# Brain and Aortic Aneurysm Screening (BAAS) Study - UVA

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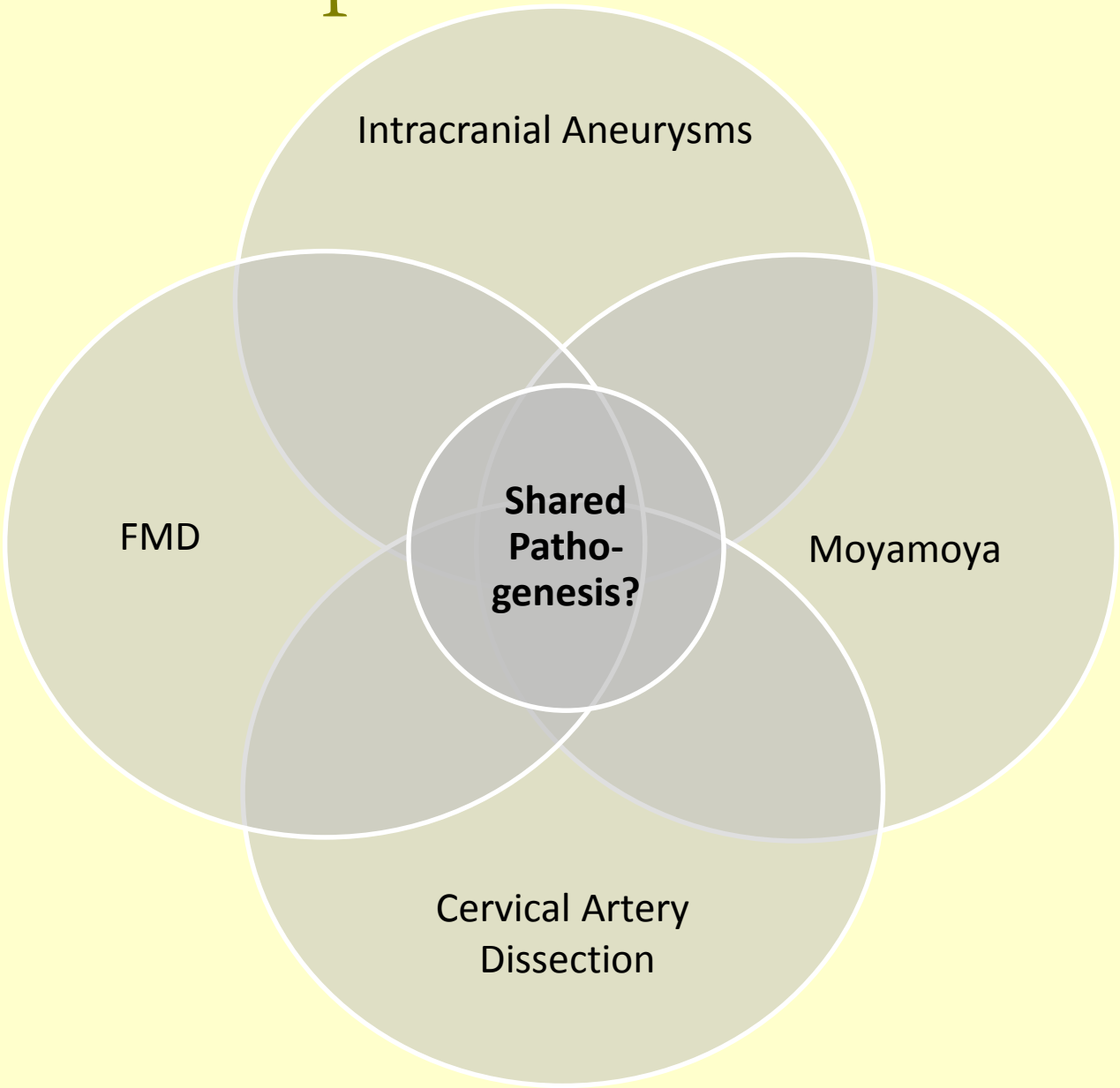
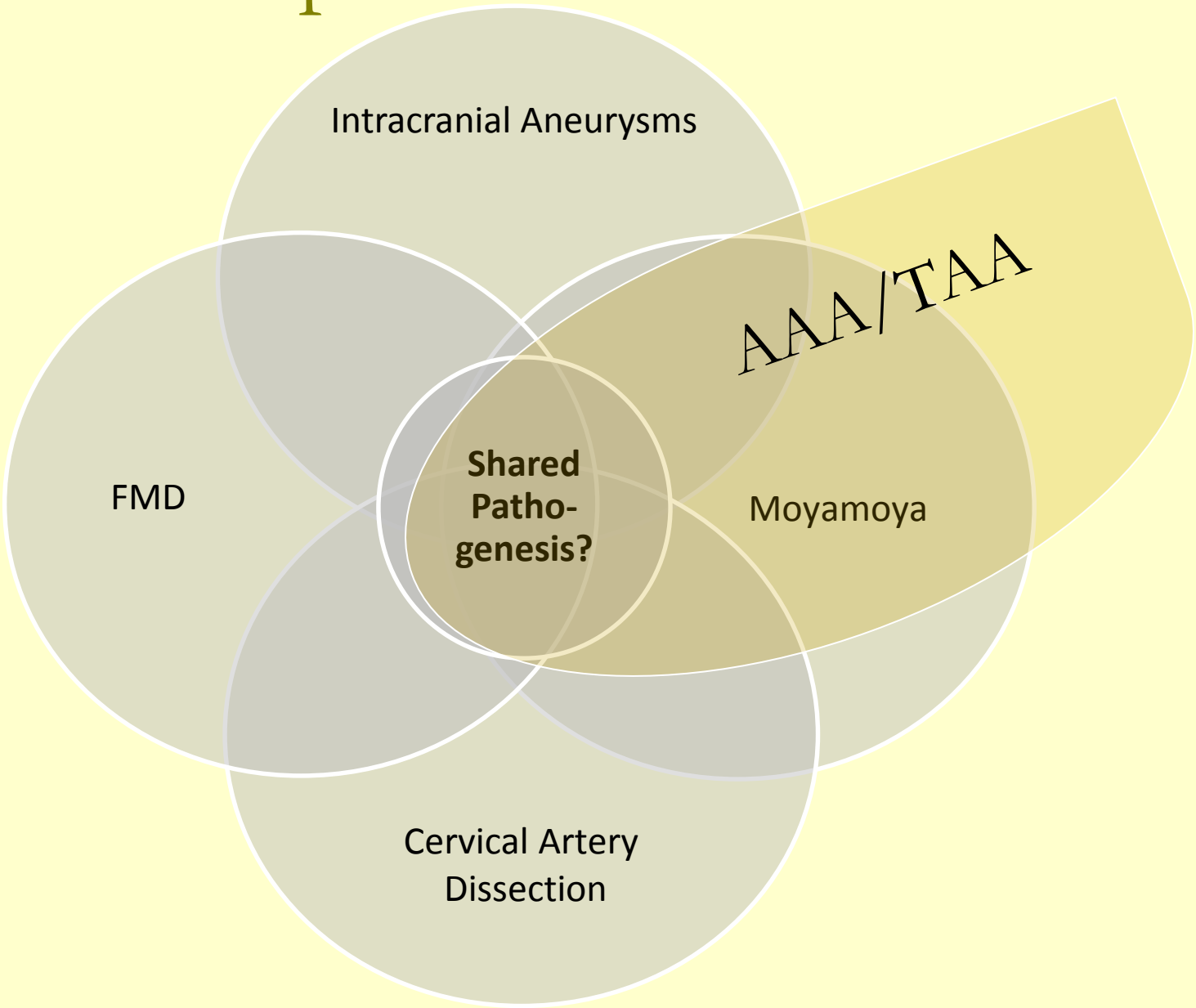
# Conceptual Framework



# Summary

- Reframing of clinical phenotypes bringing together previously disparate conditions and clinicians
- Focus on shared pathology among these arteriopathies could guide future association studies and the search for therapeutic targets

# Conceptual Framework



# Abdominal Aortic Aneurysms

- High death toll
- Many AAAs are not detected until rupture
- ~64% of individuals with ruptured AAA die before surgery
- 40% in-hospital mortality for those who receive surgery

# Intracranial and Aortic Aneurysms

- Risk for both intracranial aneurysms (IAs) and aortic aneurysms (AAs) is thought to be heritable with mounting evidence for genetic predisposition for each.
- Share risk factors: smoking and hypertension
- Co-occurrence of IAs and AAs within pedigrees has been estimated to be 10.5%.

# Related diseases?

| | IA | TAA | AAA |
|---|---|---|---|
| Prevalence (%) | 2 | ±1.25 | 5 |
| Incidence of rupture (per 100,000 patient-years) | 8 | 2.7 | 10 |
| Sex distribution | ♀>♂ | ♂>♀ | ♂>♀ |
| Age (years) | 50–60 | >60 | >60 |
| Atherosclerotic risk factors | Smoking, hypertension | Hypertension | Smoking, hypertension |
| Coincidence with other aneurysms | AAA? | AAA | TAA |
| Prevalence among first-degree relatives of patients (%) | 10 | 20 | 18 |
| Relative risk for siblings of patients | 2.5–7 | 11 | 12 |

[Ruigrok *et al* ***Cardiovasc Path*** 200

# IA and AA

- Differences in age of diagnosis
- Differences in demographic characteristics
- AAA in particular thought atherosclerotic
- TAA may be more strongly associate…
- Co-occurrence could be simply due to chance
- Familial aggregation studies suggest that shared genetic risk factors may contribute to IA and AA susceptibility.

# Searching for Common Susceptibility Genes for IA and AA

- Genome wide linkage analysis performed in 29 multiplex IA families having members who had thoracic or abdominal AA
  - Affected = IA, AAA, or TAA
  - 93 family members affected

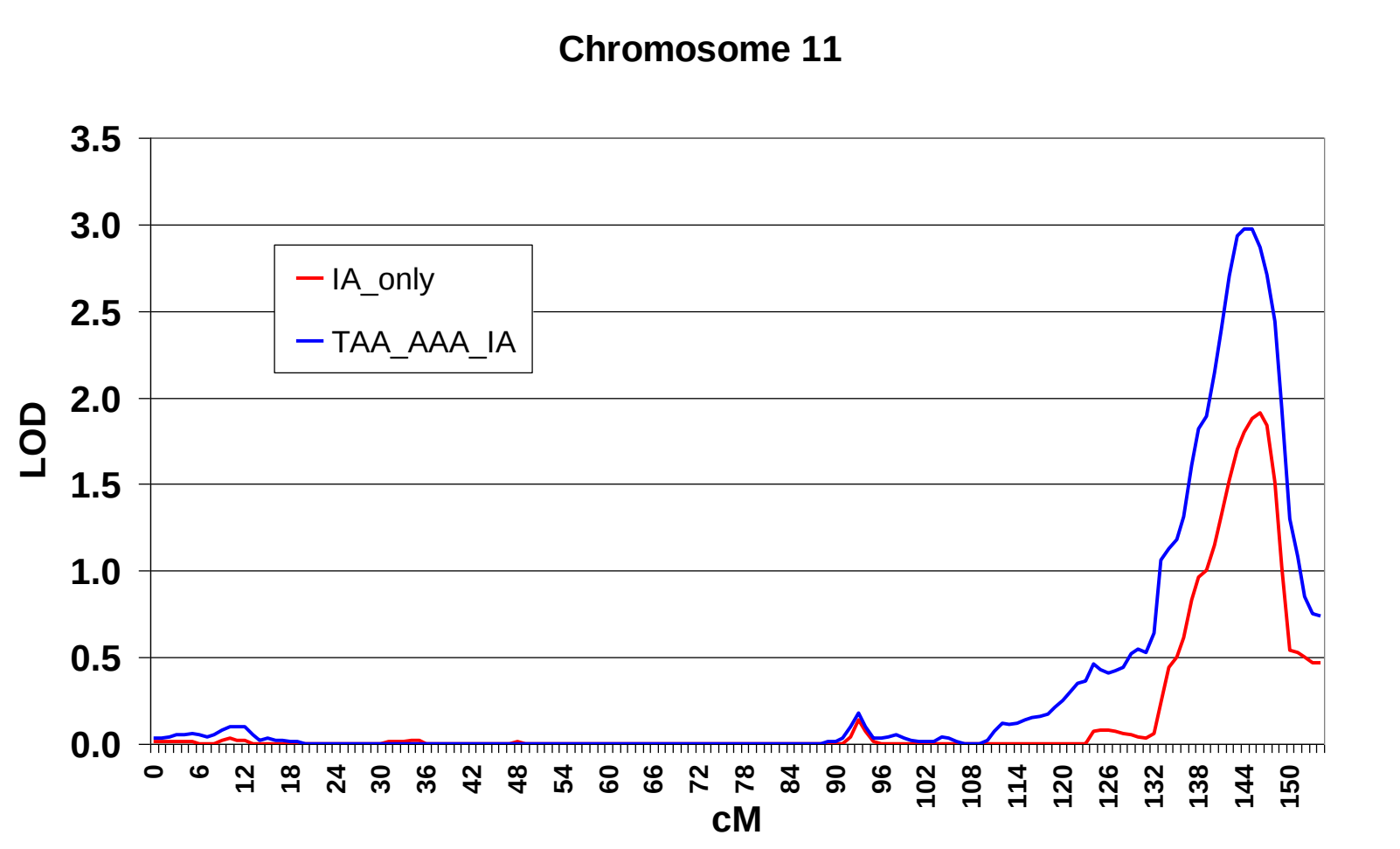
[Worrall *et al* 2009]

# Comparison of Subjects with IA to TAA/AAA

| Variable | IA | TAA/AAA | p-value | age adj. p-value |
|---|---|---|---|---|
| **Race (white)** | 91.2% | 100% | 0.399 | n/a |
| **Sex (male)** | 23.9% | 52.6% | 0.012 | 0.001 |
| **Age at Dx (yrs)** | 49.8 SD12.1) | 67.2 (SD11.3) | <.001 | n/a |
| **Smoking -current** | 50.3% | 36.8% | 0.382 | 0.601 |
| **-former** | 27.8% | 42.1% | | |
| **-never** | 21.9% | 21.1% | | |
| **Pack-Years Cigarettes** | 23.9 (SD21.8) 24.0* | 33.3 (SD15.5) 25.7* | 0.095 | 0.759 |
| **Hypertensive** | 46.4% | 73.7% | 0.021 | 0.017 |
| **Frequent Alcohol** | 39.3% | 50.0% | 0.648 | 0.557 |

SD = standard deviation
* denotes age adjusted means for continuous variables

# 11q24-25




[Worrall *et al* 2009]

# FAA1 locus on Chr. 11q

- FAA1 locus on 11q23-24 was linked to familial aortic aneurysms (both TAA and AAA)
- FAA1 locus has been associated with a more widespread vasculopathic process
- None of the genes in the region are strong mechanistic candidates for aneurismal disease

*[Vaughan et al **Circulation** 2001]*

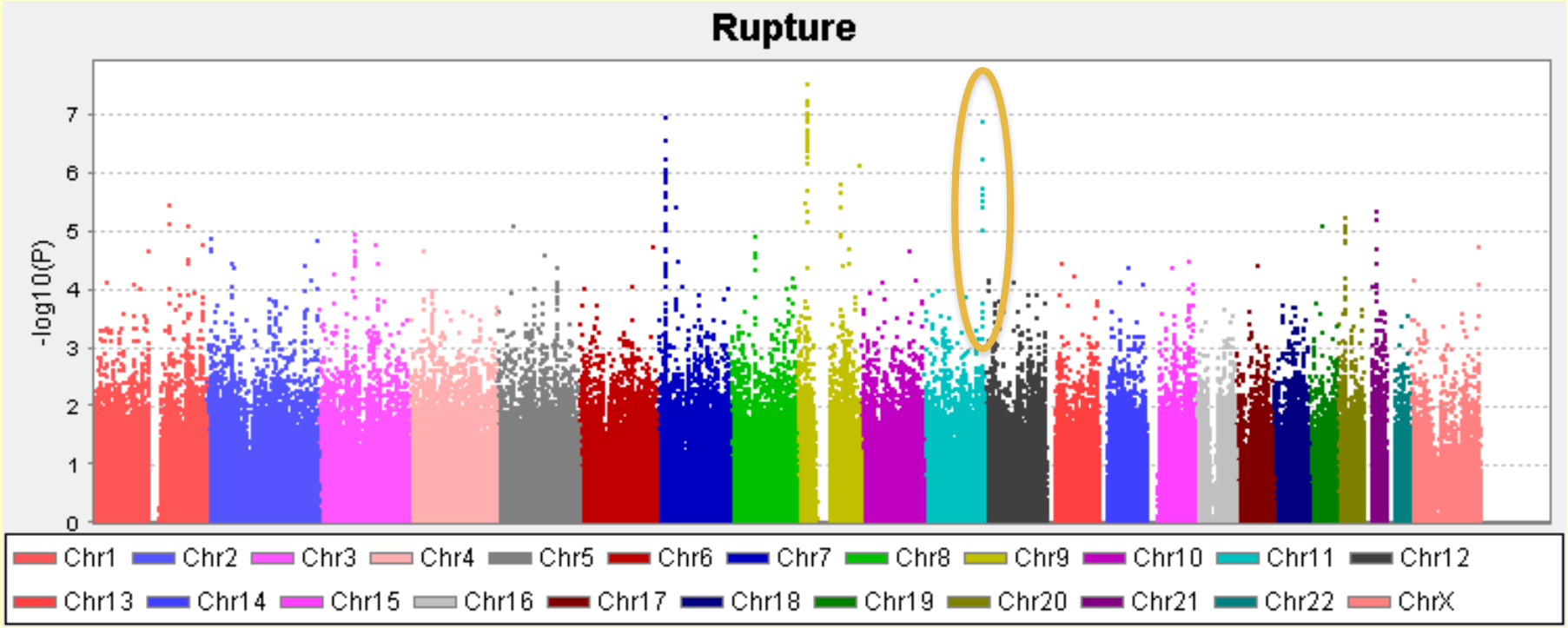
- Linkage found in two large IA pedigrees
- Inclusion of two AAA cases in the linkage analysis increased the LOD score

*[Ozturk et al **Stroke** 2006]*

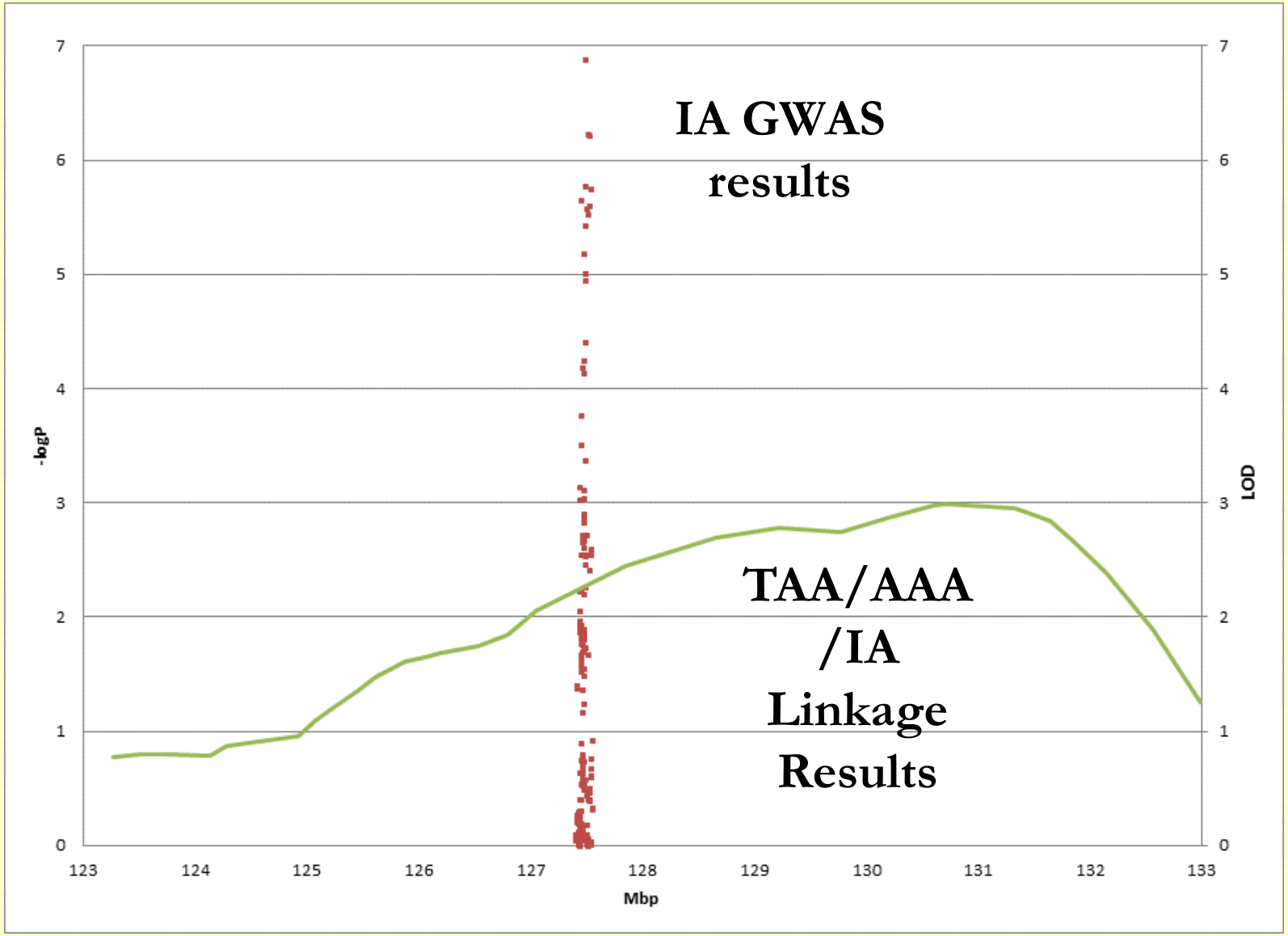
- Same region was associated with IA phenotype in a meta-analysis

*[Biros et al Neurosci Letters 2008]*

# Rupture result (GC corrected)



# Chromosome 11: GWAS and Linkage



# Shared Risk: GWAS data

- Two common sequence variants on 9p21 previously associated with CAD and T2DM
- rs10757278-G associated w/ aneurismal disease
  - AAA (OR = 1.31, $P = 1.2 \times 10^{-12}$)
  - IA (OR = 1.29, $P = 2.5 \times 10^{-6}$),
- Looked at IA and AAA as separate phenotypes

[Helgadottir *et al* ***Nature Genetics*** 2008]

# Screening for AAA in IA

- Shared environmental and genetic risk
- IA typically occurs at earlier age than AAA
- Screening cheap and non-invasive

*Hypothesis* - screening for AAA in a population with IA is a cost-effective strategy

[Ball *et al* ***ISC*** 2013]

# Conclusions:

- Screening for AAA in individuals with IA has an incremental cost-effectiveness ratio of $34.31/QALY
- Societal threshold for cost-effectiveness <$60,000/QALY
- Screening arm dominated:
  - Co-prevalence of AAA in those with IA = 7.5%
  - Sensitivity of ultrasound screening of 91%
  - 6 year timeframe for f/u

# Screening for IA in AAA

- Shared environmental and genetic risk
- IA typically occurs at earlier age than AAA
- Screening not quite as cheap
- Complexity – location, size, and multiplicity
- Different thresholds for intervention

*Hypothesis* - screening for IA in a population with AAA is a cost-effective strategy

[Jiang *et al* ***ISC*** 2014]

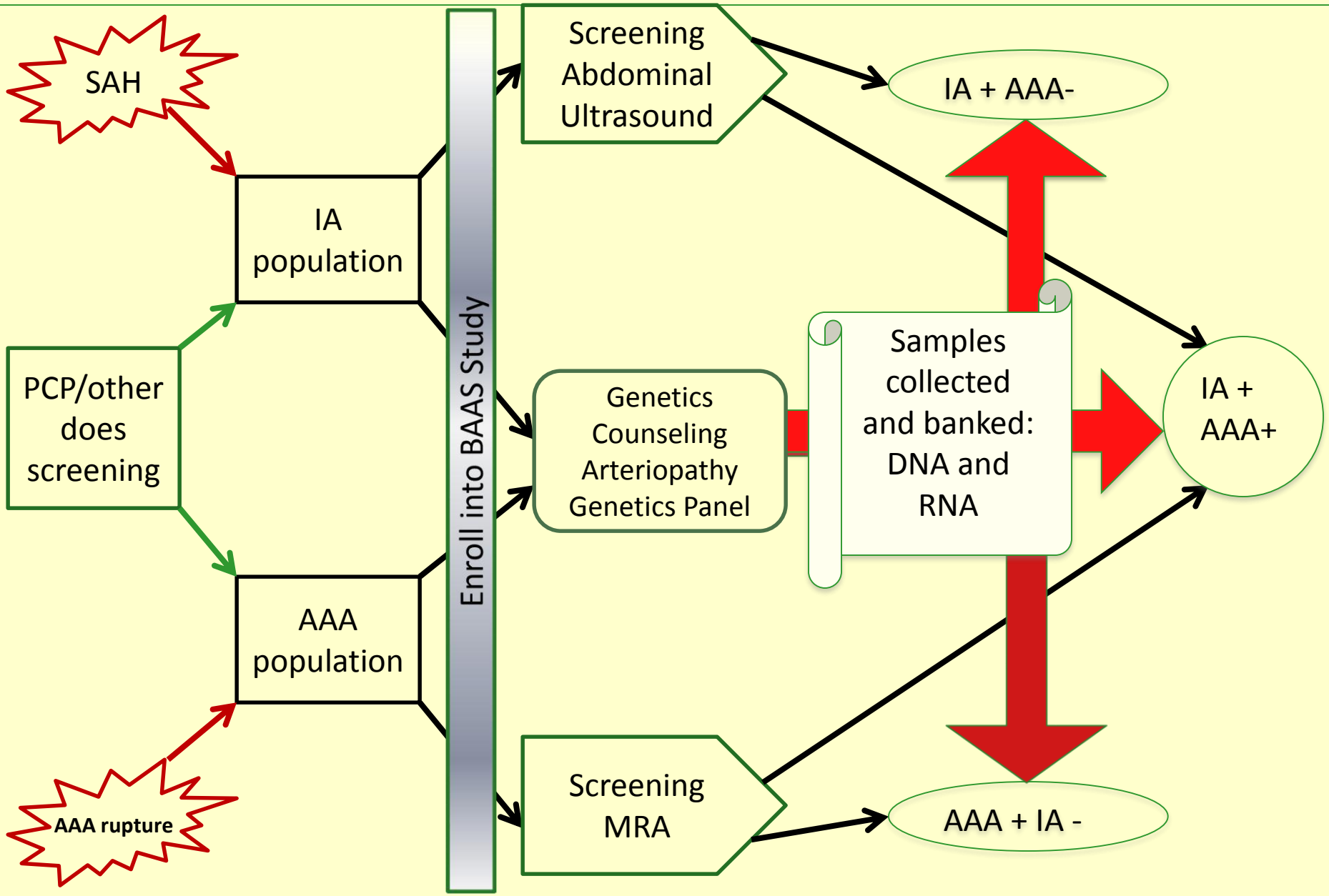
# Conclusions:

- Screening for IA in individuals with AAA has an incremental cost-effectiveness ratio of $32,037/QALY
- Societal threshold for cost-effectiveness <$60,000/QALY
- Screening arm dominated:
  - Co-prevalence of IA in those with AAA = 7.7%
  - Sensitivity of MRA screening of 86%
  - Rupture rate >4.5%/year
  - 1 year timeframe for f/u

# Proposal

Brain and Aortic Aneurysm Screening (BAAS) Study

# BAAS work-flow



# Genetic counselor

- All individuals will be interviewed by a genetic counselor – mapping a detailed FHx
- Individuals will have DNA and RNA collected and banked
- Those suspected of CVD tested in clinical (CLIA) lab (outside of research)

# Covariates

- Age
- Sex
- Race
- Smoking Status
- HTN
- Rupture Status
- EtOH
- Family History
  - Maternal
  - Paternal
  - Sibling (Sister/Brother)

# The BAAS team

- Brad Worrall (Overall PI)
- Andy Southerland (Vascular Neurology)*
- Gib Upchurch (Vasc. Surgery)
- Kenny Liu (Vasc. Neurosurgery)
- John Gaughen (Interventional Neuroradiology)
- Matt Thomas (Genetic Counseling)*
- Clinical Research Coordinator
- Steve Rich/ Michele Sale (Research Genetics)
- Wei-min Chen (Biostats)
- Donna Chen (Bioethics)
- Boxiang Jiang (Student)
- Ben Ball (Student)