Weird gene in a weird mammal:
A highly divergent pancreatic duodenal homeobox 1 (*Pdx1*) gene in the fat sand rat

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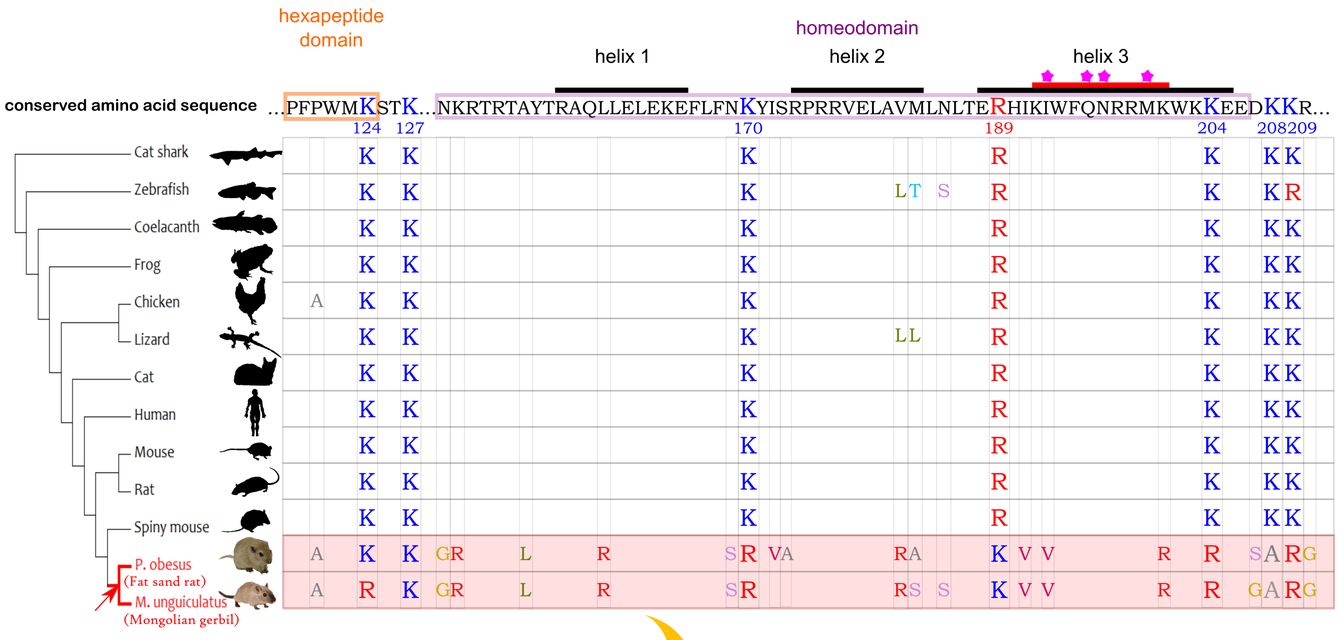
Introduction

- Pancreatic duodenal homeobox 1 (PDX1) is a transcription factor necessary for pancreatic development during embryogenesis and a maintainer of β cell function in adults[1, 2].
- Mice without functional PDX1 fail to develop a pancreas, while mice with lower than normal levels of PDX1 form a pancreas but show type II diabetes symptoms[1, 3].
- The PDX1 homeodomain is highly conserved, with 100% similarity between mouse and frog, and changes in this region can cause pancreatic agenesis in humans[2, 4].
- *Psammomys obesus* (fat sand rat) is a desert rodent that is prone to developing type II diabetes[5].
- We have located the sand rat *Pdx1* gene in a genomic region with elevated GC-levels, and we show that sand rat PDX1 has a highly divergent amino acid sequence[6].

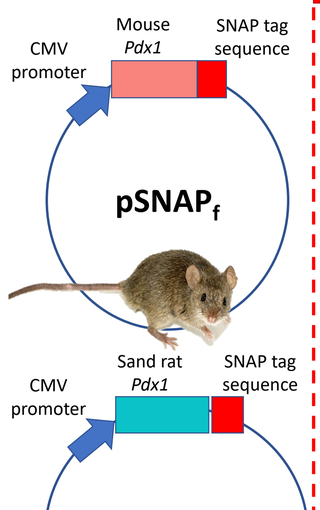
Result 1 The PDX1 homeodomain in gerbils is highly divergent

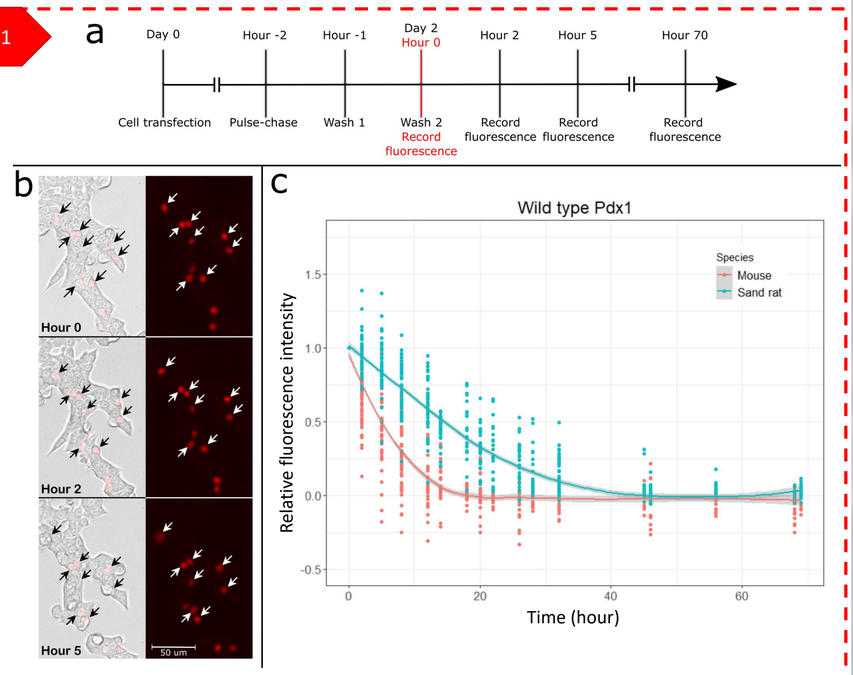


Questions

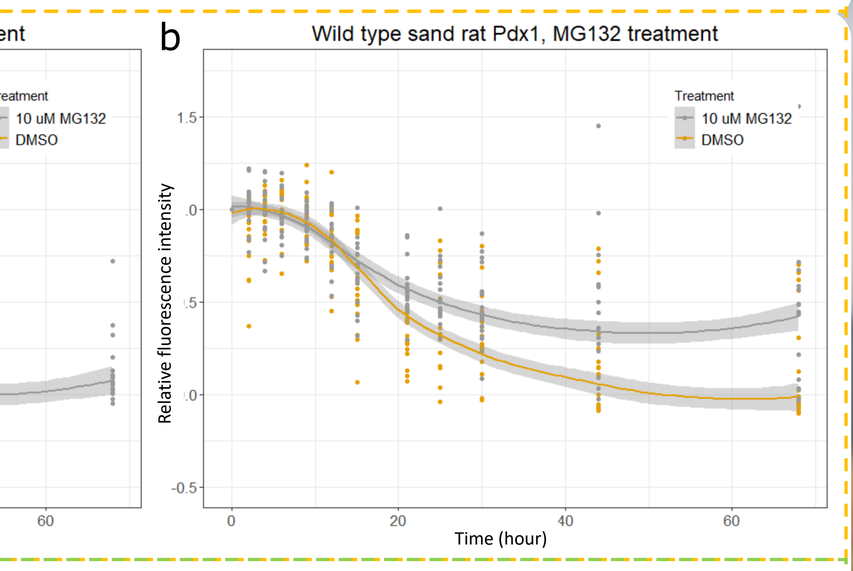
1. How does this affect the biochemical properties of gerbil PDX1?
2. How does this affect the biological function of gerbil PDX1?

Result 2 Due to loss of a conserved ubiquitination site in the homeodomain, gerbil PDX1 has a longer protein half-life

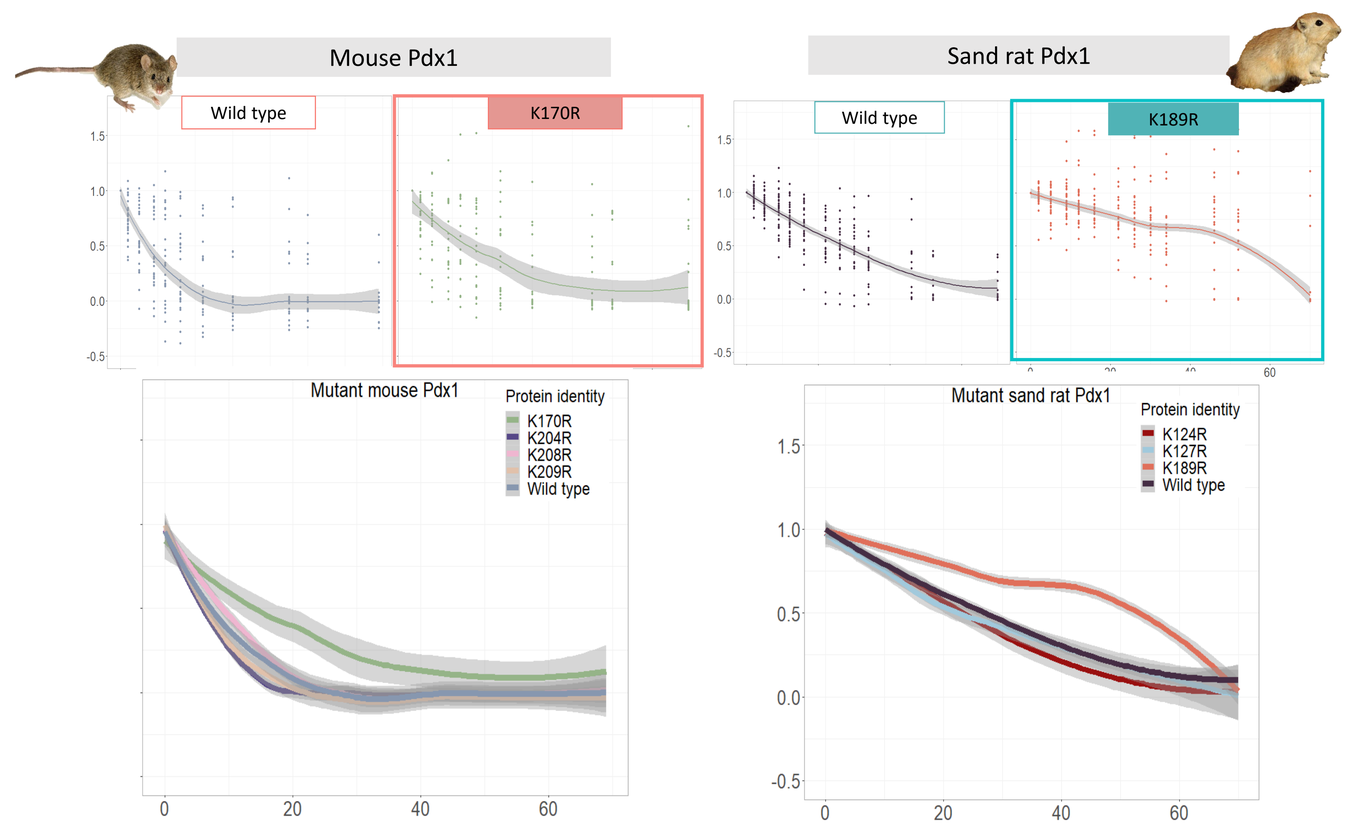




2 **MG-132**: a reversible inhibitor of the 26S proteasome. Cells were treated for 6 hours with MG-132



3 ***In vitro* mutagenesis**: point mutations are indicated in the homeodomain alignment shown in **Results 1**.

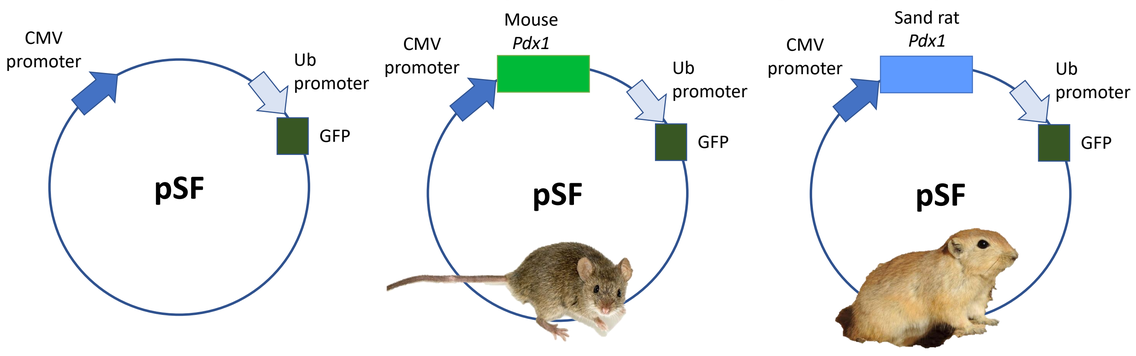


Protein without lysine cannot be degraded — **Conflict** — GC-skew removes codons for lysine (AAA, AAG)

Natural selection vs GC-skew

Sand rat PDX1 has only one ubiquitination site, and this site is inferred to be a compensation for loss of other ubiquitination sites due to GC-rich mutation.

Result 3 Sand rat PDX1 is less capable of stimulating *insulin* expression



Functional differences exist

Sand rat PDX1 is significantly worse at stimulating rat insulin gene expression under high glucose levels

Conclusions

- The sand rat has the most divergent *Pdx1* gene in the entire vertebrate lineage. We infer this affects the entire gerbil subfamily.
- The loss of ubiquitination sites in sand rat PDX1 shows the impact of GC-skew in the local genomic region, while the presence of a new, gerbil-specific ubiquitination site indicates natural selection fighting back to retain basic protein functionality
- Sand rat PDX1 is less capable of stimulating insulin expression under high glucose conditions.
- The reason for the divergence remains unknown. However, it is possible that this region in the gerbil genome is fragile and susceptible to DNA breaks, thus leading to accumulation of mutations in the genes in this region.

Meeting attendance sponsored by:

This work and my study in Oxford were funded by:
RHODES SCHOLARSHIP
UNIVERSITY OF OXFORD Department of Zoology
LEVERHULME TRUST

If you would like to read more about this work:

Dai, Y., & Holland, P. W. (2019). The interaction of natural selection and GC skew may drive the fast evolution of a sand rat homeobox gene. *Molecular biology and evolution*, **36**(7), 1473-1480.

References

1. U. Ahlgren, J. Jonsson, L. Jonsson, K. Simu, H. Edlund, *Gene Dev.* **12**, 1763-1768 (1998). 2. Offield, M. F. *et al.*, *Development* **122**, 983-995 (1996). 3. J. Jonsson, L. Carlsson, T. Edlund, H. Edlund, *Nature* **371**, 606-609 (1994). 4. V. M. Schwitzgebel *et al.*, *J. Clin. Endocrinol. Metab.* **88**, 4398-4406 (2003). 5. M. Y. Donath *et al.*, *Diabetes* **48**, 738-744 (1999). 6. A. D. Hargreaves *et al.*, *PNAS* **114**, 7677-7682 (2017).