*Nature Reviews Cardiology* | Published online 22 Jan 2016; doi:10.1038/nrcardio.2016.3

CARDIOMYOPATHIES

# Genetic overlap between peripartum and dilated cardiomyopathies

> PPCM shares significant genetic overlap with DCM, and ... they may even be ... different manifestations of the same disease

Women with peripartum cardiomyopathy (PPCM) and individuals who develop dilated cardiomyopathy (DCM) might share a genetic predisposition. This finding comes from a gene-sequencing study published in *N. Engl. J. Med.* in which PPCM was found to be associated with truncating variants in various genes that are also associated with DCM.

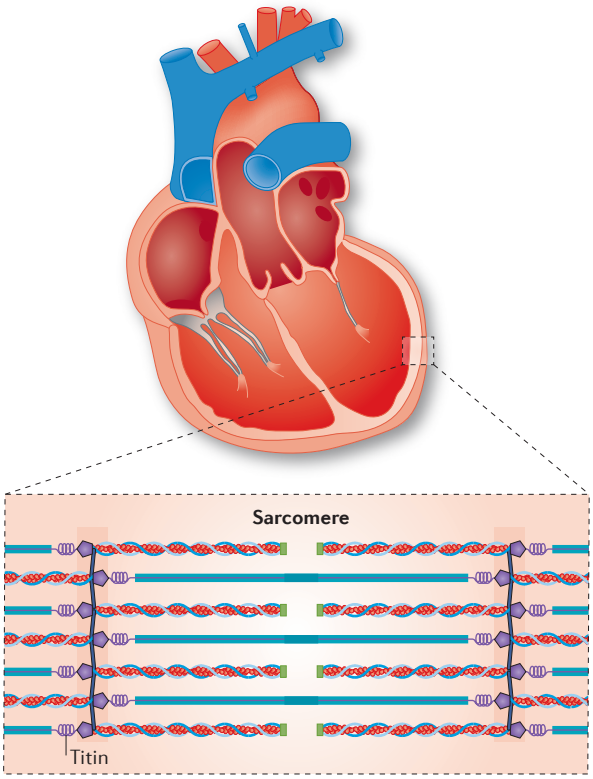
Women with PPCM develop marked systolic heart failure either late in pregnancy or early in the postpartum period. The pathophysiology of the disease is uncertain, with previous studies indicating that it is a vascular disease; potential underlying mechanisms include fetal autoimmunity or microchimerism, myocarditis, and dietary excess of salt or deficiency of selenium. To investigate whether the disease has a genetic component, Zoltan Arany and colleagues recruited 172 women with PPCM and sequenced 43 genes with variants known to be associated with DCM. One-third of the women were of African descent. The results were compared with a cohort of 332 patients with DCM, and a population of 60,706 control individuals.

Genetic sequencing identified 26 rare heterozygous truncating variants in eight different genes (17 in *TTN*, two in *SYNM*, two in *TPM1*, and one each in *DMD*, *DSP*, *LAMP2*, *MYH6*, and *VCL*). The prevalence of truncating variants in women with PPCM (15%) was similar to that in individuals with DCM (17%), and significantly higher than in the reference population (4.7%). The majority (65%) of the truncating variants were discovered in the gene encoding titin, and four were identical to variants previously identified in patients with DCM. A total of 14 out of the 17 *TTN* variants were located in the A-band portion of the protein — a region in which truncating mutations associated with DCM also tend to cluster.

The investigators conclude that "many of these truncating variants lead to a strong genetic predisposition to PPCM". Commenting on their findings, Zoltan Arany says "this means that PPCM shares significant genetic overlap with DCM, and that they may even be, in many cases, different manifestations of the same disease". If so, Arany believes that "it may become relevant to test women with PPCM for the presence of genetic variants in the titin gene. The approach would be particularly relevant if we found that women with mutations in titin had a worse prognosis than women without mutations." This question is still under investigation. In a subgroup of 83 women with PPCM, cardiac function was not significantly different at baseline between those with a *TTN*-truncating variant and those without. After 1 year, those with a *TTN*-truncating variant had a lower ejection fraction (44 ± 17%) than those without (54 ± 8%; $P = 0.005$).

James Fett, a co-director of the Investigations in Pregnancy-Associated Cardiomyopathy (IPAC), believes that "the presence of the *TTN* gene [variants] may contribute to both a higher incidence of PPCM and a poorer prognosis for those with African heritage". *TTN*-truncating variants were observed in 13% of women with PPCM of African descent, compared with 8% of women of European descent. The corresponding values in the control population were 2.1% and 1.1%, respectively. Fett comments that "up to 15% of patients with PPCM seem to have a strong genetic predisposition to develop PPCM, [but] this genetic predisposition ... may require additional triggering factors to develop the disease. Triggering factors could be hormonal and angiogenic imbalances, ... presence of gestational hypertension or pre-eclampsia, and cardiomyotropic virus infections."

*Gregory B. Lim*




**ORIGINAL ARTICLE** Ware, J. S. *et al.* Shared genetic predisposition in peripartum and dilated cardiomyopathies. *N. Engl. J. Med.* doi:10.1056/NEJMoa1505517