DNA Methylation Signatures in MZ Twins Discordant for Smoking

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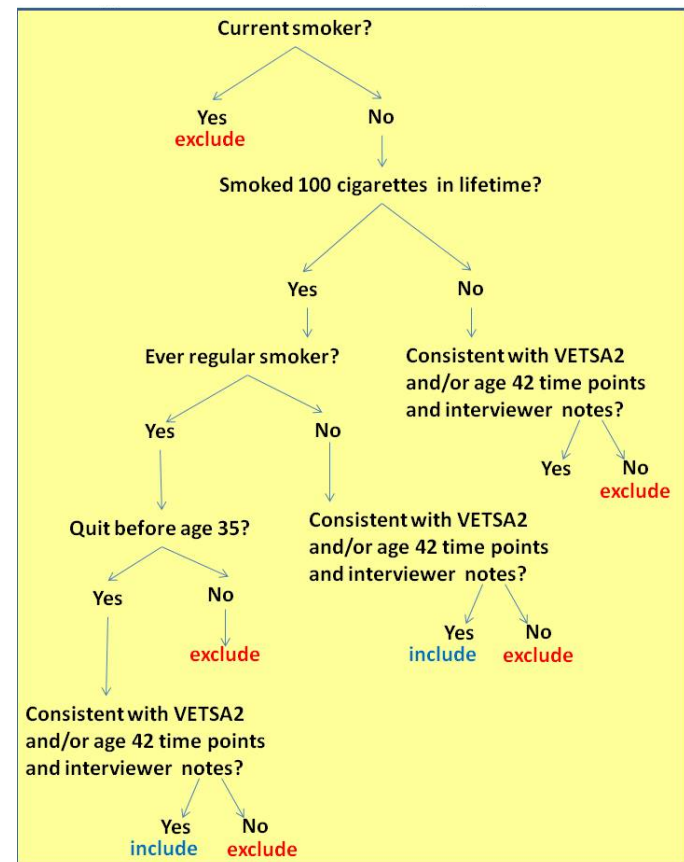BGA Session 28
"Genes, Epigenetics, and Substance Use"
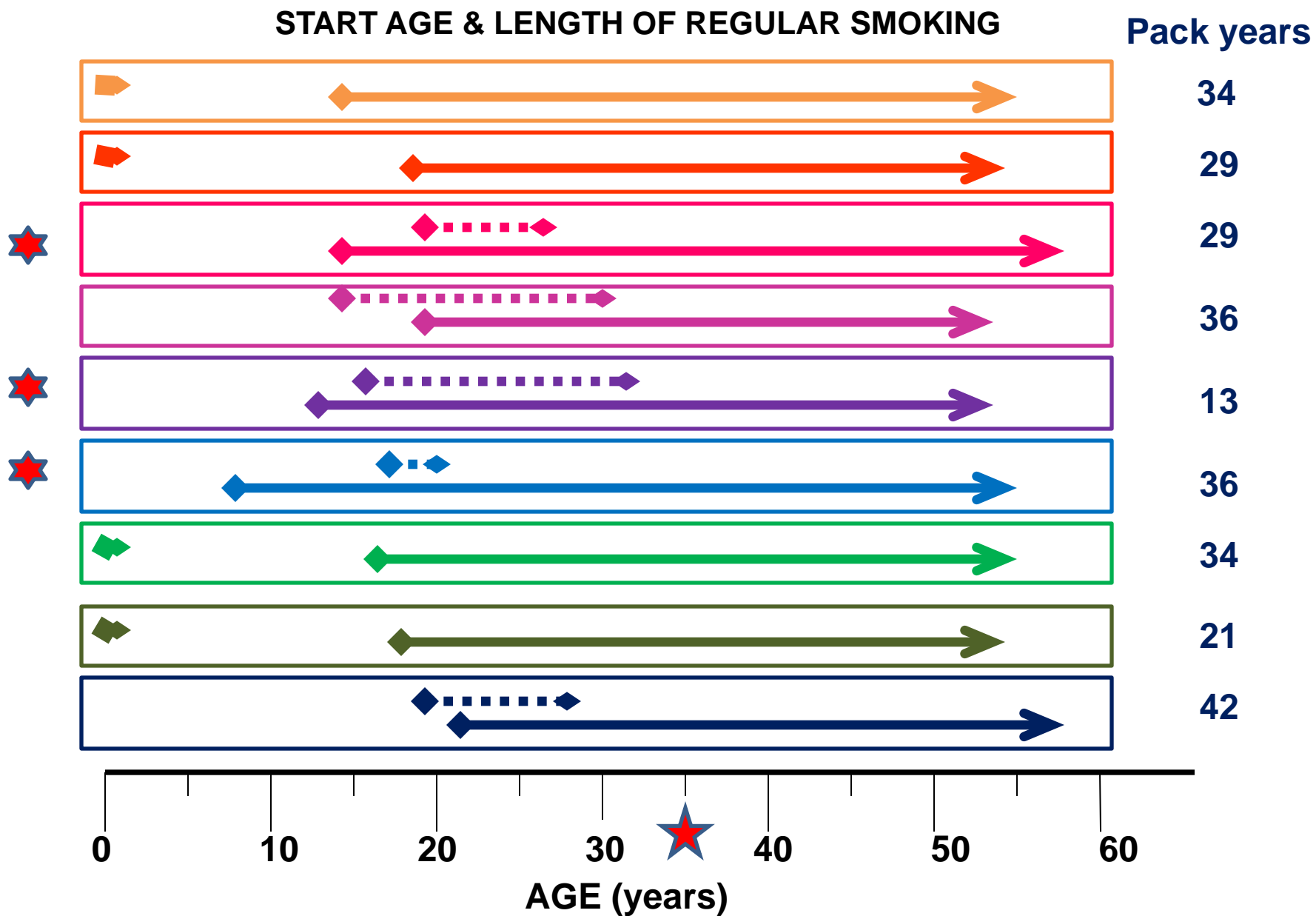June 20, 2015

Wave 1: 349 Male MZ Twin Pairs
         51-59 years old

Pilot Study:
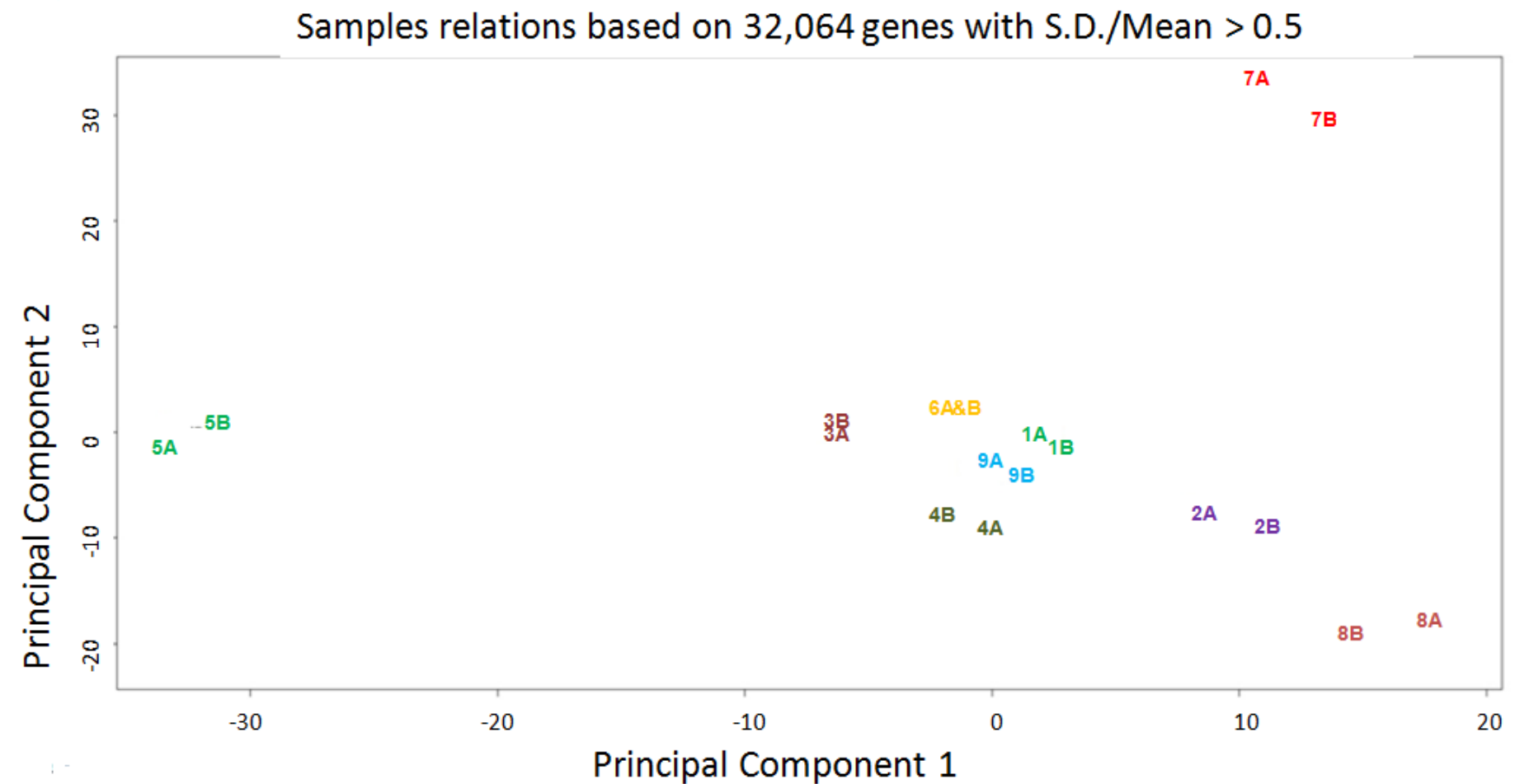9 MZ Twin Pairs Discordant for Smoking

Tobacco use and history assessed through a 40-item questionnaire administered during a face-to-face interview

TWIN PAIRS DISCORDANT FOR CURRENT SMOKING

START AGE & LENGTH OF REGULAR SMOKING

Pack years

34

29

29

36

13

36

34

21

42

AGE (years)

Samples relations based on 32,064 genes with S.D./Mean > 0.5

Identification of Three Sites Differentially Methylated between Smokers and Non-Smokers at Genome-Wide Significance Levels

CpG Locus	Gene	Protein	Mean β-value Difference	unadjusted p value	FDR adjusted p value
cg05575921	*AHRR*	Aryl hydrocarbon receptor repressor	-0.268	1.5×10^{-9}	0.00056
cg09935388	*GFI1*	Zinc Finger Protein Gfi-1	-0.158	2.9×10^{-8}	0.00493
cg03636183	*F2RL3*	Protease-activated receptor 4	-0.159	1.1×10^{-6}	0.10083

β-value Difference = β-value Smokers - β-value Non-smokers
β-value in Non-smokers higher for all three loci → hypomethylated in smokers

CpG Locus	Gene	Protein	Our Pilot Data 9 Discordant MZ twin pairs Current smoker vs. non-smoker European Illumina 450K BeadChip			Zeilinger et. al (2012) N=262 Current Smokers N=749 Never smokers European Illumina 450K BeadChip		Elliott et al. (2014) N= 36 Current Smokers N=129 Never smokers South Asian & European Illumina 27K BeadChip		Elliott et al. (2014) N= 190 (smoker non-smoker breakdown not available)	
			Mean β-value Difference[a]	unadjusted p value	FDR adjusted p value	Median β-value Difference	unadjusted p value (rank[b])	Median β-value Difference	unadjusted p value (rank[b])	Median β-value Difference	unadjusted p value (rank[b])
cg05575921	AHRR	Aryl hydrocarbon receptor repressor	-0.268	1.5×10^{-9}	0.00056	-0.244	2.5×10^{-18} (1)	-.22	6.1×10^{-59} (1)	-.14	1.7×10^{-9} (1)
cg09935388	GFI1	Zinc Finger Protein Gfi-1	-0.158	2.9×10^{-8}	0.00493	n.s.	n.s.	-.30	1.0×10^{-10} (6)	n.s.	n.s.
cg03636183	F2RL3	Protease-activated receptor 4	-0.159	1.1×10^{-6}	0.10083	-0.1474	2.4×10^{-80} (4)	-.12	10×10^{-17} (3)	-.07	3.8×10^{-7} (4)

[a] Median β-value Difference = β-value Smokers - β-value Non-smokers
[b] Rank of locus by p value in each study
n.s. = not significant at epigenome wide level in study

Conclusion

With only 18 samples (9 twin pairs discordant for smoking), we were able to identify three loci, with genome wide significance, that were hypomethylated in smokers versus their non-smoking co-twin.

1. *Aryl Hydrocarbon Receptor Repressor (AHRR):* part of the aryl hydrocarbon pathway that metabolizes cigarette smoke components (dioxins).

2. *F2RL3*: A GPCR involved in platelet activation. F2RL3 hypomethylation associated with increased mortality among individuals with coronary heart disease [Eur Heart J 33(22):2841–2848 (2012)]

3. *GFI1*: Transcription repressor essential for hematopoiesis. Mutations that alter the expression of this gene cause neutropenia.

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