 2021

Looking for genetic modifiers associated with severe outcomes



Considerations for improving power for modifier studies in small sample size



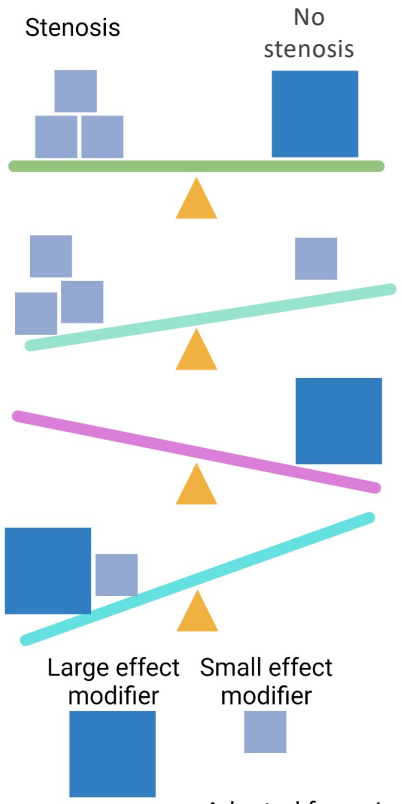
Parrish et al (Kozel lab),
Hum Mol Genetics 2020

Hypothesis:

Variation in multiple genes contribute to the ultimate phenotype.

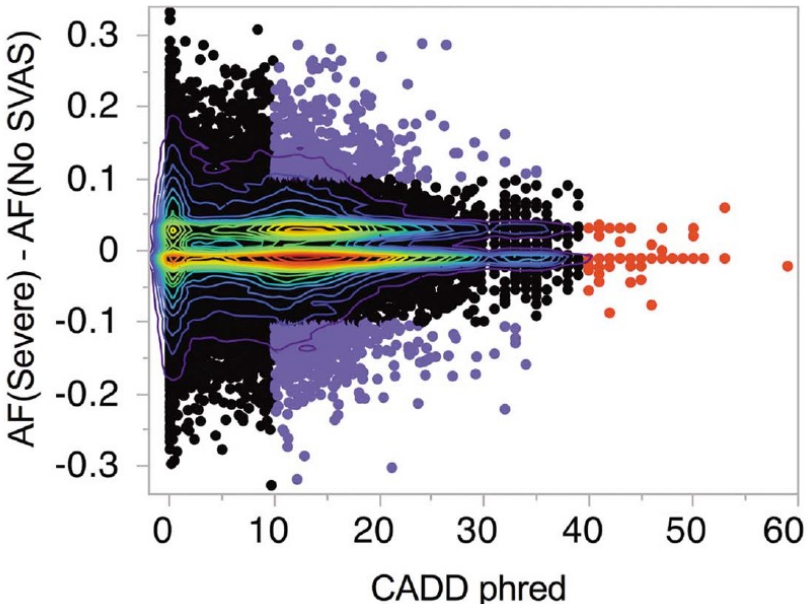
Variants may synergize to amplify the phenotype

Modifiers work in combination to generate the final phenotype



Adapted from: Luperchio and Kozel, Current Opinion in Genes and Development 2022

Finding modifiers by putting our focus where it matters



Combined Annotation Dependent Depletion (**CADD**) phred

Approach:

Extreme phenotypes

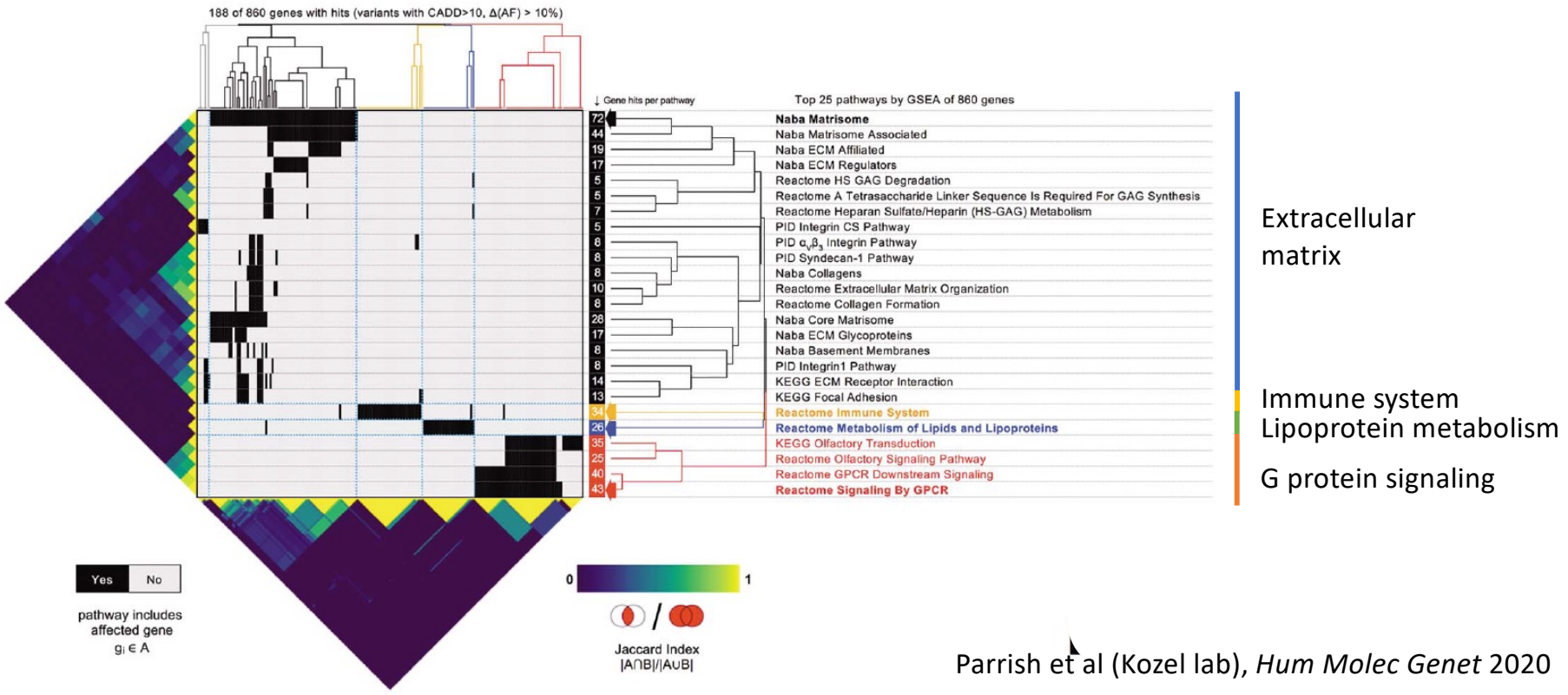
Limit variants evaluated

Increased likelihood of pathogenicity

Condense search to pathways rather than individual variants or genes

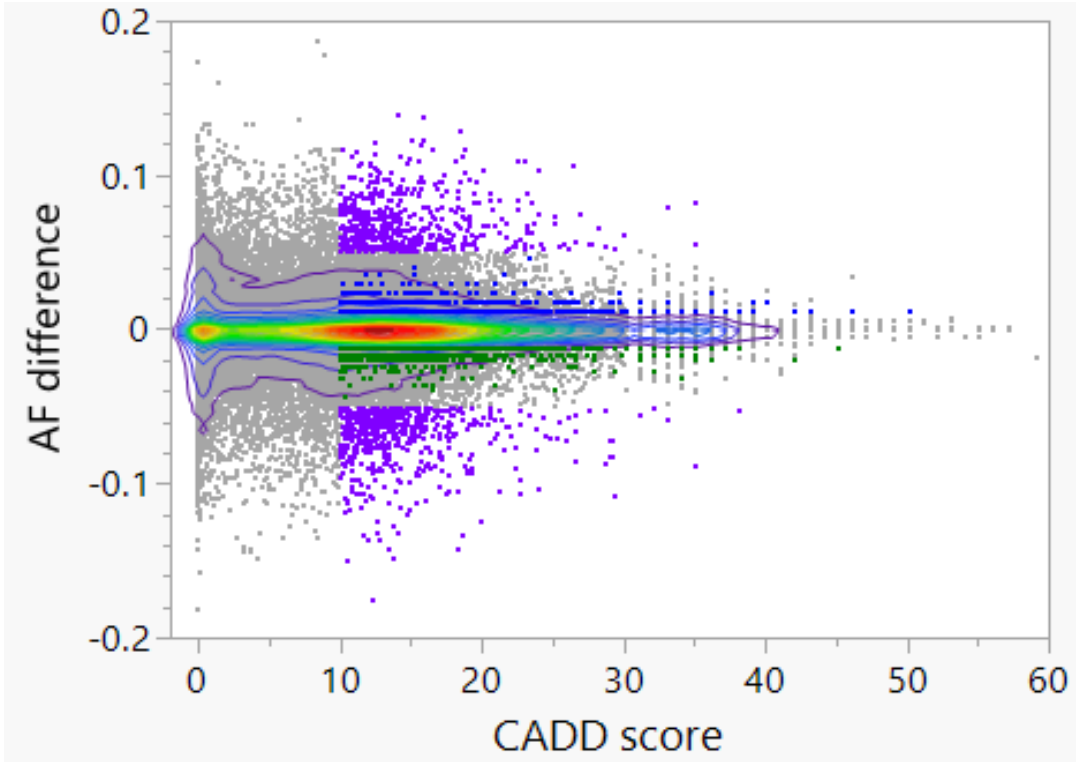
Parrish et al (Kozel lab), *Hum Molec Genet* 2020

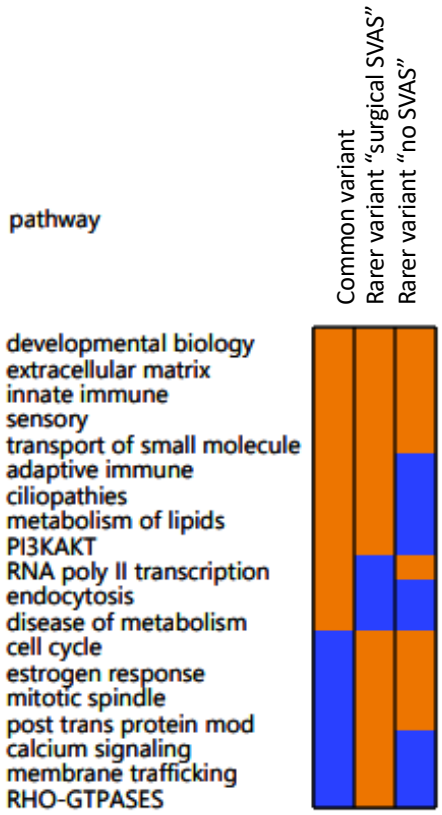
Finding modifiers by putting our focus where it matters



Parrish et al (Kozel lab), *Hum Molec Genet* 2020

Common and rare variant analyses reveal 14 pathways in which variation is associated with SVAS outcomes

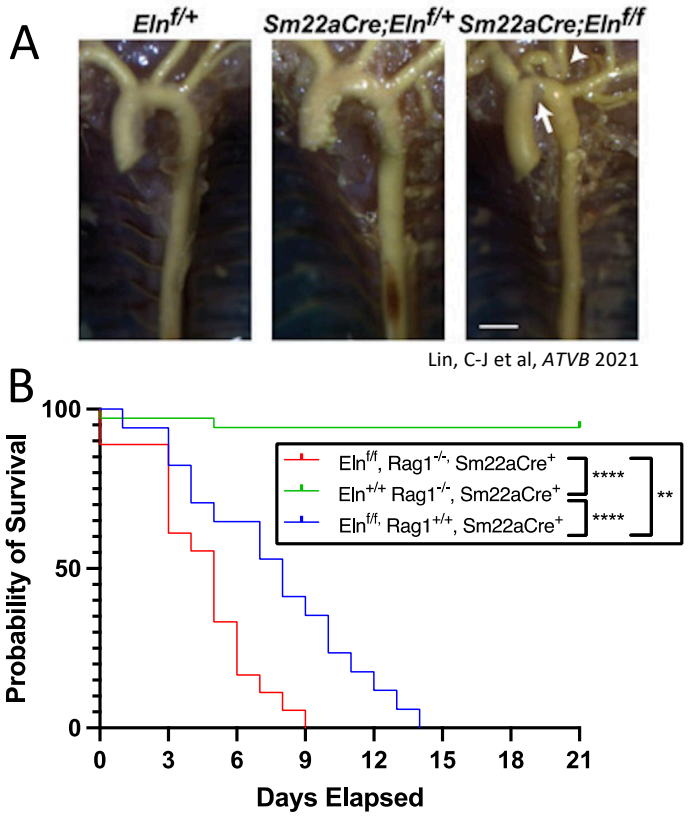


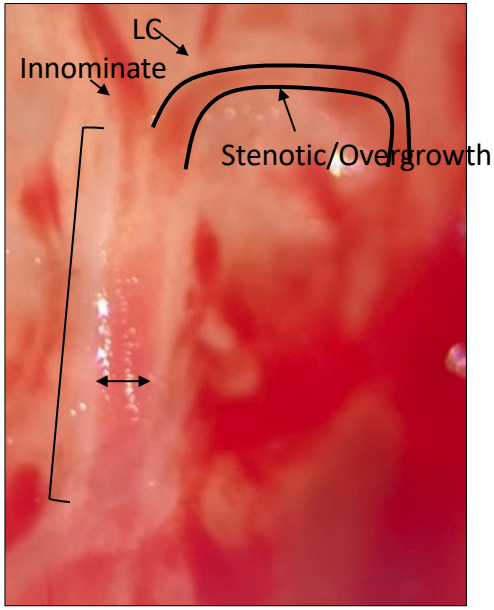


Liu et al, Submitted, 2022

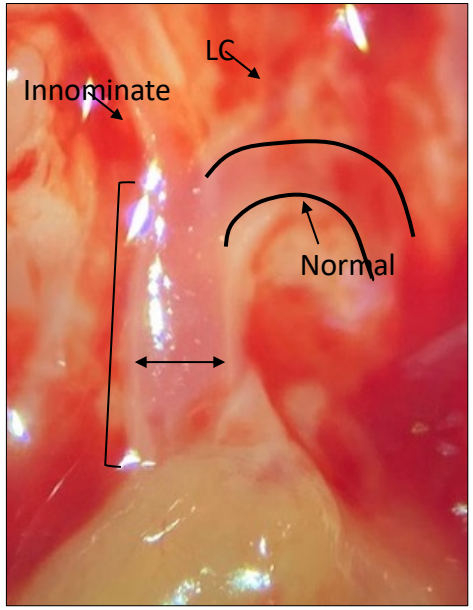
Elucidating the role of immune dysfunction on stenosis risk:

Loss of T and B cells leads to earlier death in a conditional elastin knockout model



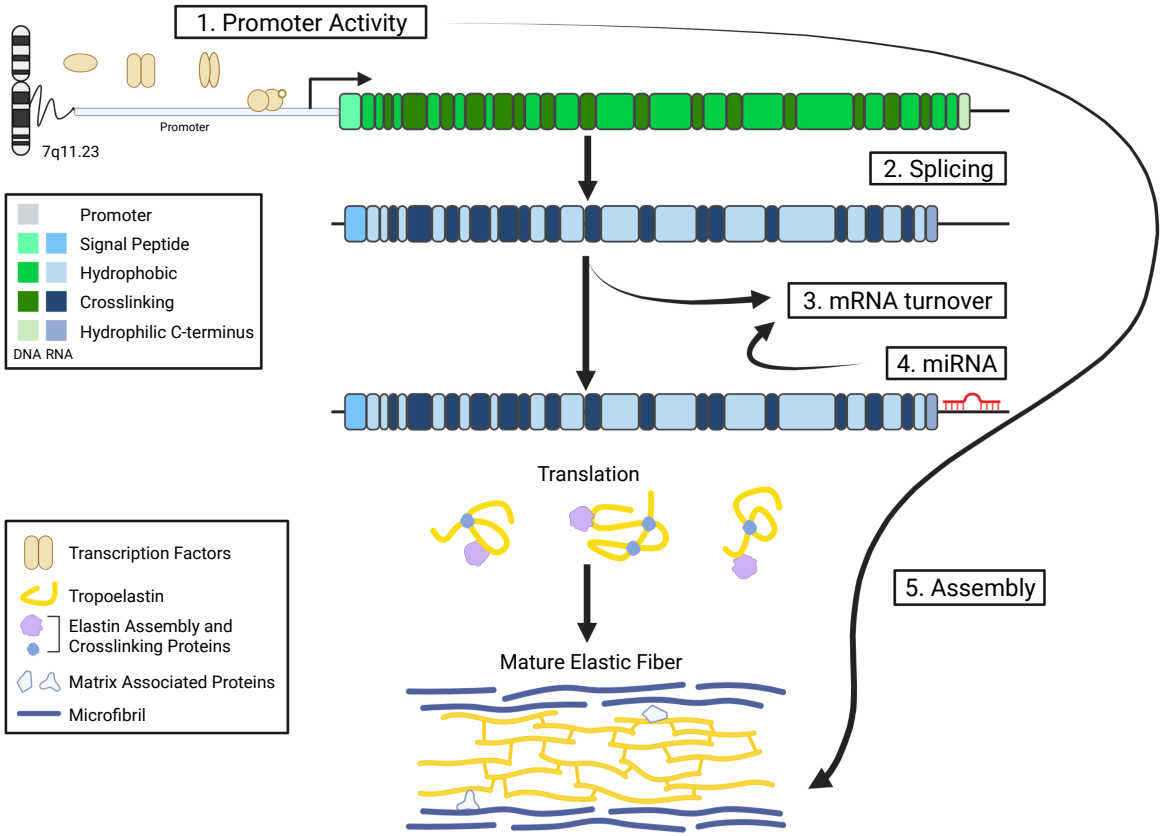


Sm22a+; Eln F/F; Rag1-/-



Sm22a+; Eln+/+; Rag1-/-

Knutsen and McIntosh, Unpublished



Missing heritability/sources of variability

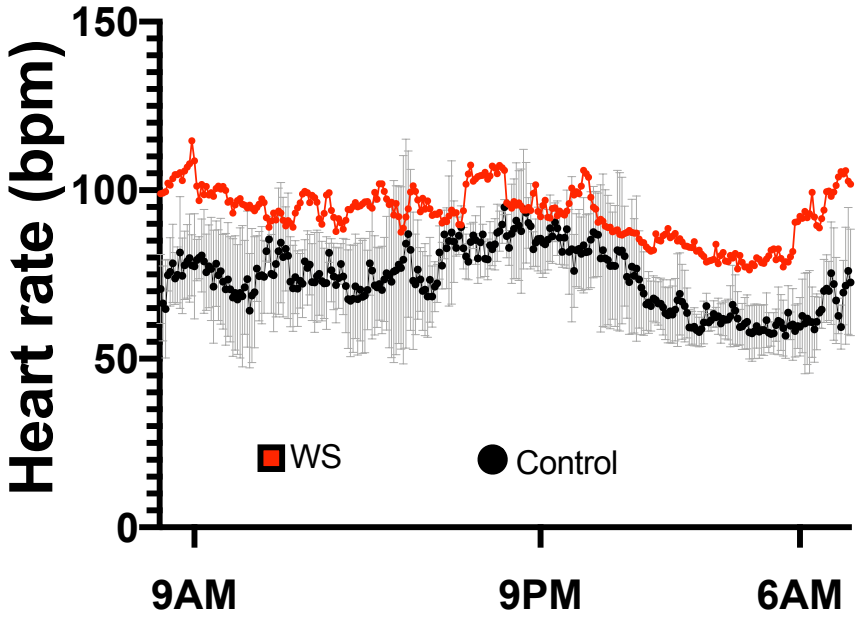
- Non-coding
- Splicing
- Epigenetic modification
- RNA stability control
- Control of assembly

Procknow and Kozel, *AJP Cell* 2022

Conclusions:

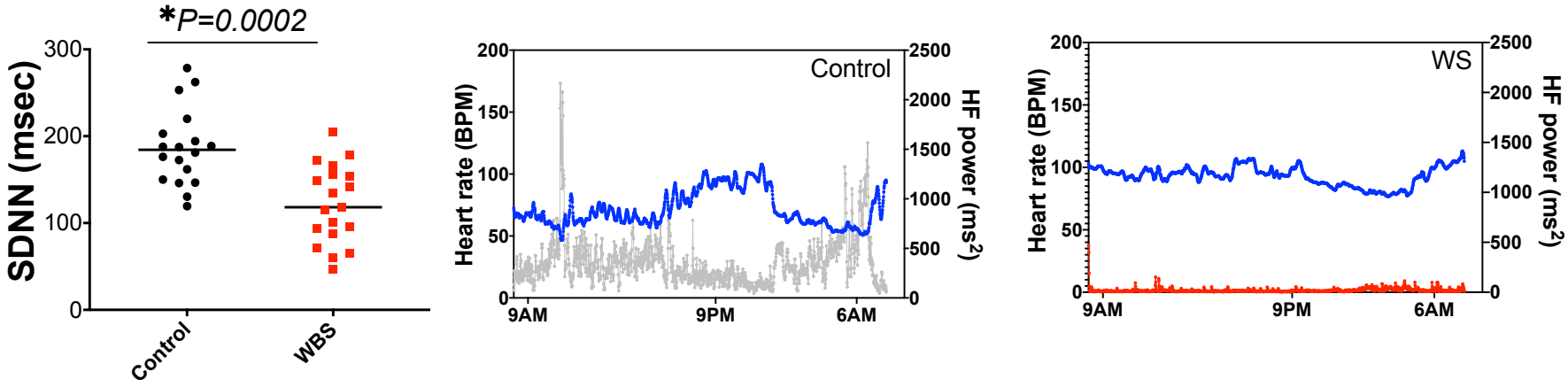
- Variation within and at a distance from the WS deletion region influences outcomes
- Modifier studies are possible in small, rare disease cohorts
- Candidates identified benefit from replication and further mechanistic validation
- In the case of WS, our study identified several key pathways that have the potential to influence vascular outcomes
- Several have already been evaluated for a role in this condition
- Pathways identified may be key to developing new therapeutics

Clinical Observation: Elevated heart rate in people with WS



Levin et al, *JACC EP* 2022

Individuals with WS exhibit decreased heart rate variability



Levin et al, *JACC EP* 2022

Impact of HRV differences in WS

- Increased time in “fight or flight”
- Decreased time in “rest and digest”

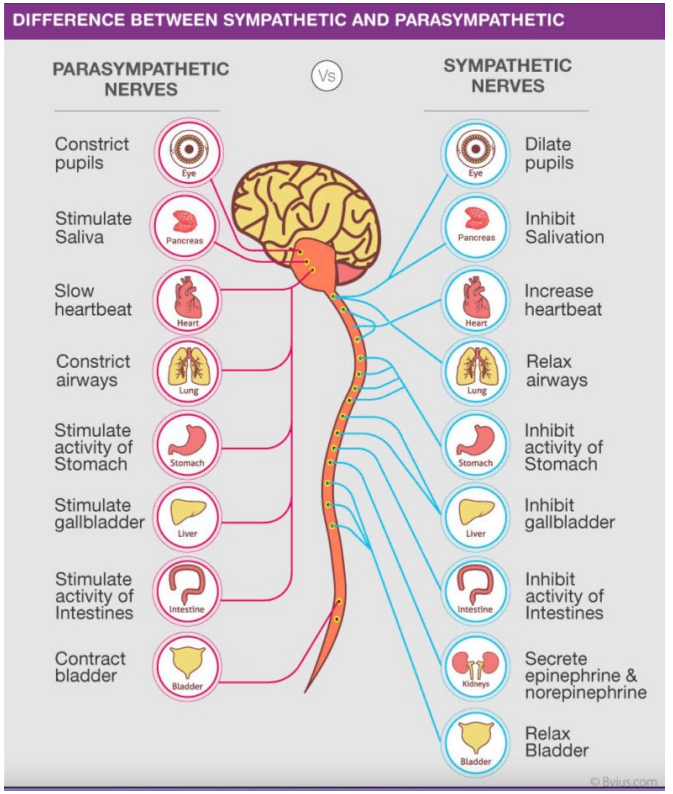


Image from byjus.com

Implications for:

- Anxiety
- Executive processing
- Abdominal pain
- Sleep

- NIH team members/Collaborators
  - Delong Liu, PhD
  - Mark Levin, MD
  - Kit Man Tsang, PhD
  - Neelam Raja, APNP
  - Sharon Osgood, RN, MS
  - Daniel Chertow, BA
  - Joy Freeman, RN
  - Elahe Hasanzadeh, MD
  - Sara Procknow, MD, PhD
  - Emily Ruiz Escobar, BS
  - Likitha Nimmagadda, BS
  - Teresa Luperchio, PhD
  - Grace Ge, BS
  - Yi-Ping Fu, PhD
  - Russ Knutsen, BA
- Past Lab members with work relevant to this presentation
  - Phoebe Parrish, BS (U Washington PhD Prog)
  - Charles J. Billington, Jr., MD, PhD (U Minn)
  - Zoe Wong, BS (NIH OxCam Fellowship)
  - Angela Troia, MD (Georgetown U Residency)

Thank you

- NIH Clinical Collaborators
  - Laryssa Huryn, MD
  - Marcus Chen, MD
  - Amisha Barochia, MD
  - Audrey Thurm, PhD
  - Colleen Hadigan, MD
- USUHS Sequencing Collaborators
  - Clifton Dalgard, PhD
  - C. Alba and DH Hupalo

- Clinical Collaborators
  - Elisa Biamino, MD (Univ of Turin)
  - Maria Francesca. Bedeschi, MD (Granda Ospedale Maggiore Policlinico)
  - Maria Cristina Digilio , MD (Bambin Gesu Ospedale)
  - Giuseppe Merla, MD (Univ of Naples Federico II, Casa Sollievo della Sofferenza)
  - Carolyn Mervis, PhD (University of Louisville)
  - Colleen Morris, MD (UNLV)
  - Lucy Osborne, PhD (University of Toronto)
  - Barbara Pober, MD (Harvard/Mass General)
  - Amy Roberts, MD (Boston Children's Hospital)
  - Gabriella Maria Squeo, MD (Fondazione IRCCS Casa Sollievo della Sofferenza)
  - Roberto Villa, MD (Granda Ospedale Maggiore Policlinico)
- The WSA and all of the families and participants

Thank you!

Contact with questions:

Beth.Kozel@NIH.gov

Abstract:
Williams syndrome is associated with a characteristic set of developmental and medical features. However, the number and severity of symptoms vary from person to person. The Kozel lab at the NIH works to identify genetic changes that influence those outcomes. The presentation will outline 1) the impact of atypically large WS deletions, which produce important but rare phenotypes in people with WS, 2) more subtle differences in deletion size within the low copy number repeat regions that impact hypertension risk, and 3) the role of exome-wide single nucleotide variation on SVAS. Targeting these modifier genes and pathways may lead to novel therapeutics to treat health concerns in WS. If time permits, the speaker will also touch on new unpublished findings relating to non-coding variation in the WS region that contribute to stenosis risk and a brief overview of a recently completed study on heart rate variability and autonomic response.