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Causal mechanisms and balancing selection inferred from genetic associations with polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is the most common reproductive disorder in women, yet there is little consensus regarding its aetiology. Here we perform a genome-wide association study of PCOS in up to 5,184 self-reported cases of White European ancestry and 82,759 controls, with follow-up in a further ~2,000 clinically validated cases and ~100,000 controls. We identify 6 signals for PCOS at genome-wide statistical significance ($P<5\times10-8$), in/near genes *ERBB4/HER4, YAP1, THADA, FSHB, RAD50* and *KRR1*. Variants in/near 3 of the 4 epidermal growth factor receptor genes (ERBB2/HER2, ERBB3/HER3 and ERBB4/HER4) are associated with PCOS at or near genome-wide significance. Mendelian randomization analyses indicated causal roles in PCOS aetiology for higher BMI ($P=2.5\times10-9$), higher insulin resistance ($P=6\times10-4$) and lower serum sex hormone binding globulin concentrations ($P=5\times10-4$). Furthermore, genetic susceptibility to later menopause is associated with higher PCOS risk ($P=1.6\times10-8$) and PCOS-susceptibility alleles are associated with higher serum anti-Müllerian hormone concentrations in girls ($P=8.9\times10-5$). This large-scale study implicates an aetiological role of the epidermal growth factor receptors, infers causal mechanisms relevant to clinical management and prevention, and suggests balancing selection mechanisms involved in PCOS risk.

Biography

Felix Day is a Career Development Fellow in the Growth and Development Program at the Medical Research Council Epidemiology Unit, University of Cambridge, UK, where he also did his PhD. Before moving to Cambridge, he studied at the University of Oxford, UK, and the London School of Hygiene and Tropical Medicine, UK. His research interests include the links between reproductive phenotypes and disease, particularly metabolic disorders. This research includes using methods in both genetics and epidemiology to understand causality in these conditions.

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