Supplementary material: **The generalized profile method**

For the discovery of distant protein relationship, the generalized profile method was used. The method and its applications have been described previously in full details (Bucher et al 1996). In brief, the method starts from a multiple sequence alignment of established members of a protein or domain family. Subsequently, a 'profile' is calculated from the alignment and a suitable substitution matrix. Unlike the classical Smith-Waterman search, where all sequence positions are treated equally, a profile has the property that positions highly conserved in the initial alignment will have a much higher weight in the calculation of the overall alignment score. Similar differences concern the treatment of insertion/deletion penalties, which depend on the presence of a gap in the initial alignment. In the next step, the profile is run against a surrogate database consisting of randomized sequences that mimic the properties of real proteins. After an analysis of the resulting score distribution, the profile is run against the target database. All sequences giving statistically significant scores ($p<0.01$ for expecting this score in an equally sized random database) are considered relatives of the original family. New sequences can then be incorporated into the initial alignment enabling a refinement of profile construction and repetition of the search process.

In the present study, a starting profile was built from the conserved D2 region of established ODC antizyme sequences, including members from vertebrates, insects, nematodes, and three *Schizosaccharomces* sequences from *S. pombe* (Q9USQ5)*, S. japonicus* (Q9HFU9) and *S. octosporus* (Q9HFU8). During the first rounds, the family was completed by including significant matches from further nematodes (*Onchocerca volvulus*, *Pristionchus pacificus*) and various fungi (*Fusarium gramineum, Emericella nidulans* and *Neurospora crassa),* but not including any hemiascomycete yeast. The resulting profile yielded a significant match to a pioneer hemiascomycete sequence from *Saccharomyces kudriavzevii* with a p value of 0.01. In the final profile round, highly significant matches to peptide sequence encoded by the *Saccharomyces cerevisiae* ORF YPL052w and other fungal orthologues appeared.

To further support this finding, we performed reverse profile searches starting from a multiple alignment of the yeast Oaz1 sequence and its relatives from other hemiascomycete fungi such as *Ashbya gossypii* and *Kluyveromyces waltii.* Due to the limited sequence variability in this small subfamily, we did not find any database match fulfilling our stringent significance criterion. Nevertheless, the best-scoring match in the protein database was the established OAZ from *S. pombe* with a score just below the significance threshold.