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SDH6 A NEW GENE OF *SACCHAROMYCES CEREVISIAE* REQUIRED FOR ASSEMBLY OF COMPLEX II

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Yeast is recognised as a model for approaching human diseases-associated gene functions particularly concerning mitochondrial ones due to the yeast ability to survive without a functional mitochondrial respiratory chain, provided that a fermentable carbon source is made available.

Succinate dehydrogenase or complex II is composed of four subunits (*SDHA-D* in humans, *SDH1-4* in yeast), all encoded by nuclear genes. Despite the extensive knowledge on structural and catalytic properties of the complex, only recently two assembly factors specific for the SDH has been found: *SDHAF1* and *SDHAF*2. The *SDHAF1* gene has been identified in humans because linked to infantile leukoencephalopathy. A yeast strain deleted in *SDH6*, the *SDHAF1* ortholog, was OXPHOS incompetent, due to a severe and specific reduction of SDH activity. However, the Km value for succinate was similar in wild-type and in the null mutant, suggesting that defective SDH activity was caused by reduced number of enzyme units rather than by qualitative alterations of complex II. In agreement with the reduction of SDH activity, we found a reduction in the amount of SDH complex on 2D-BNGE. In addition *SDHAF1* is not physically associated and stably bound to complex II. Furthermore, a co-immunoprecipitation study was undertaken in order to determine whether *SDHAF1* interacts with a subunit of SDH. The two pathogenic alleles, R61P and G63R, have been tested for their capability to be translocated into mitochondria.

To gain insight into the molecular basis of the Sdh6-less phenotype, we screened a genomic library for multicopy suppressors of acetate-negative phenotype and characterized the genes identified. Two genes *YAP1* and *YAP2*, encoding transcription factors necessary for the stress response, were found to suppress the OXPHOS growth phenotype of the *sdh6* null mutant, but failed to increase SDH enzymatic activity. These results suggest that Sdh6 might play an additional role besides the SDH assembly.