Expression Quantitative Trait Locus Analysis from Primary Immune Cells Identifies Novel Regulatory Effects Underlying Intracranial Aneurysms Susceptibility

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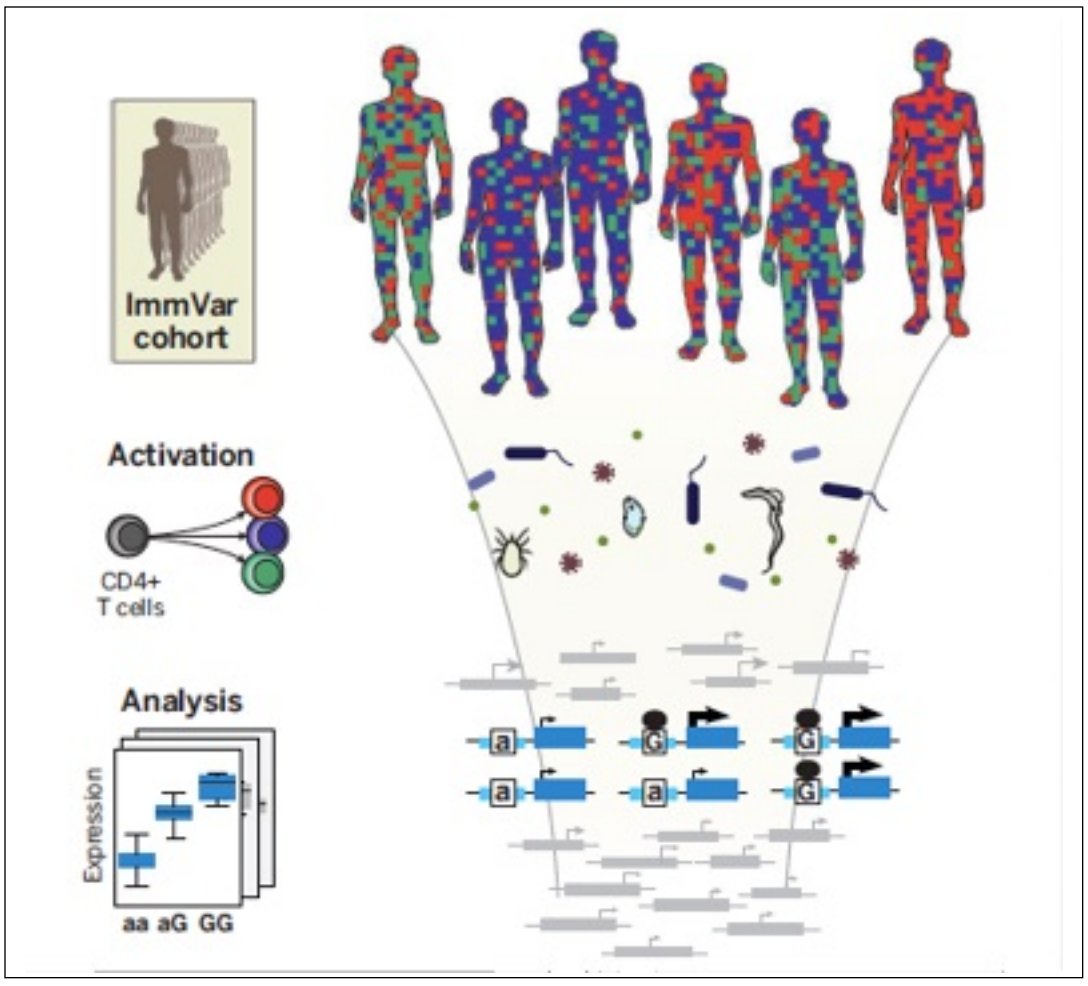
Introduction

Genome-wide association studies (GWAS) have identified many common variants (SNPs) associated with Intracranial Aneurysms (IA). There is a genetic component in IA pathogenesis, but we do NOT know the functions and potential therapeutic targets. Both pre-clinical and clinical studies have demonstrated that immune cells have a critical role in the pathway of IA formation and progression.

Methods

We have performed a genome-wide expression and splicing quantitative trait locus (eQTL and sQTL) study of highly purified T-cells and monocytes from gene expression studies of 461 healthy individuals of European, African American and East Asian ancestry.



Conclusions

This study identifies many novel regulatory effects that functionally implicate an immune cell type in genetic susceptibility to IA pathogenesis. Future fine-mapping and functional studies will explore the mechanism by which these cis-eQTLs are associated with IA pathology

Learning Objectives

By the conclusion of this session, participants should be able to:

1)describe the importance GWAS studies in identifying the genetic variants associated in intracranial aneurysms formation.

2) Discuss the candidate causal genes (NT5C2, BET1L, FGD6, ANKRD44, and SF3B1) involved in aneurysm formation.

References

1. Yasuno K et al. Genome-wide association study of intracranial aneurysm identifies three new risk loci. Nat Genet. 2010 May;42(5):420-5. doi: 10.1038/ng.563.
2. Bilguvar K et al. Susceptibility loci for intracranial aneurysm in European and Japanese populations. Nat Genet. 2008 Dec;40(12):1472-7. doi: 10.1038/ng.240.
3. Chen J et al. A functional variant of the collagen type III alpha1 gene modify risk of sporadic intracranial aneurysms.Hum Genet. 2012 Jul;131(7):1137-43. doi: 10.1007/s00439-012-1138-6.

Results

Amongst genetically mapped traits, we observed that susceptibility alleles for IA affect gene expression and splicing of nearby genes in both monocytes and T-lymphocytes. Specifically, we identified 7 IA associated SNPs that are cis-eQTLs in monocyte- and T-cells. Using a Bayesian colocalization method, we demonstrated that at least 5 of these are likely to be truly driven by regulatory effects and thus, likely to be the candidate causal genes (NT5C2, BET1L, FGD6, ANKRD44, and SF3B1).