WWOX Demonstrates Ancestry-Specific Associations with ARDS Risk in Sepsis

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BACKGROUND

- Acute respiratory distress syndrome (ARDS) is a common and fatal cause of respiratory failure
- Genetic and environmental factors govern ARDS risk
  - Clinical factors alone incompletely explain risk
  - Risk factor identification may improve risk prediction and provide mechanistic insights
- Genetic determinants of ARDS have primarily been conducted in European ancestry (EA)

OBJECTIVES

- To identify single nucleotide polymorphisms (SNPs) associated with ARDS risk in EA subjects
- To test for replication of SNPs associated with ARDS risk in EA subjects in African (AA) subjects

METHODS

Design: Single center prospective cohort study
Study Population: ICU subjects with sepsis or septic shock per Sepsis-2 consensus criteria
Case/Control: ARDS or non-ARDS per Berlin criteria
Genotype Ascertainment:

- Whole blood collected on day 0 (ICU admission)
- Genotyping per Affymetrix Tx v1 array

Statistical Analysis: Genome-wide association study

- **Logistic regression (LR):** To test the association between SNPs and ARDS adjusting for confounders
- **Potential confounders**: Age, gender, genetic ancestry, and pulmonary source of infection
- **Genetic ancestry**: HapMap-3 consortia populations
- **Significance threshold(s):** Traditional GWAS (5x10-8), suggestive (1x10-5), and nominal (0.05)

RESULTS

Table 1. Study population characteristics.

Patient Characteristics	ARDS Cases (n=692)	ARDS Controls (n=1,041)	P-value
Age (median, IQR)	60 (51, 69)	62 (52, 71)	0.05
Female Sex (n, %)	264 (38.2)	460 (44.2)	<0.01
Ancestry (n, %)			
European	473 (41.6)	662 (58.4)	0.03
African	219 (36.6)	379 (63.4)	
Source (n, %)			
Pulmonary	384 (55.4)	329 (31.6)	<0.01

Figure 1. ARDS Manhattan plot for EA.

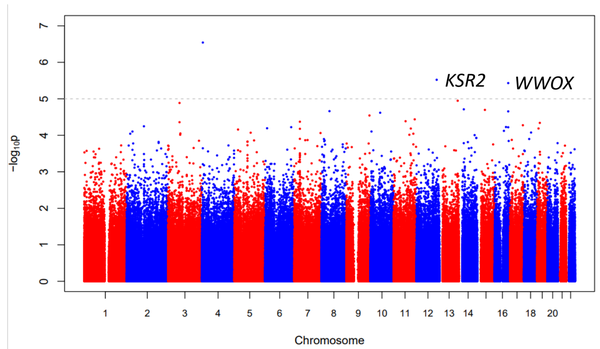


Table 2. *WWOX* rs12934553 associates with ARDS.

Ancestry	ARDS OR [95%CI]	P-value
EA	0.66 [0.56, 0.79]	3.7x10-6
AA	1.76 [1.20, 2.60]	4x10-3

Rs12934553 is a SNP within *WWOX*. The ancestry-specific associations demonstrated opposite directionality.

Table 3. *KSR2* rs2592293 associates with ARDS.

Ancestry	ARDS OR [95%CI]	P-value
EA	2.88 [1.85, 4.51]	3.01x10-6
AA	4.83 [1.25, 18.64]	0.02

Rs12934553 is a SNP within *KSR2*. The ancestry-specific associations demonstrated similar directionality.

Figure 2a. EA *WWOX* regional association plot.

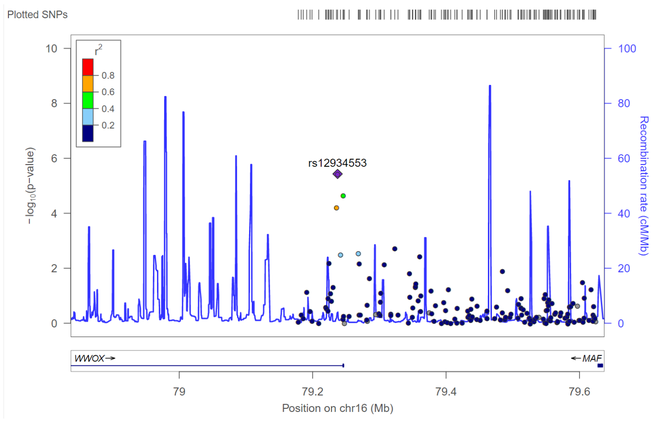
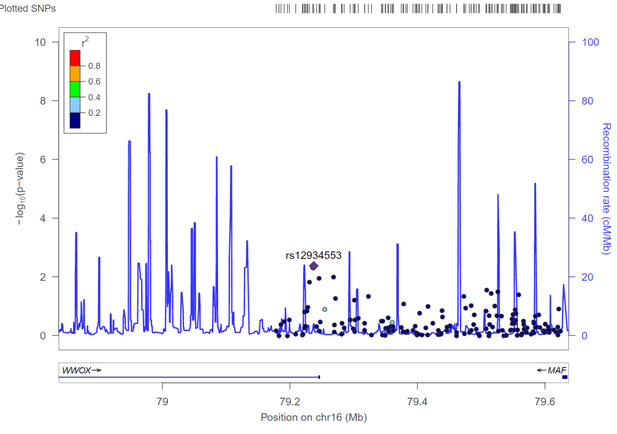


Figure 2b. AA *WWOX* regional association plot.



RESULTS

- **Multiple variants surpassed a suggestive threshold**
  - No variants at conventional GWAS threshold
  - Several loci replicated across ancestry
- **Rs12934553 was highly associated with ARDS in EA**
  - 3 loci within *WWOX* associated with ARDS risk
  - Opposite directional association in EA and AA
- **Rs2592293 in *KSR2* associated with ARDS risk in EA and AA subjects with same directionality**

LIMITATIONS

- **Single center cohort**
- **Limited sample size**

CONCLUSIONS

- ***WWOX* is implicated in neutrophilic lung injury, tobacco exposures, and vascular permeability**
- ***KSR2* is a molecular scaffolding protein involved in ERK signaling**
- ***WWOX* demonstrated associations with ARDS risk in both EA and AA with opposite directionality**
- **Co-localizing signals with opposing directionality may occur due to different genetic population structure, epigenetic changes, or interactions**

IMPLICATIONS

- **ARDS demonstrates shared and ancestry-specific genetic risk factors**
- **Increased diversity in genetic studies may enhance our potential for understanding ARDS risk**

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