Genetic susceptibility to Rheumatic Heart Disease in two African populations: Egypt and Ethiopia

HELEN BEFEKADU [MD, FRCP]

PEDIATRIC INTENSIVIST, CARDIOLOGIST

ADDIS ABABA UNIVERSITY , COLLEGE OF HEALTH SCIENCES

CARDIAC CENTER ETHIOPIA

19TH SA HEART CONGRESS *OCTOBER 2018*

Background:

- RHD is a chronic diseases mainly acquired as a long term outcome acute rheumatic fever (ARF) following GAS (streptococcus) infection
- In Africa, patients are rarely presented in the acute stage of ARF
- A leading cause of incapacity & premature death in Africa youth popn
- Host genetic susceptibility is one of the compelling feature of the disease

Epidemiology :

- Surveys conducted in Ethiopia in late 1990's reported prevalence of 4.6/1000 and 6.4/1000 in rural & urban respectively
- A recent echocardiographic collaborative study reported a definite RHD prevalence of 16/1000
- Studies conducted in Egypt among school age children showed 6.2/1000
- Overall, the global burden of disease caused by ARF/RHD falls disproportionately on children where poverty is major community problem

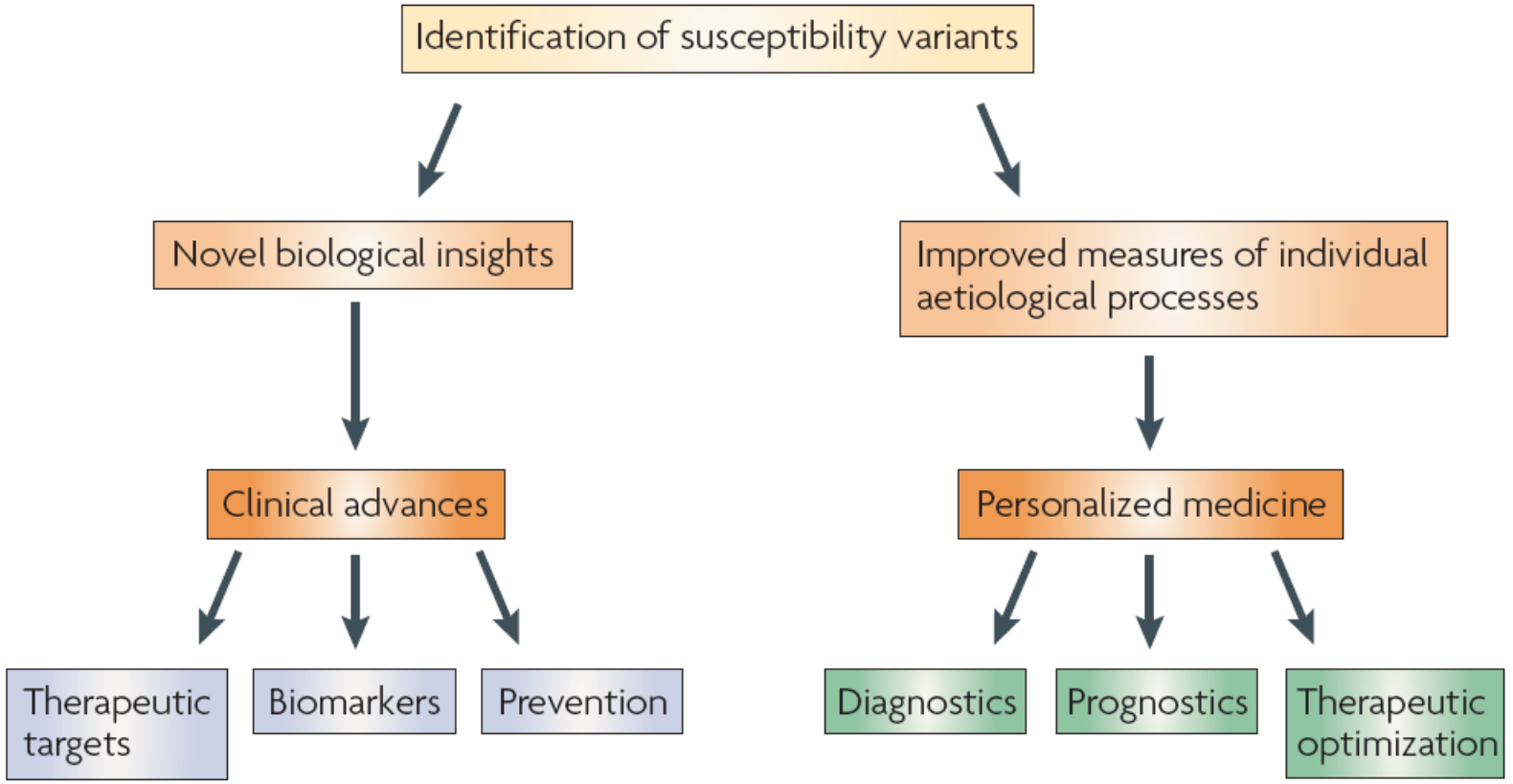
Genetics:

- GWAS **genome-wide association study** (**GWA study**, or **GWAS**), also known as **whole genome association study** (**WGA study**, or **WGAS**), is an observational genetic-variants in d/t individuals to see if any variant is associated with a trait

- It typically focus on associations between single-nucleotide polymorphisms (SNPs) and traits like major human diseases

- SNPs underlie differences in our susceptibility to disease;

Potential of GWAS



GWA is promising

- Many diseases and traits are influenced by genetic factors
  - i.e., they are caused by sequence variants in the genome
- Over 12 millions SNPs are known in the genome
  - i.e., some SNPs will be directly or indirectly associated with causal variants
- The cost of SNP Genotyping is reduced
  - i.e., it is affordable to genotype a large number of SNPs in the genome
- Large numbers of cases and controls are available
  - i.e., there is statistical power to detect variants with modest effect

GWA challenging:

- Many diseases and traits are influenced by genetic factors
  - But probably due to multiple modest risk variants
  - True associated SNPs are not necessary highly significant
- Single studies tend to be underpowered
  - False negatives
- Too many SNPs are evaluated
  - False positives due to multiple tests
- Considerable heterogeneity among studies
  - Phenotypic and genetic heterogeneity
  - False positives due to population stratification

Methodology:

- An experimental study
- 400 cases and 220 controls
- Enrolled in two categories (March to 2017-2018)
- SNPs were typed from DNA study group samples
- Discovery analysis were done by GWAS

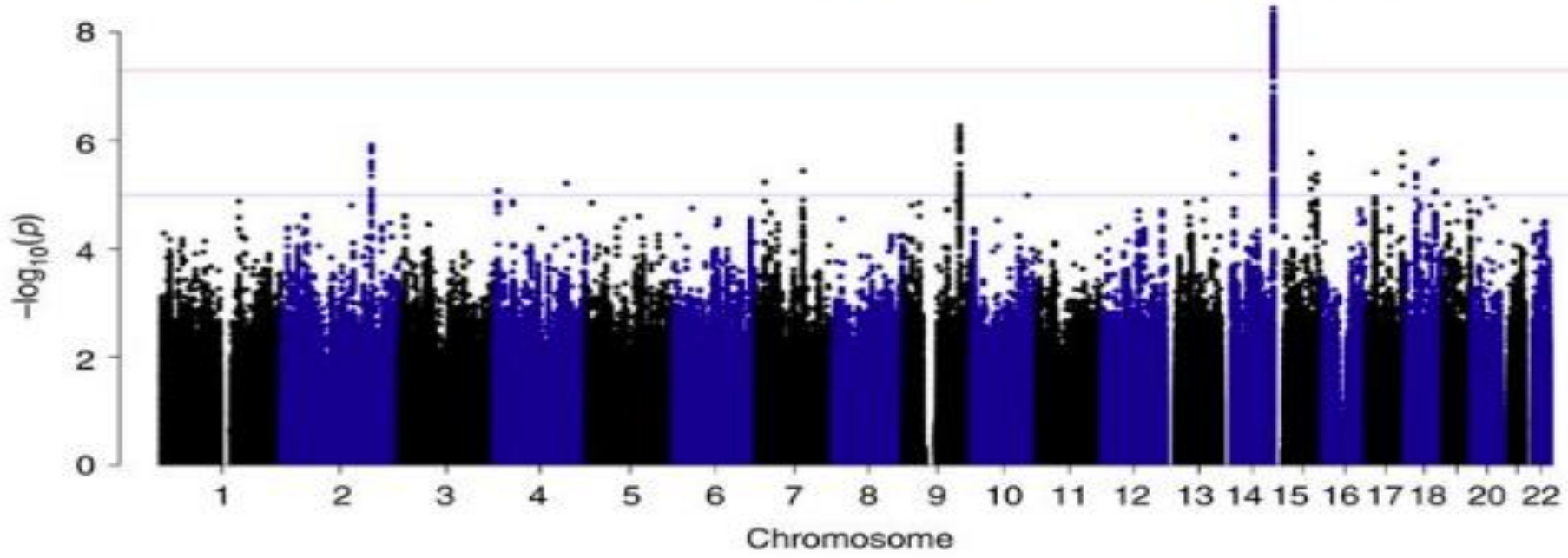
Result:

Table 1 HLA-DRB1 allelic frequencies (%) in Ethiopian group and the healthy control

HLA-DRB1 alleles	Group 2 (n=71), n (%)	Control subjects (n=130), n (%)	P	OR	95% CI
*01	15 (21.1)	16 (12.3)	>0.05	1.91	0.88 - 4.16
*04	18 (25.4)	42 (32.3)	>0.05	0.71	0.37 - 1.36
*07	19 (26.8)	17 (13.1)	<0.05	2.44	1.17 - 5.56
*08	1 (1.4)	7 (5.4)	>0.05	0.25	0.03 - 2.08
*09	0 (0.0)	1 (8)	>0.05	-	-
*11	28 (39.4)	55 (42.3)	>0.05	0.88	0.49 -1.6
*13	9 (12.7)	21 (16.2)	>0.05	0.75	0.32-1.75

CI, confidence interval; HLA, human leucocyte antigens; OR, odds ratio

Figure 2: Genome-wide meta-analysis for RHD susceptibility.



For each variant, the negative common logarithm of the *P* value from an inverse-variance weighted fixed-effects meta-analysis is plotted against genomic position. The blue horizontal line indicates suggestive significance (FE meta-analysis, $P=10^{-5}$) and the red horizontal line indicates genome-wide significance (FE meta-analysis, $P=5 \times 10^{-8}$).

In words …

- A positive association **HLA-DRB1*07 allele** was found for RHD when compared with healthy controls (49.4% vs. 23.1%; $p<0.01$) and also for recurrent streptococcal pharyngitis: $p<0.05$

Conclusion:

- The study suggests that the HLA-DRB1*07 allele may contribute to the pathogenesis of RHD and the development of recurrent streptococcal pharyngitis in the susceptible host
- Provision of secondary prophylaxis
- A successful vaccine could address a huge unmet public health demand, and could prevent ARF as well as invasive GAS disease

Limitation:

- By standard GWAS our sample size is small
- The study analysis provides little insight variant with population specific effects

In General

- GWAS is a modern “Big Data” challenge
- Proper analysis is a major statistical/methodological challenge,
  - Controlling and using structure
  - Finding complex associations
- We have learned a lot – but not as much as we hoped
- We are still improving on both major fronts:
  - Size and extent of data available
  - Advanced statistical methods

Got out of the routine & do it !

Thank you