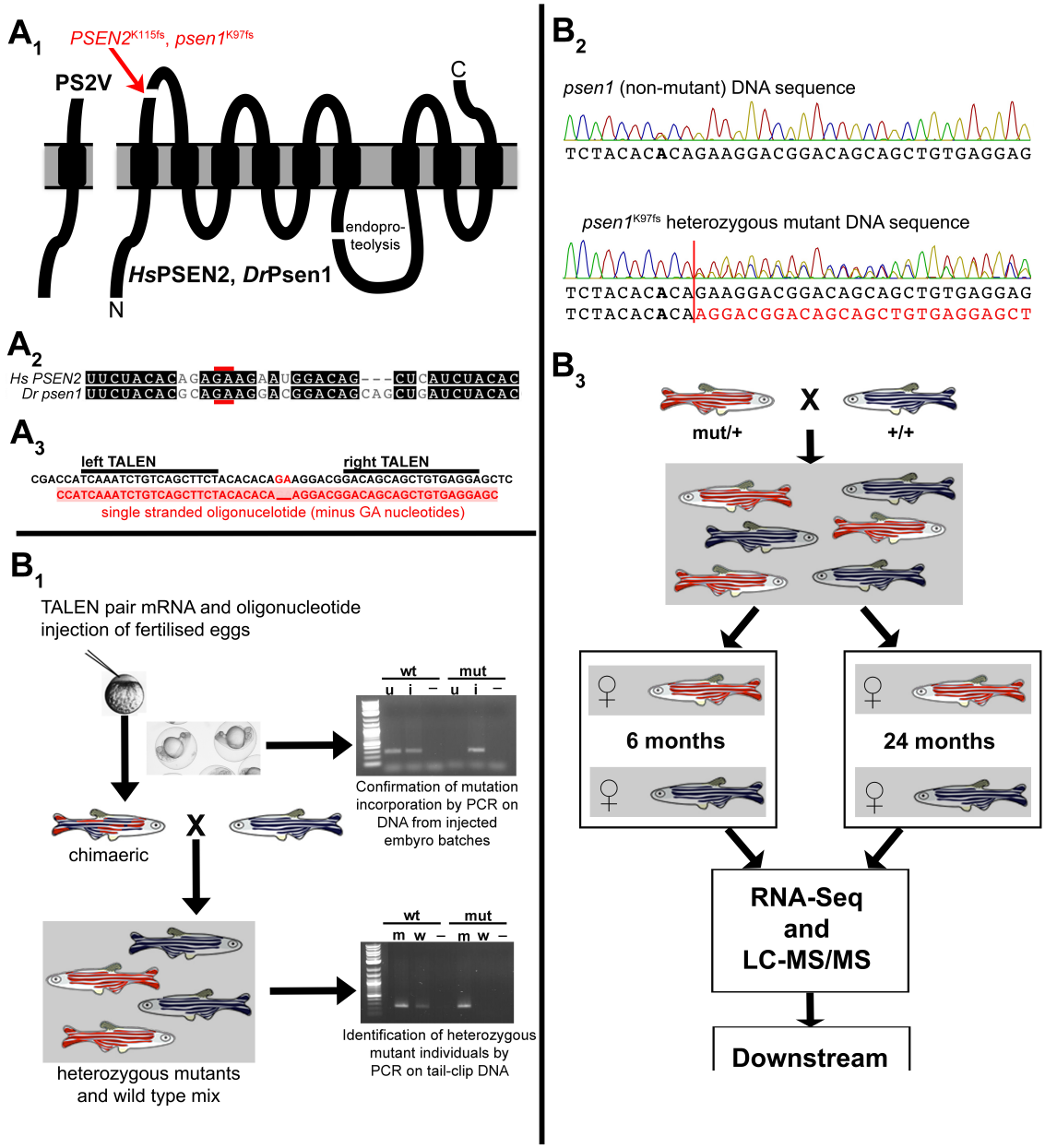
Supplementary Methods 1: Gene editing in zebrafish to produce the *psen1* K97fs mutation.



A1. PRESENILIN and PS2V protein structure. The lipid bilayer is shaded grey and the transmembrane domains are indicated by black ovals. The site of the *Homo sapiens* (*Hs*) *PSEN2* K115fs and *Danio rerio* (*Dr*) *psen1* K97fs mutation is indicated in red.

A2. A section of the *Hs PSEN2* and *Dr psen1* nucleotide alignment around the K115fs (K97fs) mutation site.

A3. Section of genomic Dr *psen1* sequence around the GA target site with TALEN binding sites indicated and the single stranded oligonucleotide sequence below.

B1. Flow diagram for creation of the *Psen1* K97fs heterozygous mutation model. Upper agarose gel image is of amplified genomic DNA from 24hpf uninjected (u) embryos, injected (i) embryos and water negative control (-).

PCR reactions containing either wild type (wt) detecting or mutation (mut) detecting primers. Lower agarose gel image is of amplified genomic DNA from adult tailclips from a wild type (w), a K97fs heterozygous germline mutant (m) and water negative control (-). The amplified DNAs are from PCR reactions containing either wild type (wt) detecting or mutation (mut) detecting primers.

B_2. Chromatographs of a section of genomic *psen1* sequence around the K97fs deletion site for wild type DNA and for K97fs heterozygous mutant DNA. Red sequence is the altered DNA sequence after GA dinucleotide deletion.

B_3. A K97fs heterozygous mutant (red stripes) was pair mated with a wild type (Tübingen) to produce a tank of fish that is ~1:1 mutant:non-mutant. At 6 months and 24 months of age, brains were removed from female K97fs heterozygous mutant adults and non-mutant adult siblings. Mutant and non-mutant brains were subjected to either RNAseq or LC-MS/MS procedures followed by downstream analysis of the data.