TITLE: Twinning as a phenotype: GWAS and EWAS meta-analyses

FULL AUTHOR LIST: Dorret I. Boomsma¹, Hamdi Mbarek¹², Jenny van Dongen¹, Nick G. Martin, the Twinning Genetics Consortium⁴

AFFILIATIONS:
¹ Netherlands Twin Register, Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam Development and Reproduction Institute, The Netherlands
² Qatar Genome Program, DOHA, Qatar
³ Queensland Institute Medical Research, Brisbane, Australia
⁴ http://www.twinningconsortium.org/

KEYWORDS: Twinning, zygosity, gene-finding, GWAMA, epigenetics, EWAS

ABSTRACT:
The classical twin design has been referred to as a perfect ‘natural experiment’, or the ‘working horse’ of behavior genetics and continues to be of enormous value to explore total trait heritability, the aetiology of comorbidity and model causality. Twinning as the phenotype of interest in genetic analyses is more rare. We have performed genome-wide association meta-analyses (GWAMA) of spontaneous dizygotic (DZ) twinning in mothers of twins (MoDZT) and of the proxy phenotype “Are you a DZ twin” and meta-analyzed these results together.

DZ spontaneous twinning is a complex polygenic trait, for which we reported the first 2 replicated genes, FSHB and SMAD3 a few years ago (Mbarek et al. 2016). FSHB had been hypothesised (but never shown) to be implicated in DZ twinning while SMAD3, which regulates the response of the ovaries to FSH, was not implicated in twinning before. We have now extended the discovery set for MoDZT and will present the meta-analysis results, combined with the proxy phenotype “being a DZ twin”.

In contrast to DZ twinning whose familial / genetic aetiology is well established in family and pedigree studies, the aetiology of monozygotic (MZ) twinning is much more unclear. We also
performed genome-wide association studies of “being a MZ twin”, obtaining only one genome wide significant finding. However, the first epigenome-wide association study of MZ twinning has generated a plethora of results. We detected a MZ twin-specific DNA methylation signature in whole blood samples, which showed marked replication in 4 independent twin cohorts and in samples from a different cellular lineage.


GRANT SUPPORT: KNAW Academy Professor Award (PAH/6635) to DIB.