Stepwise functional evolution in the Ffz sugar transporter family

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Sugars are favorite carbon and energy sources in all domains of life, making sugar transport a biological process of vital importance. In fungi, specifically in ascomycetous yeasts, hexose transporters can accept several hexoses as substrates, but glucose is normally more efficiently transported [1]. In biotechnological processes such as wine fermentation where fructose and glucose are present in similar concentrations, faster consumption of glucose by glucophilic wine yeasts can lead to slow or incomplete fermentations with concomitant fructose accumulation. Therefore, shifting the metabolic behavior of wine yeast towards fructophily is an important goal for the wine industry. Recently, a novel family of fungal sugar transporters were identified that contrary to other yeast hexose transporters known, mediate fructose uptake with high capacity and specificity. These transporters, named Ffz [2], were first identified in the fructophilic *Zygosaccharomyces* yeasts where they play a crucial role in fructophily [3]. While most sugar transporters from all kingdoms of life belong to the Sugar Porter Family, the Ffz facilitators are instead closely related to a functionally distinct family, the drug antiporter family 1 (DHA1) [2,3], suggesting an independent evolutionary history. In this work, we focused on understanding the evolutionary trajectory of this peculiar family of transporters while also trying to uncover the origin of fructophily in yeasts. We started by exploiting the wealth of fungal genomic data publicly available to delimite the Ffz-like transporter family, and we showed that they are only present in the sub-kingdom Dikarya, being absent outside the fungal kingdom. *In vivo* characterization of Ffz homologues brought to light a variety of biochemical properties among extant transporters, suggestive of stepwise changes in substrate range. Subsequent phylogenetic analyses revealed a patchy distribution of the gene in all Dikarya lineages, driven both by complex patterns of gene losses and duplications, and by horizontal gene transfer (HGT) events. One such HGT event seems to have set the stage for the onset of fructophilic metabolism in yeasts, a trait that seems to be the metabolic hallmark of approximately one hundred yeast species dwelling in sugar rich environments.

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