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

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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.

Mbarek H, Steinberg S, Nyholt DR, Gordon SD, Miller MB, McRae AF, Hottenga JJ, Day FR, Willemsen G, de Geus EJ, Davies GE, Martin HC, Penninx BW, Jansen R, McAloney K, Vink JM, Kaprio J, Plomin R, Spector TD, Magnusson PK, Reversade B, Harris RA, Aagaard K, Kristjansson RP, Olafsson I, Eyjolfsson GI, Sigurdardottir O, Iacono WG, Lambalk CB, Montgomery GW, McGue M, Ong KK, Perry JRB, Martin NG, Stefánsson H, Stefánsson K, Boomsma DI. Identification of Common Genetic Variants Influencing Spontaneous Dizygotic Twinning and Female Fertility. *Am J Hum Genet.* 2016; 98(5):898-908. doi: 10.1016/j.ajhg.2016.03.008

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