70th ESCVS

7th IMAD

Can modifiers help in risk prediction ?

Bart Loeys, MD, PhD

Antwerp University Hospital, Antwerp and Radboud University Medical Center, Nijmegen

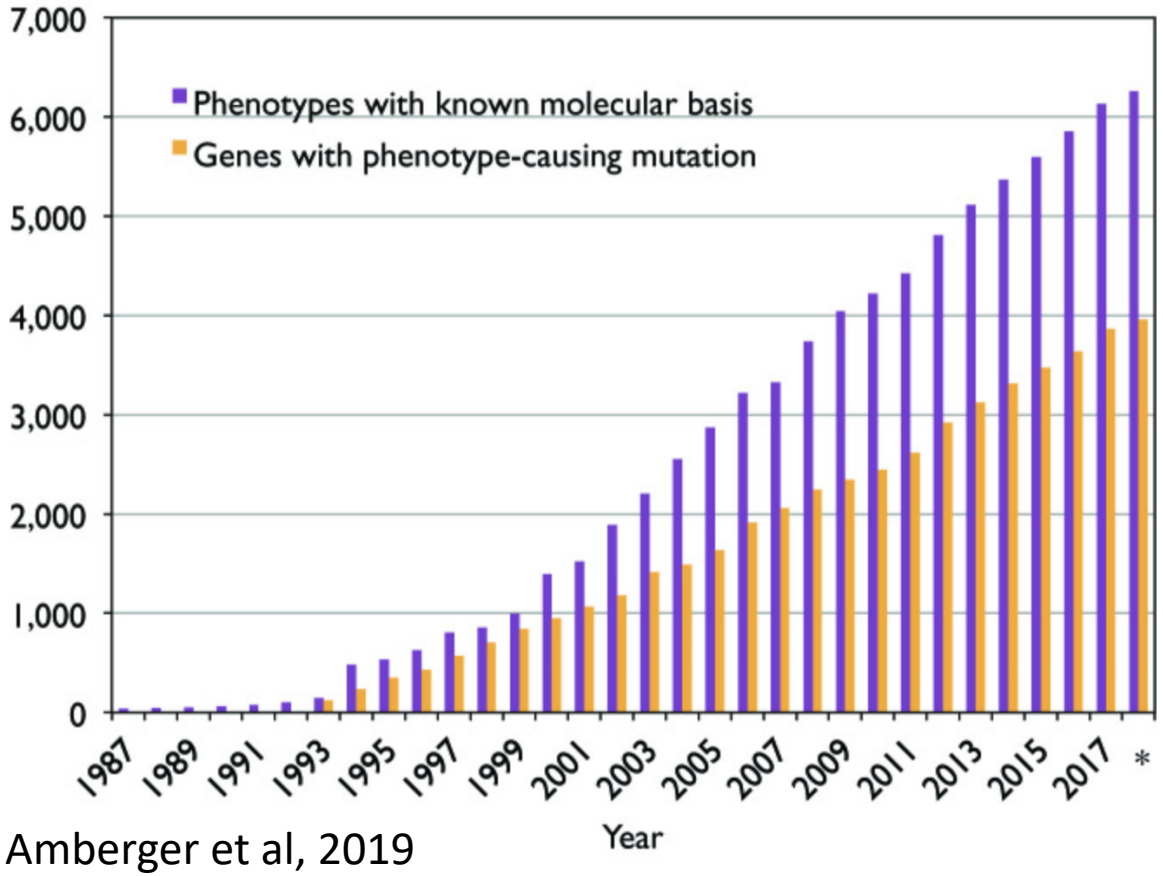
UZA Kennis / Ervaring / Zorg

Universiteit Antwerpen

Radboudumc university medical center

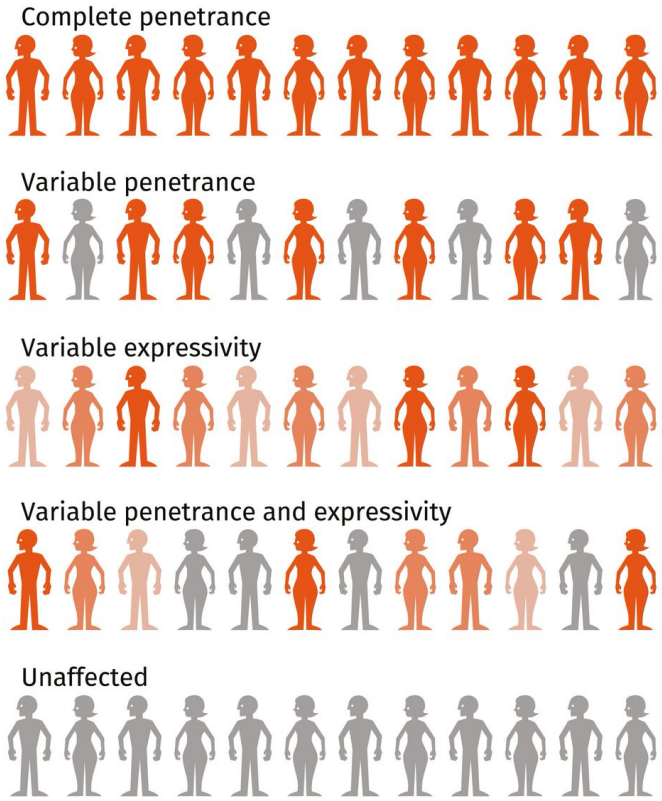
Current status

Significant progress in identifications of mutations that drive genetic disorder



Amberger et al, 2019

Modest progress in understanding the effect of genetic background on understanding of penetrance and expressivity



What's in a name ?

Epistasis

Oligogenic inheritance

Genetic interaction

Genetic modification

The effect of one gene/allele on the phenotypic outcome of a second gene/locus

Primary mutation is necessary & sufficient to cause disease:

- Disease severity
- Pleiotropy
- Endophenotype manifestation

Secondary mutation is necessary to cause disease:

- True digenic inheritance

Kousi & Katsanis, 2015

Intra- and interfamilial variable severity of aortopathy

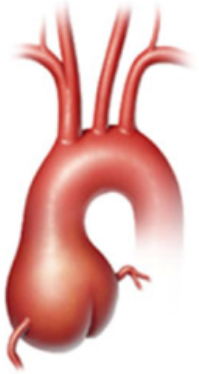
Identical TAAD-gene mutation

Variable aortopathy expressivity

Normal

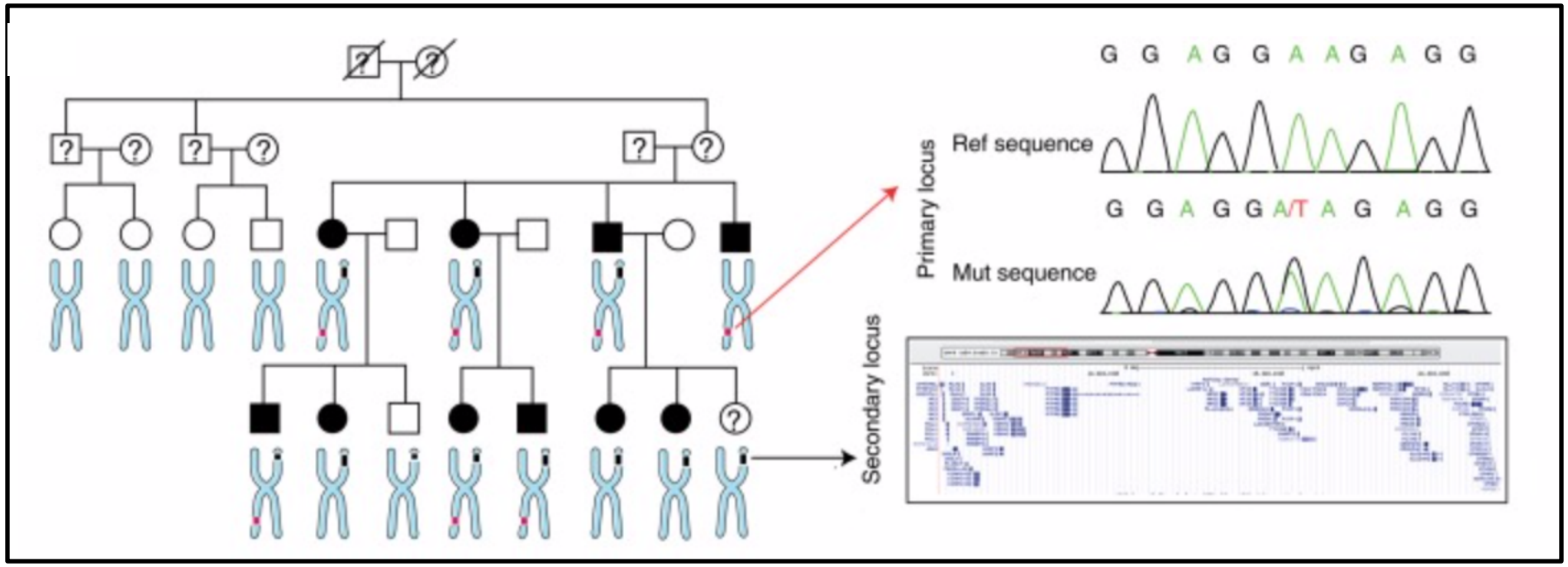
Severe

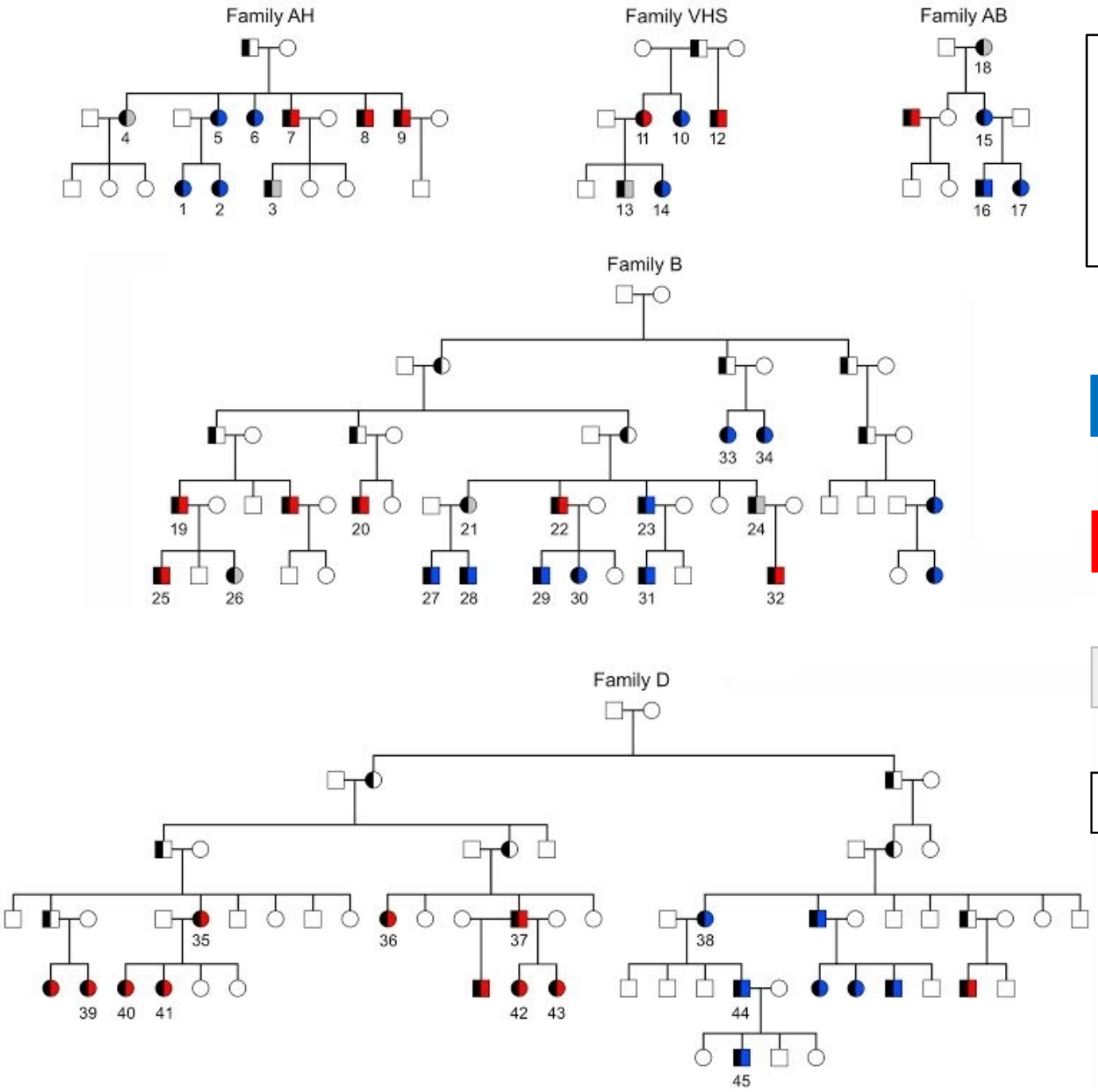
Genetic modifiers ?



Strategies for “cloning” genetic modifiers

1. Linkage analysis: discordant phenotypes with same primary locus





Five exceptional MFS families with defined ***FBN1*** mutation showing marked phenotypic variation

MFS mild aortic disease

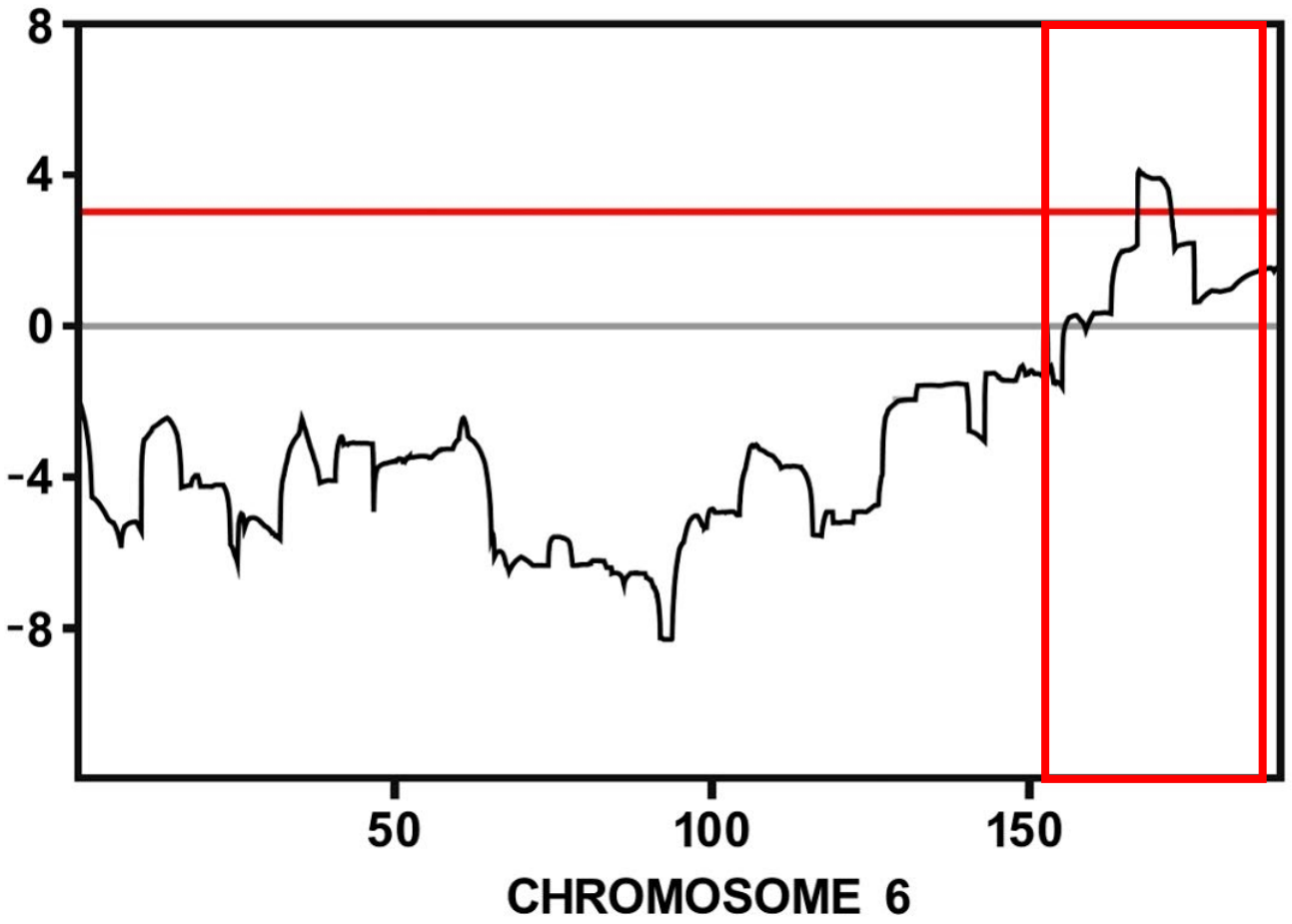
MFS with severe aortic disease

MFS with indeterminate data

No MFS

Based on aortic Z-score, events and age

Parametric linkage



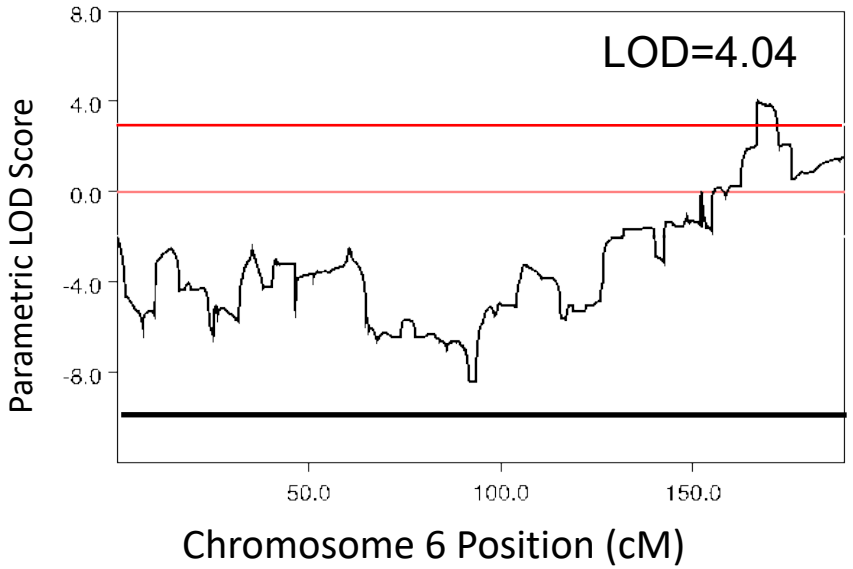
Single locus on chr 6 with LOD-score = 4

No common haplotype across families but all 20 individuals classified as having mild disease sharing a 3.9Mb familial haplotype between markers rs676017 and rs6455736.

Association between the presence of the protective haplotype and disease status (mild aortic disease 20/20 vs severe aortic disease 1/18): $p<0.0001$)

Identification of protective modifier

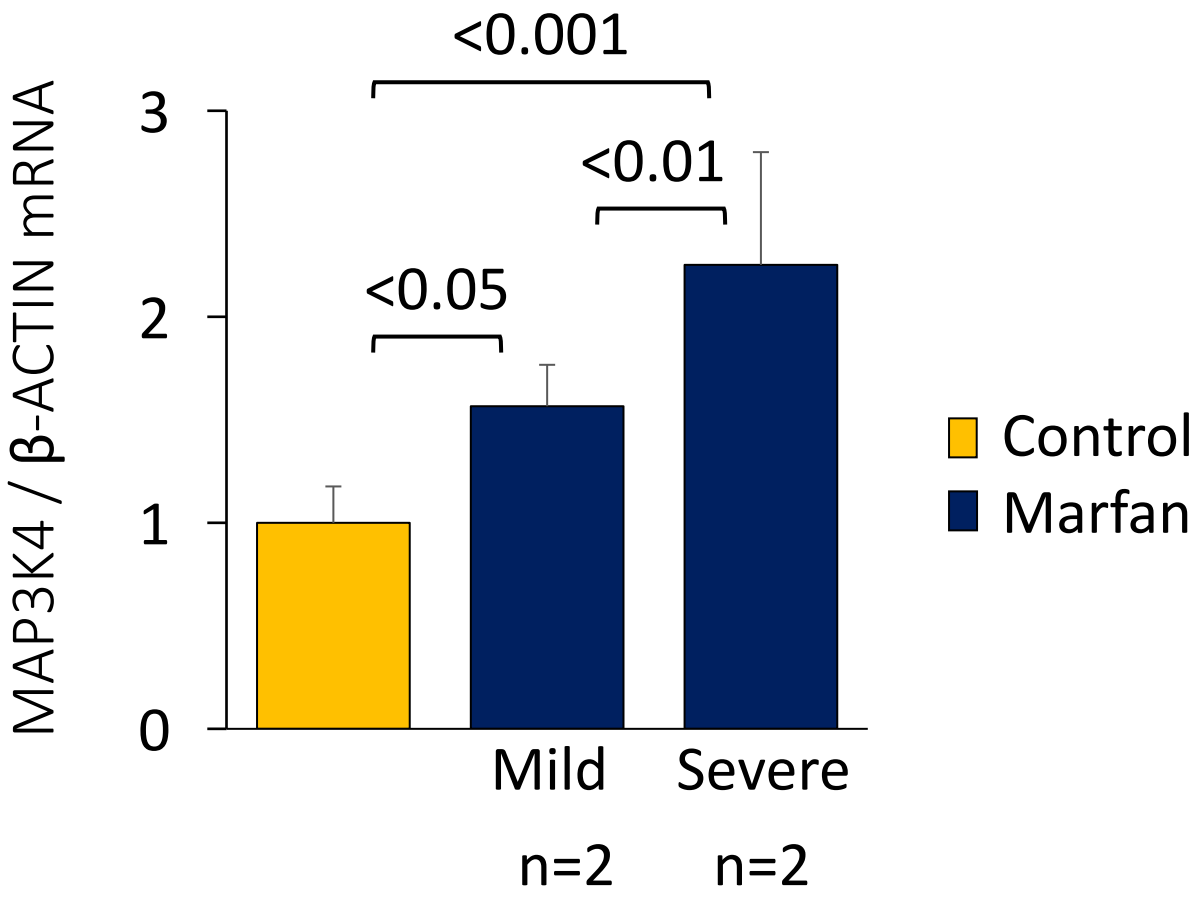
Five exceptional MFS families with defined ***FBN1*** mutation showing marked phenotypic variation



Modifier mapped on chr. 6:
MAP3K4

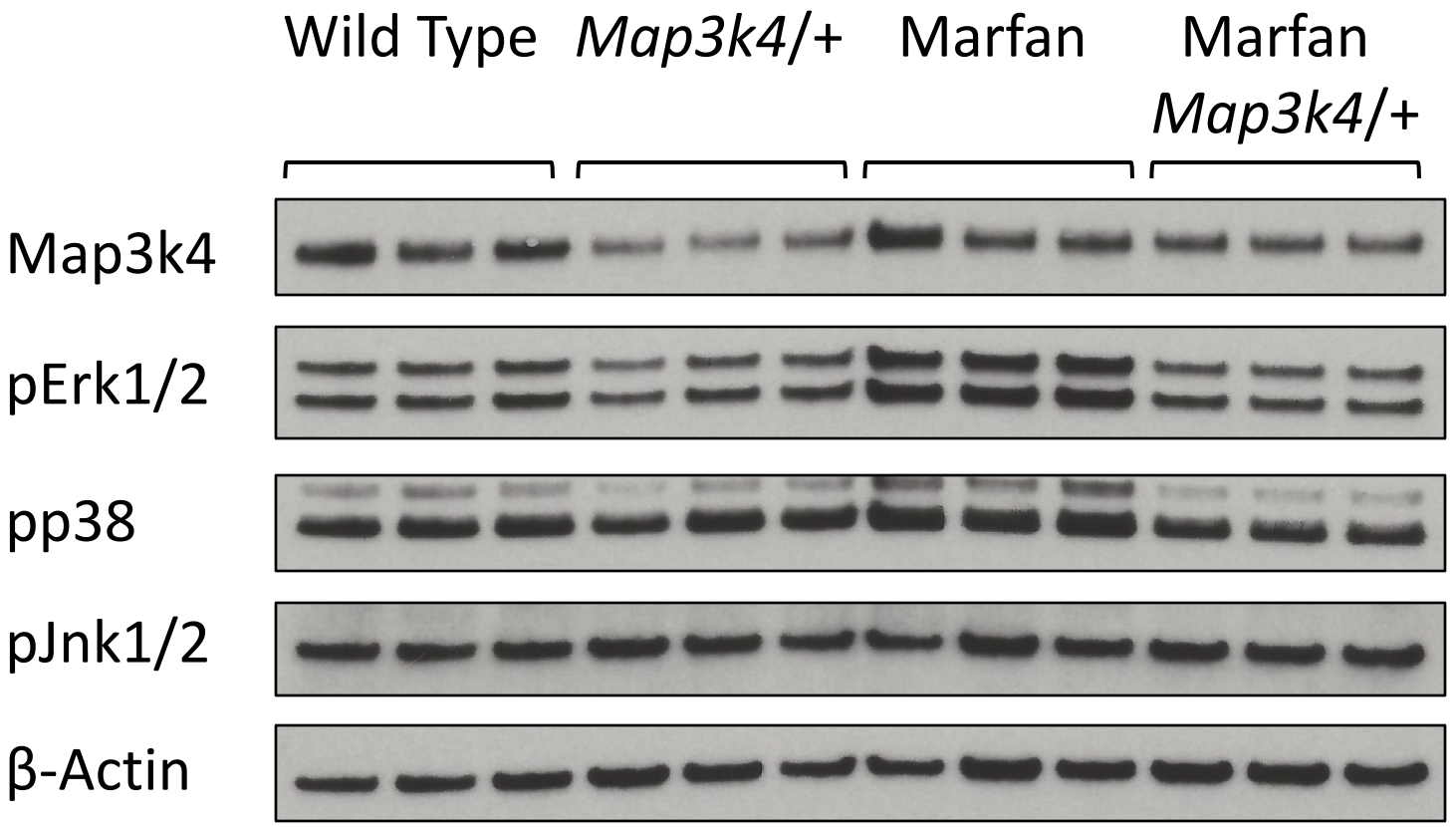
In collaboration with H Dietz, under review

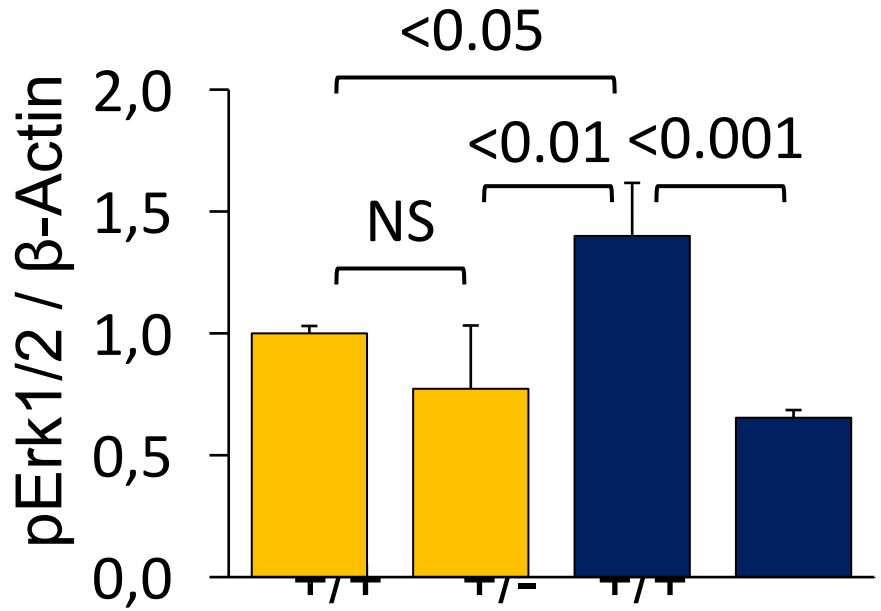
qPCR for *MAP3K4* in cultured MFS fibroblasts

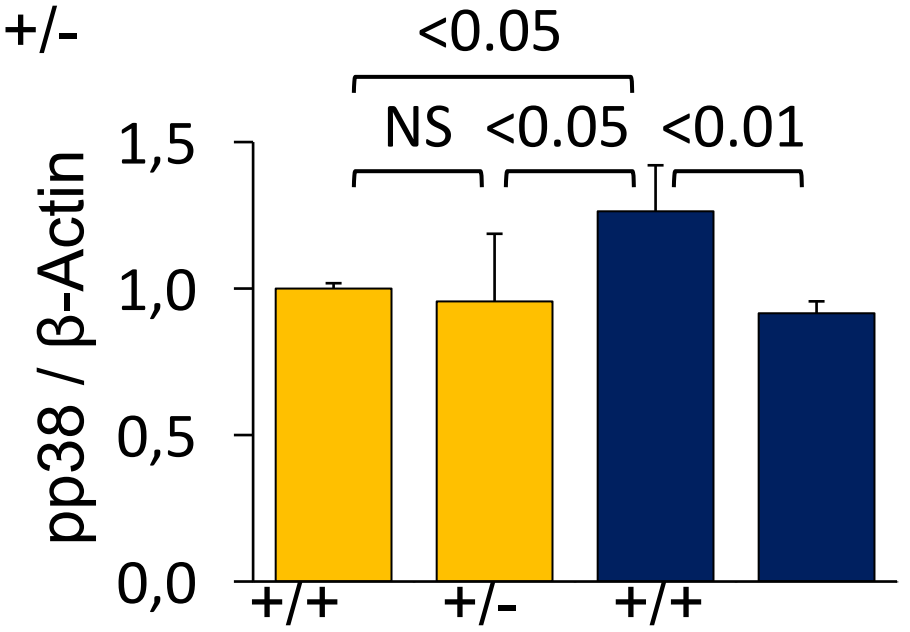


In collaboration with H Dietz
under review

Aortic wall TGFbeta-signalling





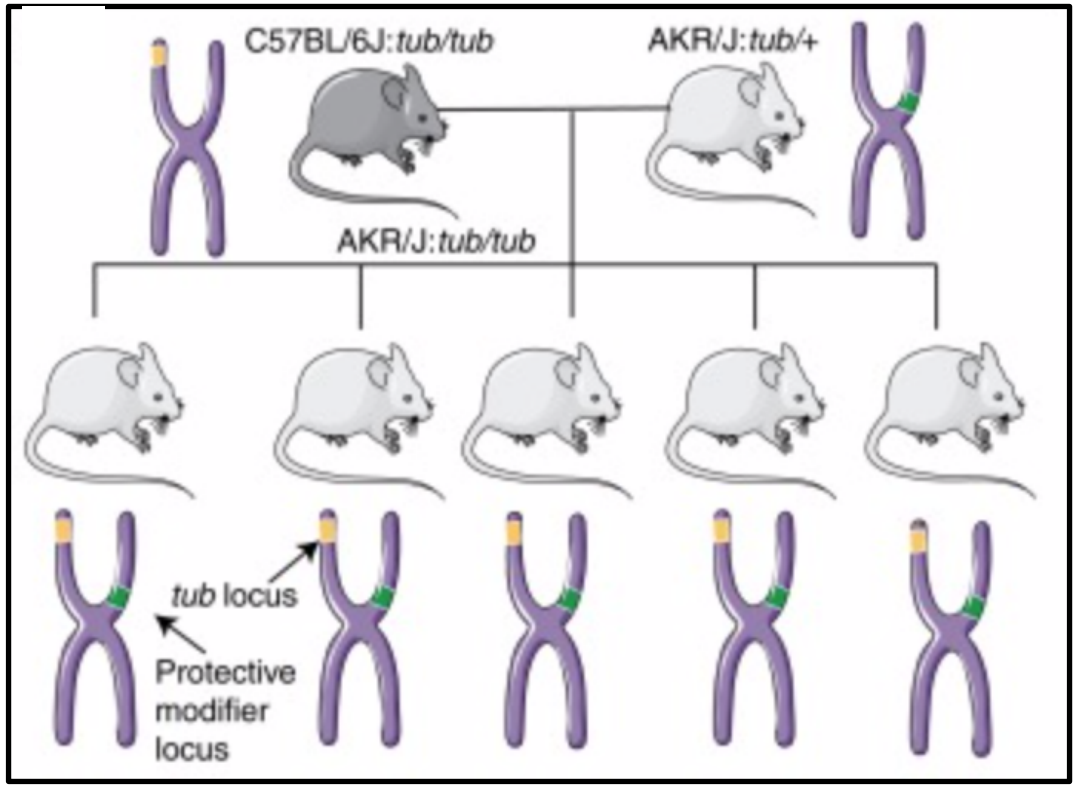


In collaboration with H Dietz
Nature Genetics, under review

Wild Type +/- Marfan +/- *Map3k4* Haploinsuffiency

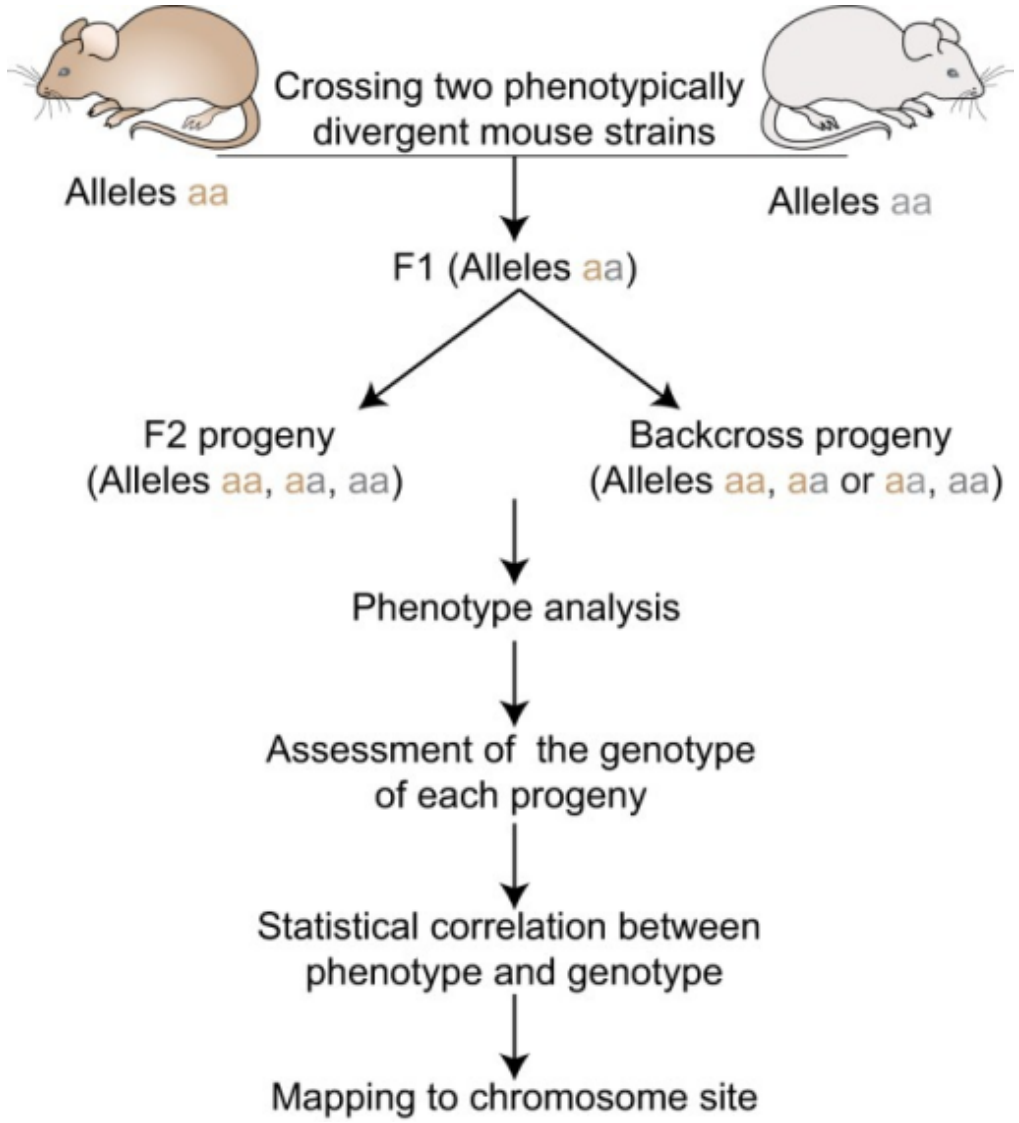
Strategies for “cloning” genetic modifiers

1. Linkage analysis: discordant phenotypes with same primary locus
2. Mapping of modifiers in congenic strains



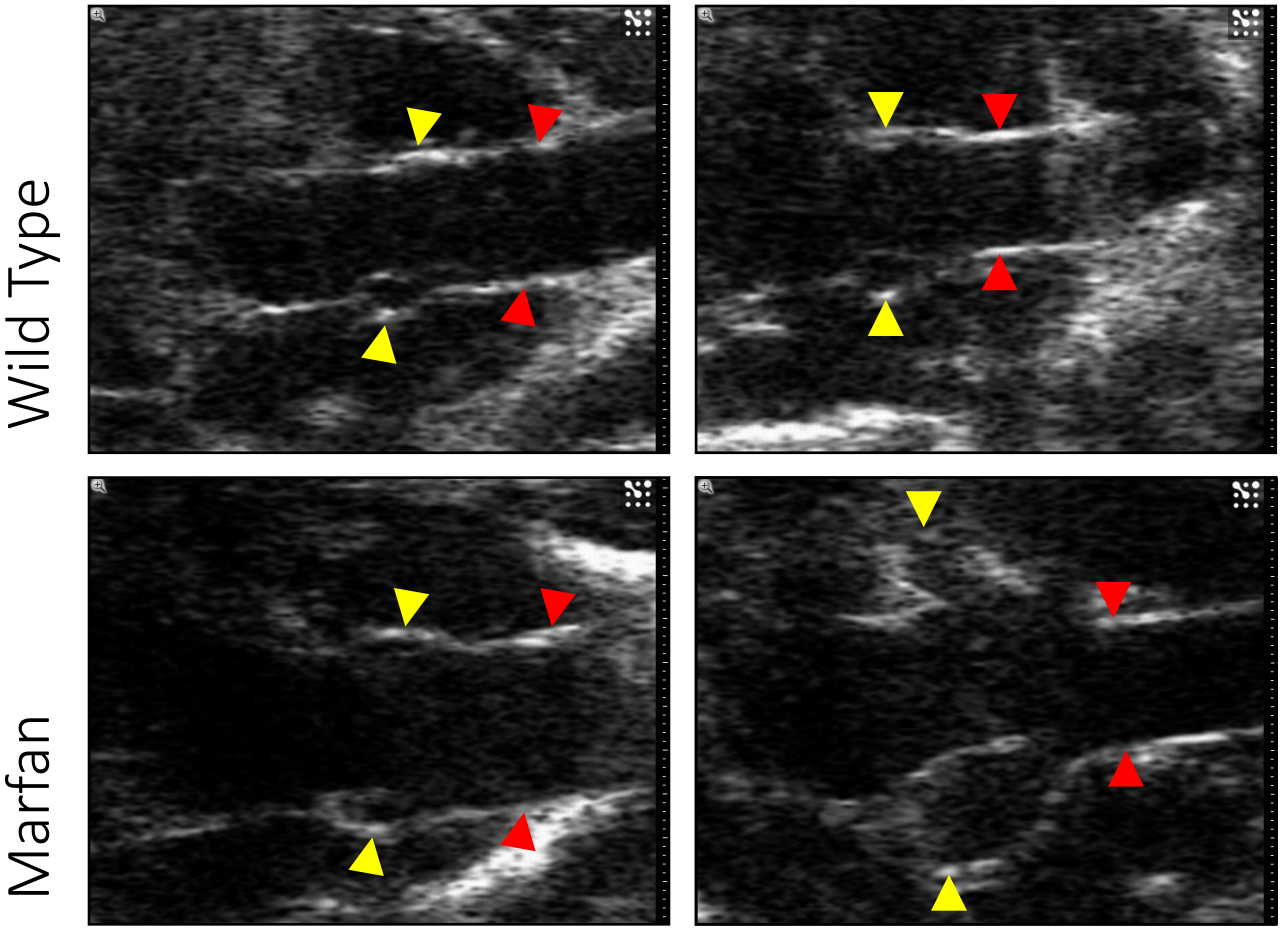
Strategy 2 – mouse background

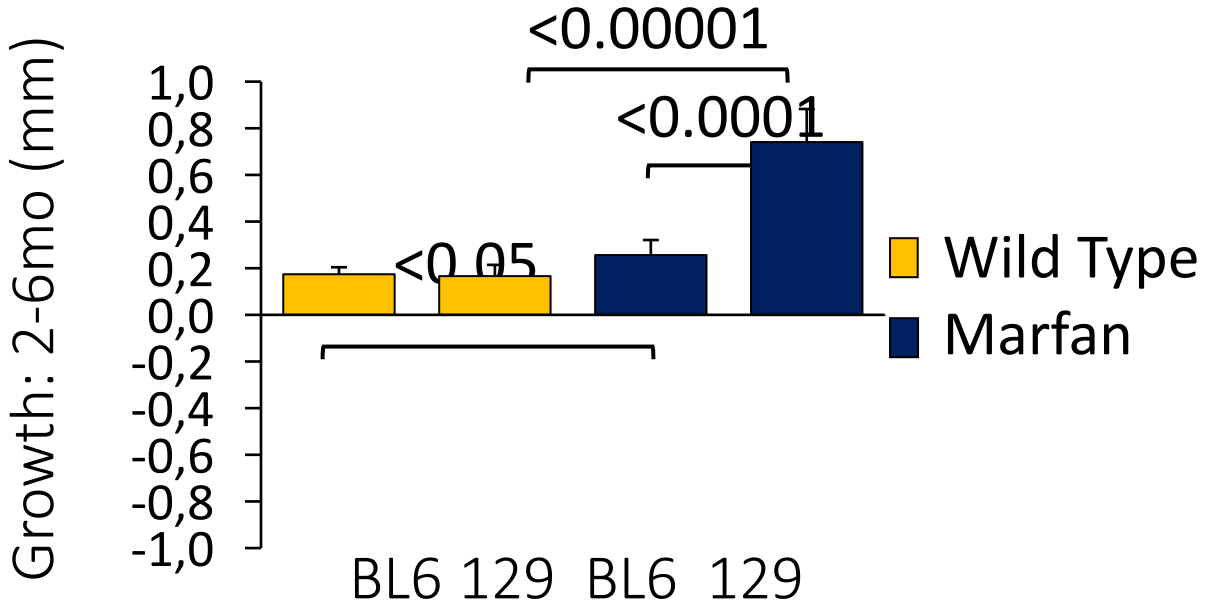
BACKGROUND A WITH aortic aneurysm/dissecti on

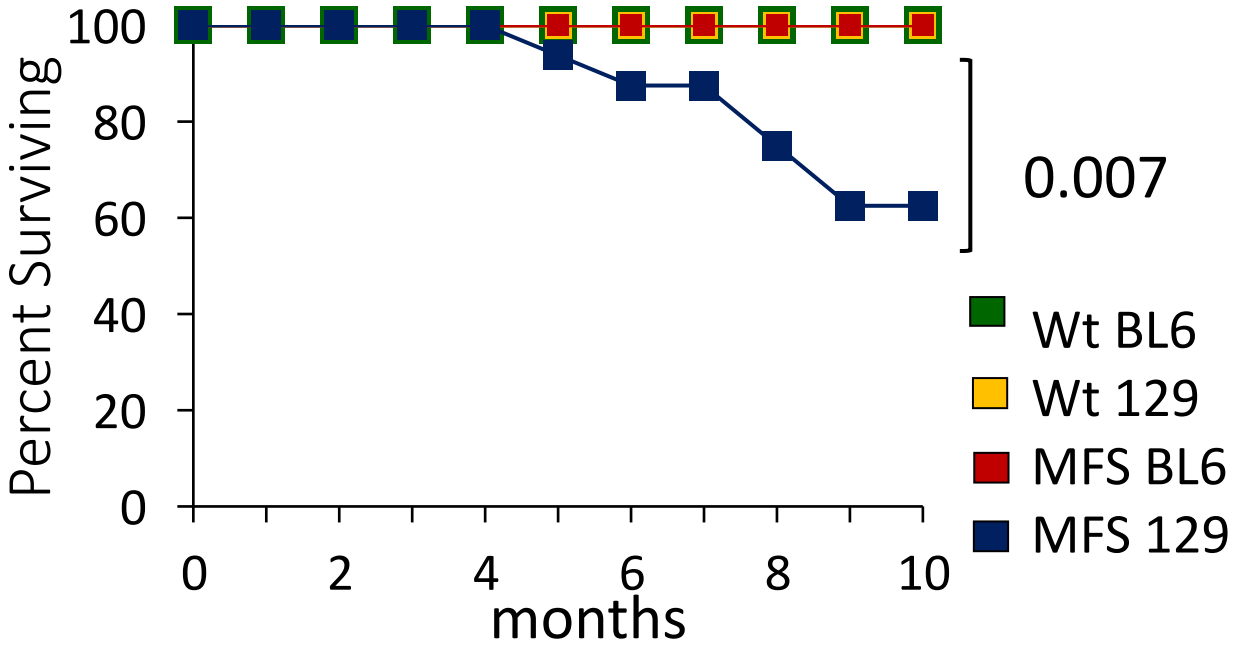


BACKGROUND B WITHOUT aortic aneurysm/dissecti on

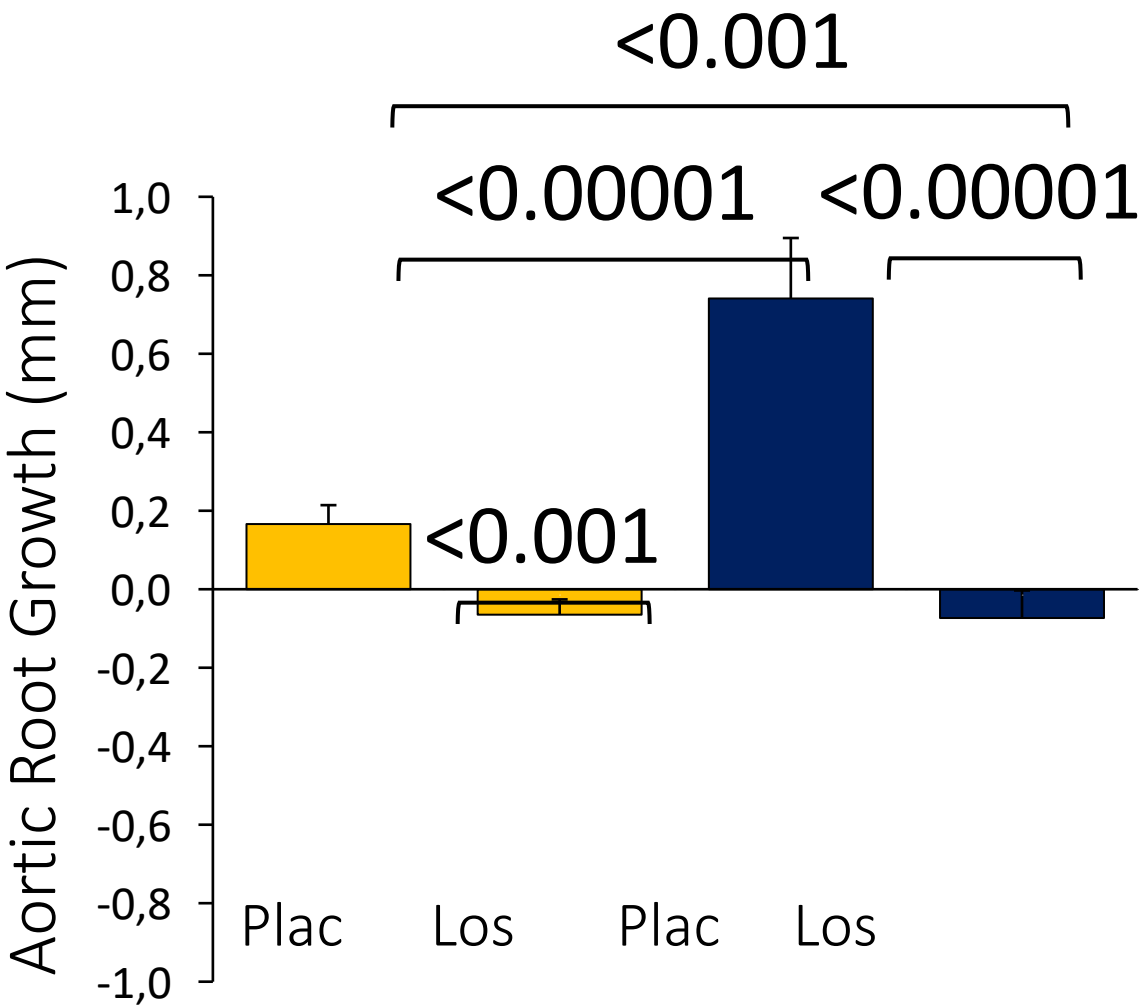
Aortic disease - more pronounced on Sv129 background





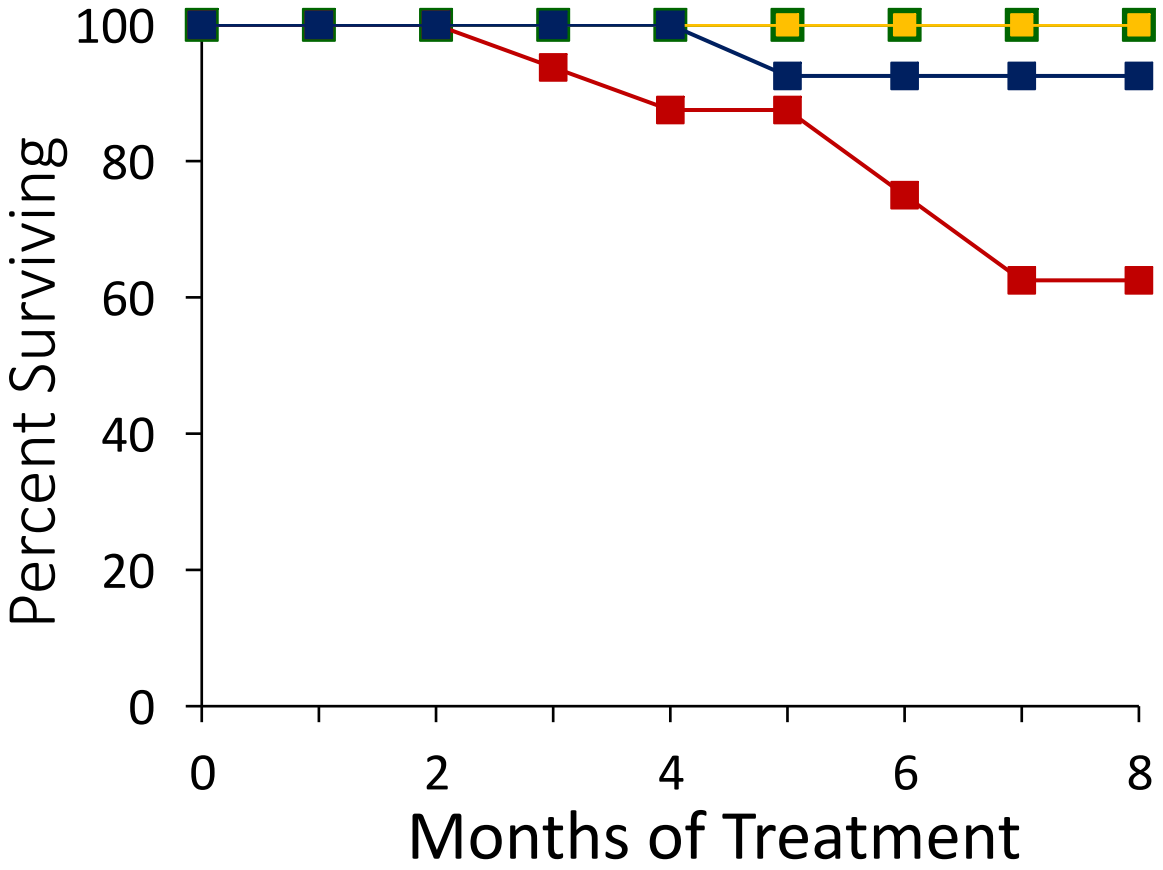


Losartan more efficacious in more severe disease



Growth over 4 months

Wt 129 MFS 129



Wt 129 Placebo MFS 129 Losartan

Wt 129 Losartan MFS 129 Placebo

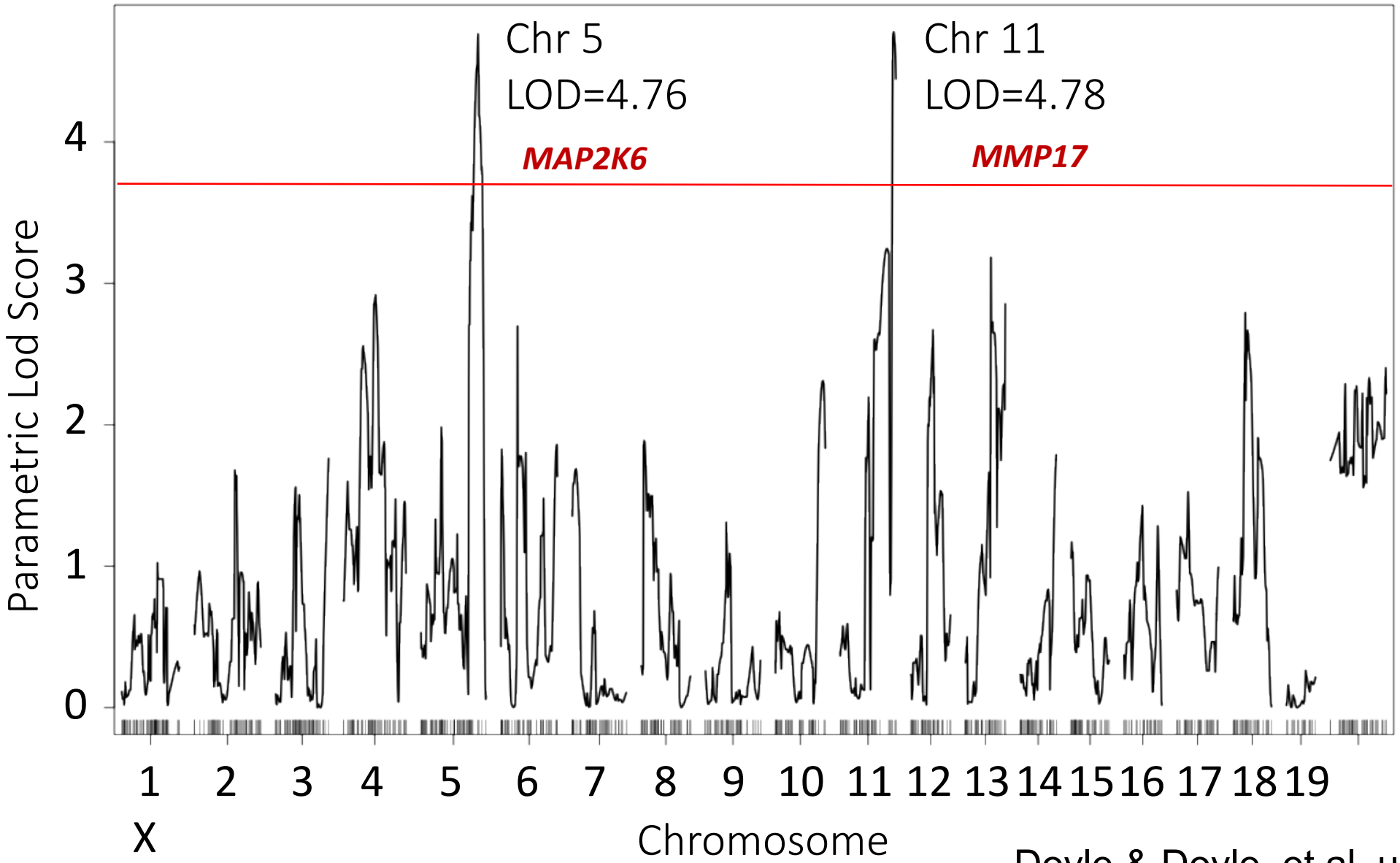
Modifier mapping in MFS mice

C57Bl/6 versus 129Sv ***Fbn1*** mice interbreeding

300 interbred mice at 6 months
Ao < 2.2 mm (n=35) versus Ao >2.7 mm (n=40)

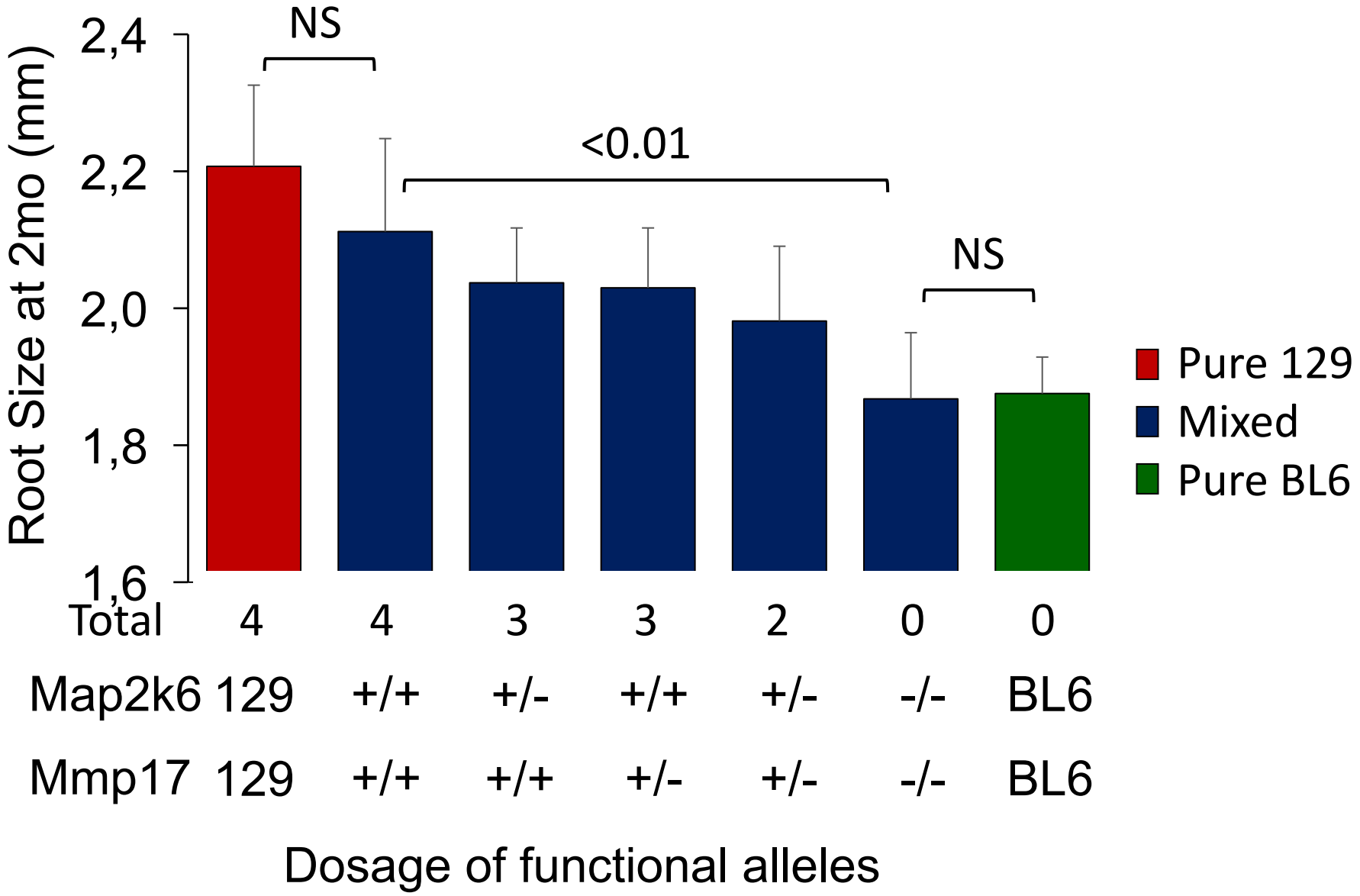
Genome-wide linkage analysis:
2 loci with evidence of epistasis between the loci (MfLOD=12.8).

Genomewide linkage in 129Sv-C57Bl/6 MFS mice

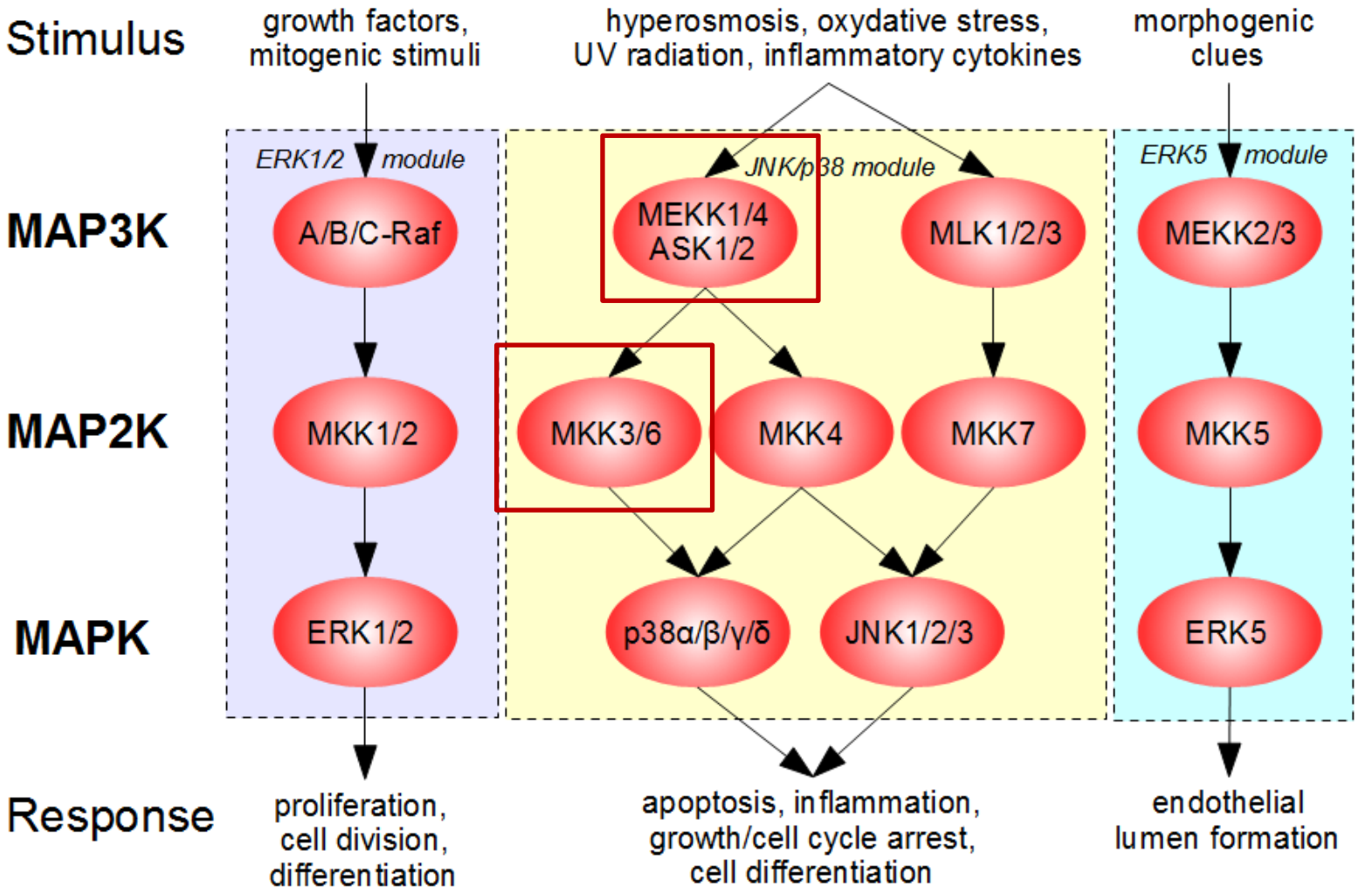


Doyle & Doyle, et al. unpublished

Epistatic effect on aortic root diameter



Mammalian MAPK cascades



Mouse background for aneurysm genes

Gene	Protective background	Aggravating background
FBN1	C57Bl6	Sv129
SMAD3	C57Bl6	Fvb1/C57Bl6
*SMAD6#**	C57Bl6, BALBc (<C57, >Sv)	Sv129
BGN	C57Bl6, C3H	BALBc
NOTCH1	C57Bl6/BTBR	Sv129
COL3A1	Sv129, BALBc	C57Bl6
IPO8	Sv129	C57Bl6

*homozygous pre-weaning lethality
#Cardiovascular issues reported in Sv129/BALBc, skeletal phenotype reported in C57Bl6/BALBc

Why modifier studies for thoracic aortic aneurysm?

No current **preventive or curative** medical treatments for thoracic aortic aneurysm/dissection

Discovering **mother nature's** own modifying capabilities in human and mouse aortopathy offers the unique opportunity to advance our current **pathophysiological understanding** of aortic aneurysmal disease and to identify new **therapeutic strategies**

Thank you !