

Characterization of yeast genes homologous to human genes involved in mitochondrial and peroxisomal function

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The *Saccharomyces cerevisiae* genes *YPR004c*, *YGR207c*, *YOR356w* and *YDR036c* homologous to human genes involved in transfer of electrons to the respiratory chain from flavin-containing dehydrogenases (ETFA, ETFB and ETFDH) and in β -oxidation (HADHA), were chosen for characterization. Mutations in ETFA, ETFB and ETFDH (orthologous to *YPR004c*, *YGR207c* and *YOR356w*, respectively) cause multiple acyl-CoA dehydrogenation deficiency, also known as glutaric aciduria II. Mutations in HADHA (orthologous to *YDR036c*) affect the α -subunit of the trifunctional enzyme that catalyzes three reactions in mitochondrial β -oxidation of fatty acids. In previous studies, all of these yeast genes have been localized in the mitochondrion. Unlike mammalian cells, fatty acid catabolism by β -oxidation in yeast takes place exclusively in peroxisomes. The aim of

this work is to contribute to understand the functional relation between mitochondria and peroxisomes, by studying lipid catabolism in yeast cells. *S. cerevisiae* mutants affected in the above mentioned genes were studied for growth on several non-fermentable carbon sources and for carbon sources, which catabolism requires peroxisomal activity (oleic acid and methanol). Growth is unaffected on non-fermentable carbon sources and is decreased for all mutants only on methanol, which suggests deficiency in peroxisomal activity concomitant with normal function of mitochondria. On the other hand, *ygr207c* and *yor356w* mutant strains present growth deficiency on oleic acid, suggesting a wider peroxisomal metabolic deficiency when compared to *ypr004c* and *ydr036c*.

Yeast genes studied, human orthologues and related diseases

Yeast gene	Human orthologue	Human disease
<i>YPR004c</i>	ETFA	Glutaric aciduria type IIa
<i>YGR207c</i>	ETFB	Glutaric aciduria type IIb
<i>YOR356w</i>	ETFDH	Glutaric aciduria type IIc
<i>YDR036c</i>	HADHA	Trifunctional enzyme deficiency

Human and yeast genes sequence homologies

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UID: ETFA Type: Protein 231 aa
Seq:
UID: YGR207c Type: Protein 241 aa
Needleman & Munch (global)
Mitschke (1)
Mitschke (1)
UID: YOR356w Type: Protein 631 aa
Seq:
UID: YDR036c Type: Protein 763 aa
Seq:
UID: YGR207c Type: Protein 499 aa
Needleman & Munch (global)
Mitschke (1)
Mitschke (1)
UID: HADHA Type: Protein 537 aa
Seq:
UID: ETFA Type: Protein 333 aa
UID: YPR004c Type: Protein 544 aa
Needleman & Munch (global)
Mitschke (1)
Mitschke (1)
    
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Potential transcriptional regulators*

Gene	Sequences	Transcription factors
<i>YPR004c</i>	TTGGGG (528) TTGGAG (528)	Adr1p
	GGTAC (129-735) GTCCAC (153-382)	Rtg1p
<i>YGR207c</i>	TTGGAG (704)	Adr1p
	GGTAC (374) GTCCAC (743)	Rtg1p
<i>YOR356w</i>	TTGGAG (772-948) TTGGGG (950)	Adr1p
<i>YDR036c</i>	TTGGAG (423)	Adr1p
	GTCCAC (445)	Rtg1p

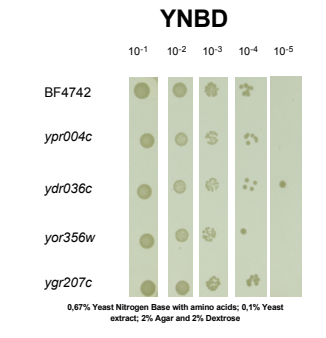
Rtg1p
 Positive transcriptional regulator controlling expression of *ADH2*, peroxisomal protein genes and genes involved in ethanol, glycerol and fatty acid utilization.

Adr1p
 Transcription factor involved in interorganelle communication between mitochondria, peroxisomes and nucleus.

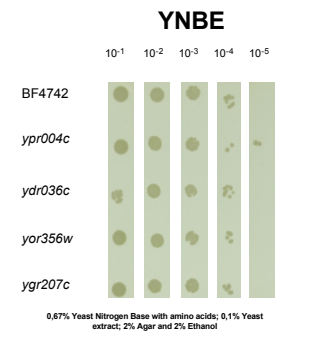
* Yeast Search for Transcriptional Regulators And Consensus Tracking (YEASTRACT), (November 28, 2005)

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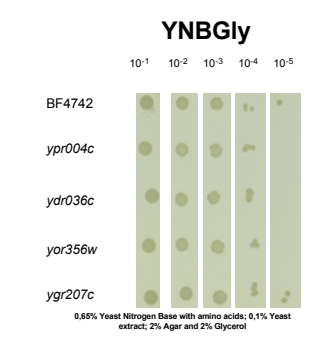
All strains grow on glucose



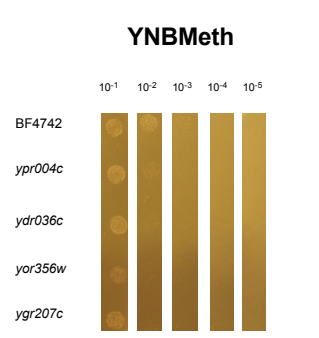
All strains grow on ethanol



All strains grow on glycerol



All mutant strains have growth deficiency on methanol



Mutant strains yor356w and ygr207c have growth deficiency on oleic acid

