Molecular Subclass of Uterine Fibroids Predicts Response to Ulipristal Acetate Treatment

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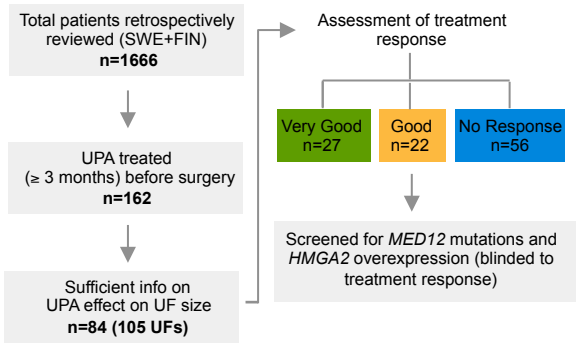
Subclass as treatment predictor

The results from this restrospective study show for the first time that genetic uterine fibroid (UF) subclasses influence drug treatment response. Our finding highlights the need of taking UF molecular subclass into account when developing and evaluating current and future therapies.

Aim

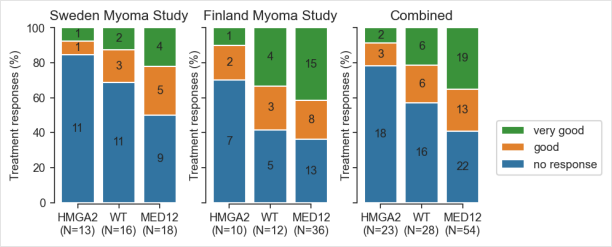
To investigate if the two most common UF subclasses, driven by aberrations in *MED12* (70%) and *HMGA2* (15%) genes respectively, influence treatment response to the selective progesterone receptor modulator ulipristal acetate (UPA).

Study material and work flow



MED12 UFs more responsive to UPA treatment

MED12 UFs were found to have 4.8 times higher odds to UPA induced size reduction compared to HMGA2 UFs (95% confidence interval (CI) 1.47-15.6; P=0.0093; VGR/GR versus NR). Initial UF size or number of UFs did not explain the observed difference.

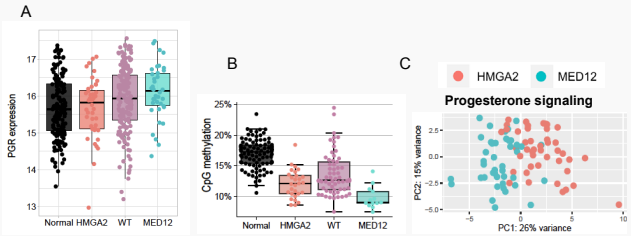


Data shown as percentages (stacked bar plot) and as exact numbers of tumors (N). Green: very good treatment response; orange: good response; blue: no response; WT: wild type for MED12 and HMGA2.

Potential underlying mechanisms

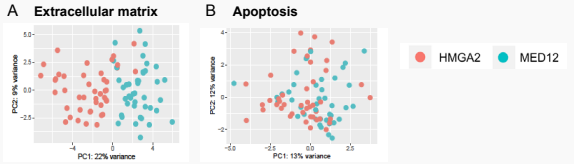
Existing RNA-sequencing and DNA-methylation data derived from MED12 and HMGA2 UFs *(Berta D. et al. Nature 2021, 596:398-403)* was used to explore potential differences in progesterone signaling, extracellular matrix composition and apoptosis.

Subclass specific differences in progesterone receptor signaling



A) Progesterone receptor (PGR) expression in normal myometrium (n=162), HMGA2 UFs (n=44), MED12 UFs (n=42) and UFs wild type for HMGA2 and MED12 (n=175). Y-axis variance stabilized gene counts. B) Average CpG methylation at PGR binding sites in normal myometrium (n=96), HMGA2 UFs (n=28), MED12 UFs (n=13) and UFs wild type for HMGA2 and MED12 (n=61). C) Principal component analysis (PCA) of 48 progesterone related genes.

Distinct extracellular matrix but not apoptosis expression signature



Principal component analysis (PCA) of A) 84 extracellular matrix related genes and B) 90 apoptosis related genes.

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