

Genomics-Driven Drug Repurposing Analyses to Guide the Identification of Novel Treatments to Improve Reproductive Outcomes in Women with Polycystic Ovary Syndrome



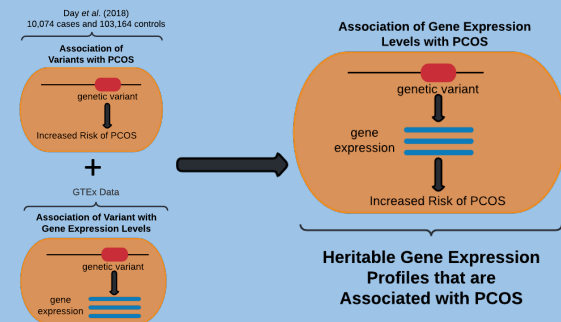
Introduction

Polycystic ovary syndrome (PCOS)

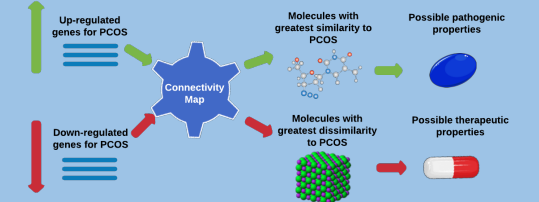
- 5-10% of reproductive age females¹
- Hyperandrogenism, ovulatory dysfunction, and polycystic ovaries²
- Trial-and-error based approach to treatment administration

Methods

Objective 1: Identify heritable gene expression profiles associated with PCOS

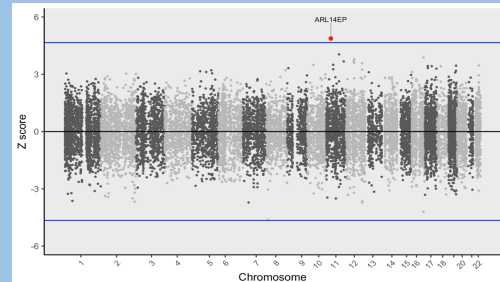


Objective 2: Genomics-driven drug repurposing analyses for the identification of new treatment options for PCOS.



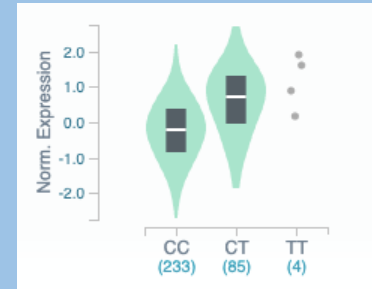
Results

1 ARL14EP is associated with PCOS



Manhattan plot of Day et al. (2018) 5-MultiXcan. Curated using R Studio and plot generated using TWAS-plotter.V1.0.r.

4 rs4071559 increases ARL14EP expression



GTEx testis data

2 Relevance of reproductive tissues

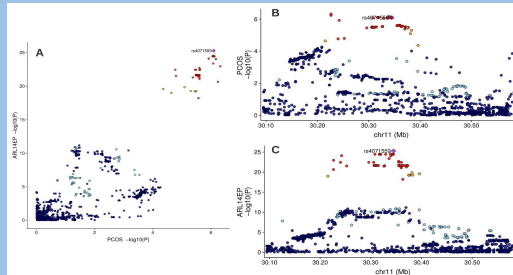
Tissue	P-value
Testes	$P=1.1 \times 10^{-6}$
Ovaries	$P=7.4 \times 10^{-6}$
Uterus	$P=1.5 \times 10^{-5}$
Vagina	$P=6.2 \times 10^{-6}$

5 Association with PCOS related phenotypes

Phenotype	P-value
Length of menstrual cycle	8.5×10^{-34}
Bilateral oophorectomy	4.0×10^{-9}
Excessive, frequent and irregular menstruation	3.9×10^{-8}
Years since last cervical smear test	1.2×10^{-7}
Endometriosis	2.0×10^{-6}
Part of a multiple birth	2.3×10^{-6}
Having a hysterectomy (womb removed)	3.4×10^{-6}
Standing height	4.2×10^{-6}
Age at first birth	1.0×10^{-5}

PheWAS UKBB phenotypic results for rs4071559

3 Colocalization of rs4071559



Colocalization results of LocusCompare.

6 Drug repurposing results

Greatest Similarity to PCOS	Greatest Dissimilarity to PCOS
BRD-K91257617	BRD-K77264230
E-2012	Iloperidone
Thioguanine	VCAP
CGI-1746	Prednisone
BRD-K56764633	Dehydroepiandrosterone
Verteporfin	BRD-K47709646

CMap drug repurposing results for PCOS

Summary

TWAS Results

Increased ARL14EP expression is associated with increased risk of PCOS

Drug Repurposing Analyses Results

Greatest similarity to PCOS Greatest dissimilarity to PCOS

Verteporfin

Prednisone

Premature oocyte differentiation³
YAP-TEAD inhibitor³
Interfering growth-promoting effects³

Glucocorticoid⁴
Induce ovulation⁴
Reduce adrenal androgen production⁴

Study's Significance

- First TWAS of PCOS performed to date
- Expanded on the mechanisms of PCOS
- Aims to improve reproductive outcomes in women with PCOS and health of their children

Future Directions

- ARL14EP over expression
- Animal model for drug repurposing analyses

References

- Li, R. et al. Prevalence of polycystic ovary syndrome in women in China: A large community-based study
- Williams, T. *Diagnosis and Treatment of Polycystic Ovary Syndrome.*
- Sun, T. & Diaz, F. J. Ovulatory signals alter granulosa cell behavior through YAP1 signaling.
- Badawy, A. & Elnashar, A. Treatment options for polycystic ovary syndrome.