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IMPACT ON MITOCHONDRIAL FUNCTION BY INCREASED LEVELS OF MITOCHONDRIAL RNA POLYMERASE

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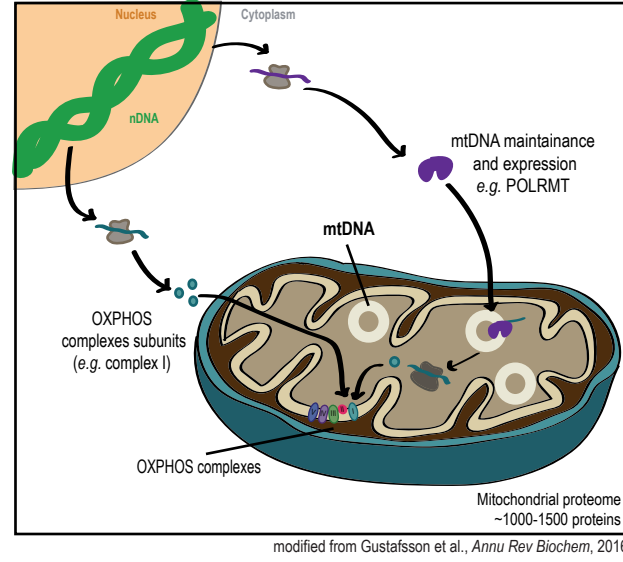
ABSTRACT

Mitochondria are eukaryotic organelles performing several essential metabolic processes, including ATP production by oxidative phosphorylation. Mitochondrial function depends on the coordinated expression of the nuclear and the mitochondrial genomes (mtDNA). Transcription of mammalian mtDNA *in vitro* requires the nuclear-encoded mitochondrial RNA polymerase (POLRMT) and the mitochondrial transcription factor B2. These factors are recruited to the heavy- and light-strand promoters on the mtDNA following the binding of mitochondrial transcription factor A. In addition, the mitochondrial transcription elongation factor enhances the processivity of POLRMT facilitating transcription of the mtDNA. Although the components that are essential for mitochondrial transcription *in vitro* are known, both, the mechanisms and the components that regulate mitochondrial gene expression *in vivo* are incompletely understood.

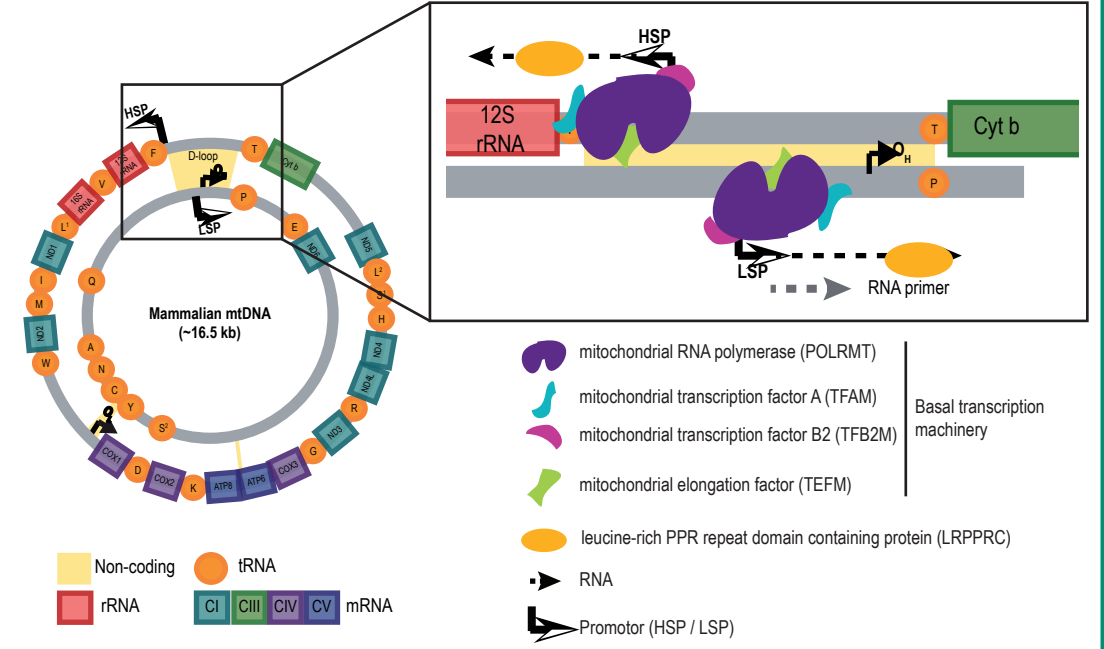
Using a knockout mouse model, we recently showed that POLRMT is the sole mitochondrial RNA polymerase transcribing mtDNA *in vivo* (Kühl et al, Nature, 2014). To further elucidate the mechanisms that dynamically regulate mitochondrial gene expression, we varied the *in vivo* expression of *Polrmt* in mice by introducing a bacterial artificial chromosome (BAC) expressing *Polrmt* into the germline. Here, we present a first analysis of these mice that have a 30-50% increase of POLRMT protein levels in heart, and a 20-30% increase in liver. Remarkably, this overexpression of *Polrmt* is accompanied by a strong increase in *de novo* mitochondrial transcription in mouse heart indicating that a ~40% increase of POLRMT is sufficient to up-regulate transcription initiation in mitochondria, underlining the key function of POLRMT in regulating mitochondrial gene expression.

POLRMT IS ESSENTIAL FOR MAINTENANCE AND EXPRESSION OF THE MITOCHONDRIAL GENOME

Mitochondrial biogenesis

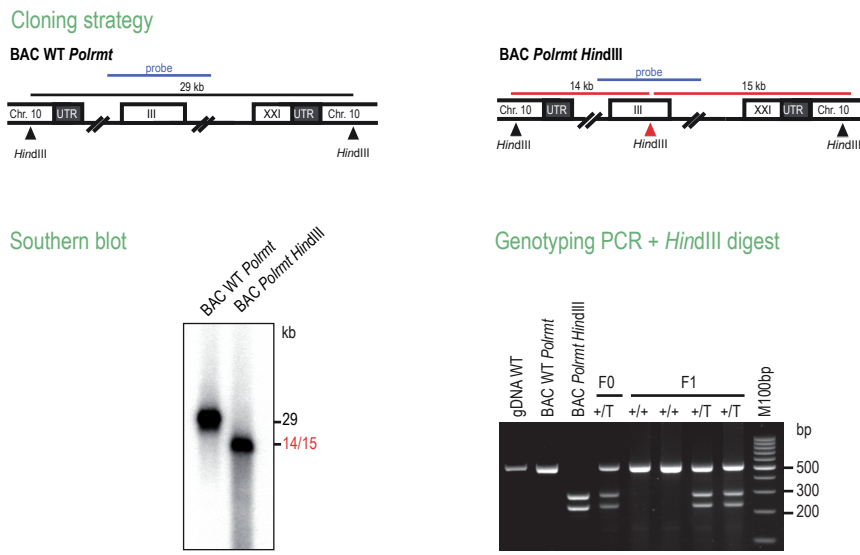


Mitochondrial genome and transcription machinery

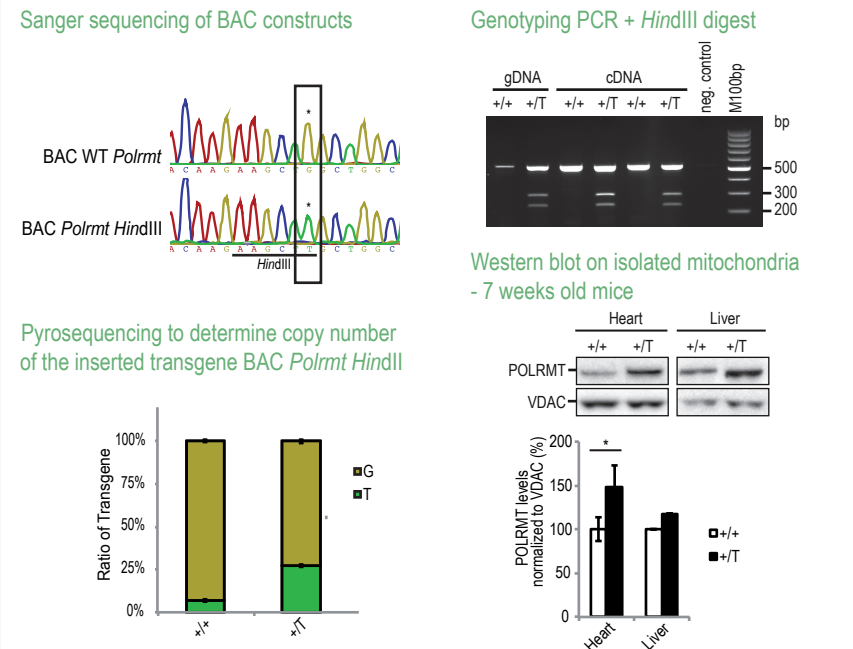


GENERATION OF POLRMT OVEREXPRESSION MICE BY BAC TRANSGENICS

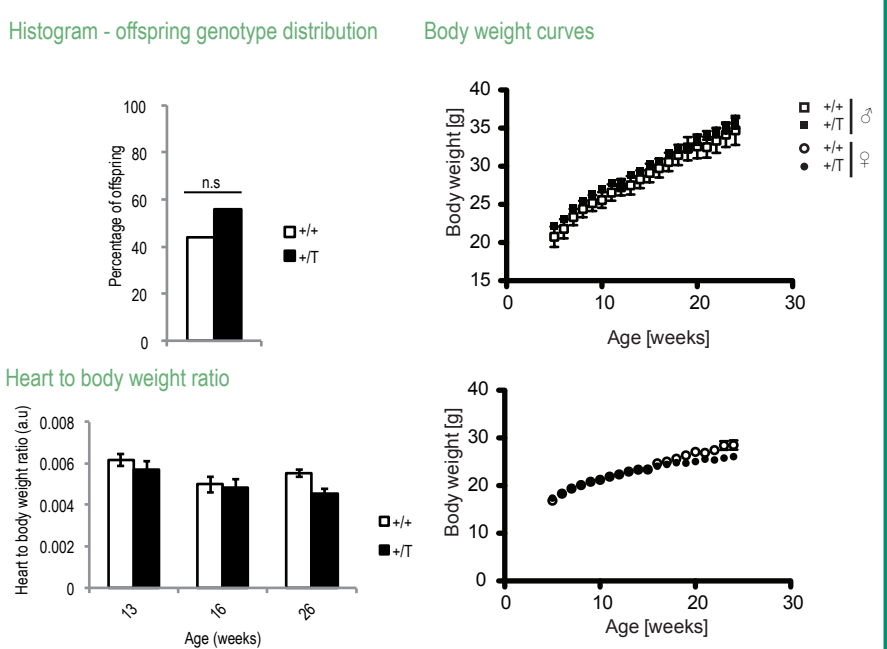
A silent point mutation leading to a *HindIII* restriction site differentiates the transgene (TG) from the wildtype *Polrmt*



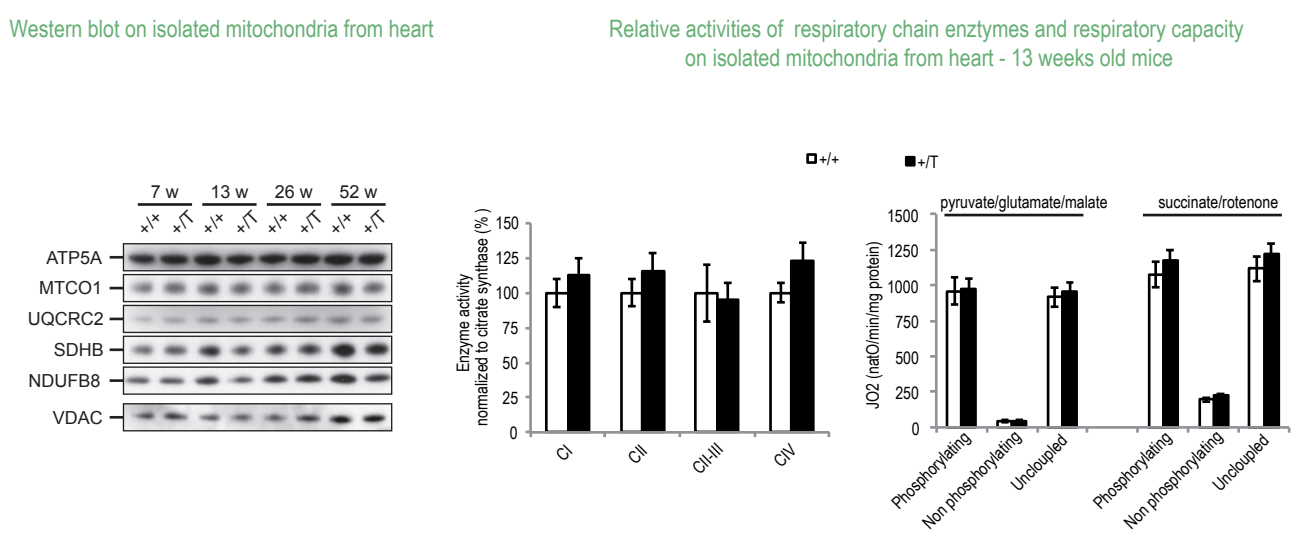
EXPRESSION OF THE *Polrmt HindIII* TG IN MICE INCREASES POLRMT PROTEIN LEVELS BY ~50%



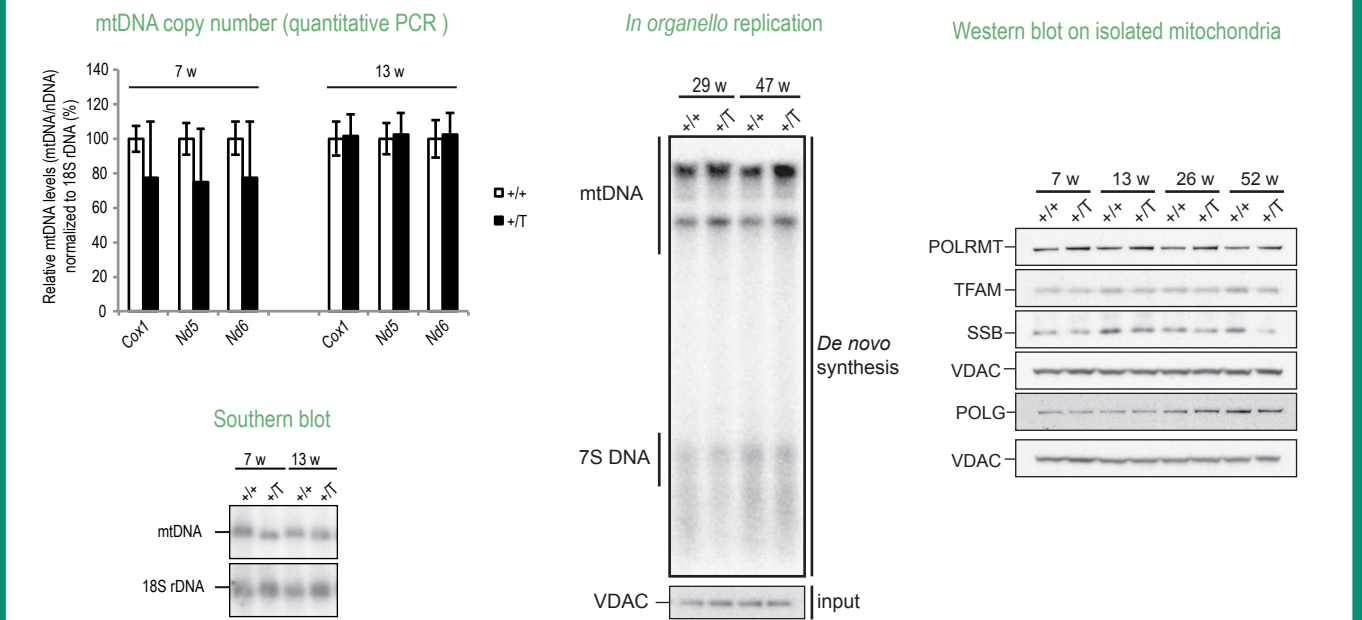
Polrmt HindIII TG IS INHERITED IN MENDELIAN RATIOS AND DOES NOT AFFECT BODY WEIGHT



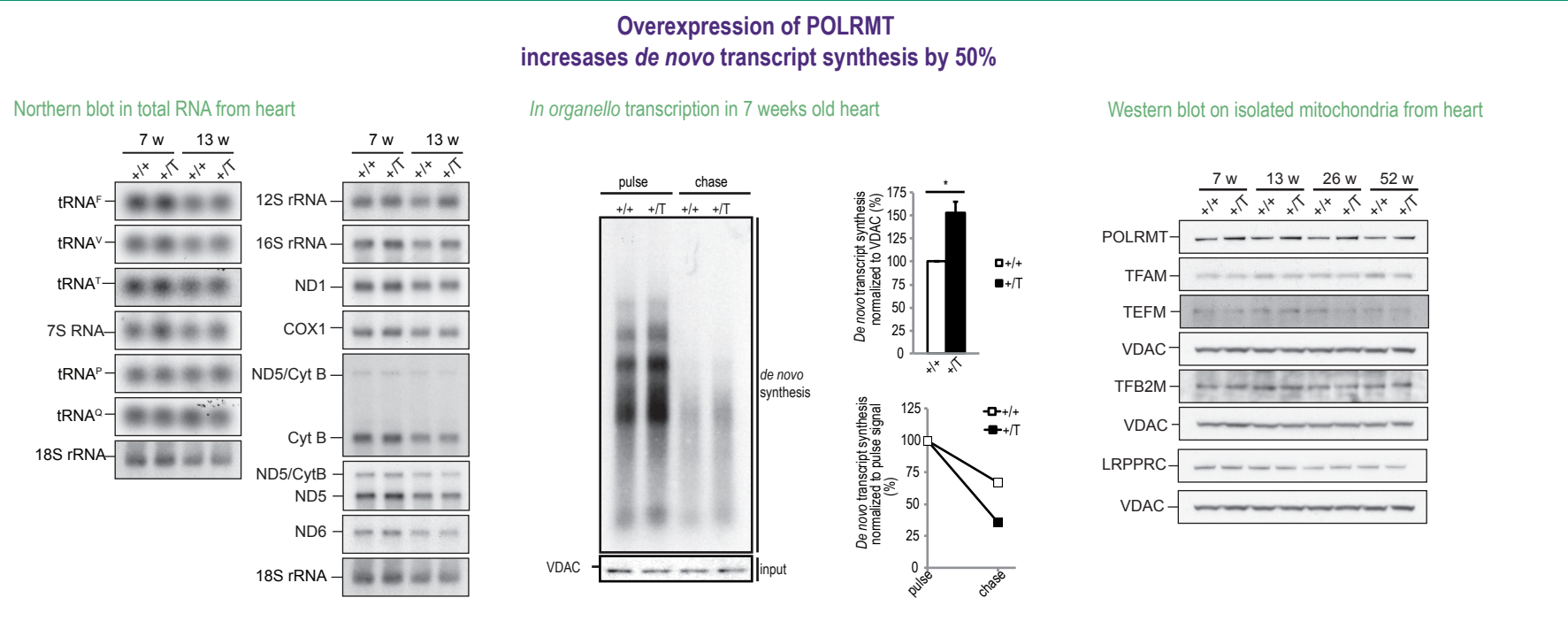
OXPHOS CAPACITY IS NOT AFFECTED IN HEART OF POLRMT OVEREXPRESSION MICE



MITOCHONDRIAL DNA REPLICATION AND MAINTENANCE IS UNCHANGED IN HEART OF POLRMT OVEREXPRESSION MICE



POLRMT OVEREXPRESSION LEADS TO A STRONG INCREASE IN DE NOVO TRANSCRIPTION IN HEART



LRPPRC MIGHT STABILIZE DE NOVO TRANSCRIPTS IN POLRMT OVEREXPRESSION MOUSE

