Supporting information

Fig. 1. ACDase cleaves ceramide more efficiently than galactosylceramide. ADCase is much less efficient at deacylating GalCer compared to ceramide (Cer). Ceramide is deacylated by ACDase at least 8-10 times more efficiently compared to galactosylceramide.

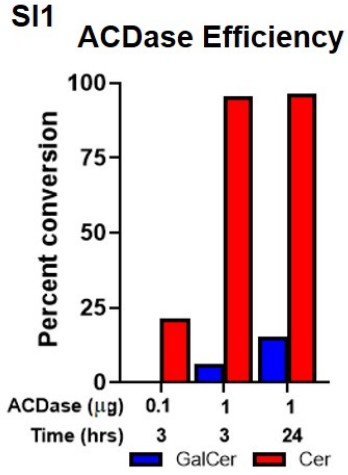
Fig. 2. Biochemically, Twi/FD mice and FD are indistinguishable at terminal age. (A) There is no psychosine accumulation in the brain, sciatic nerve, liver, or spleen of WT, FD or Twi/FD mice at a terminal time point. The Y axes in these graphs are drawn to the same scale as the y axes in Fig. 2 to facilitate comparison. Note: all of the Twi mice are dead at these time points. **(B)** There is no significant difference in the ceramide levels in the liver and spleen between terminal Twi/FD and FD mice. (* $p \leq 0.05$)

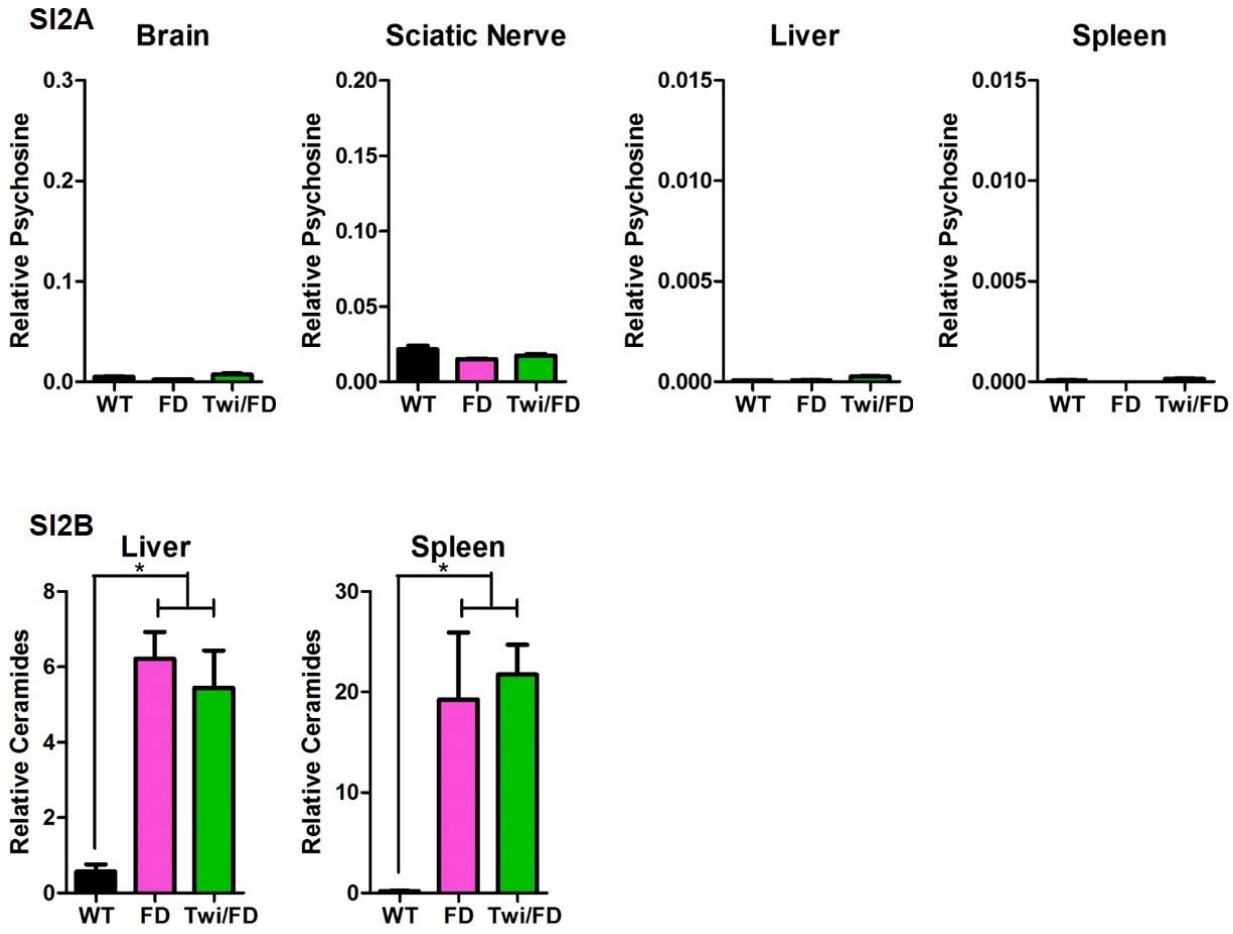
Fig. 3. Twi/FD mice and FD mice are indistinguishable hematologically and clinically at terminal time points. (A) At ~63 days, tremors of similar frequencies begin to develop in Twi/FD and FD mice. Motor impairments in **(B)** rotarod and **(C)** wirehang tests develop in FD and Twi/FD mice by ~63 days. **(D)** There is an apparent increase in circulating monocyte and neutrophil populations and a significant decrease in T cell populations at ~60 days of age in FD and Twi/FD mice compared to age-matched WT mice. Note: at ~36 days of age when Twi mice were available for comparison, there were no significant changes in the hematological parameters between any of the genotypes. **(E)** At terminal time points, there is an increase in diffuse and focal areas of activated microglia (CD68+, arrows) in FD and Twi/FD mice compared to 36 days of age. Mild structural degeneration with immune cell infiltration (arrows) is seen in FD and Twi/FD sciatic nerves at a terminal time point, but is less pronounced than 36 day-old Twi mice. **(F)** Sciatic nerve axon density trends lower in terminal FD and Twi/FD mice

relative to comparably aged WT mice, but the axon number has not decreased from 36 days of age (Fig. 3K). (ns $p > 0.05$, * $p \leq 0.05$, *** $p \leq 0.001$)

Supporting Information Figures

SI1

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Sciatic Nerve
Liver
Spleen
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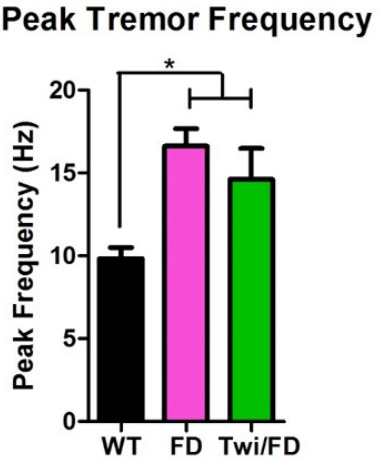
0.2
0.1
0.0
0.20
0.15
0.10
0.05
0.00
0.015
0.010
0.005
0.000
WT
FD
Twi/FD
SI2B
Liver
Spleen
Relative Ceramides
*
8
6
4
2
0
30
20
10

SI3A



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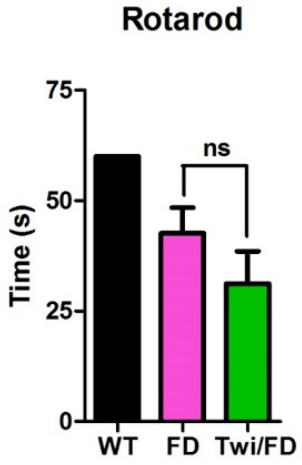

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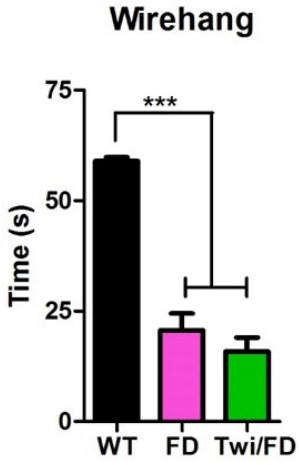

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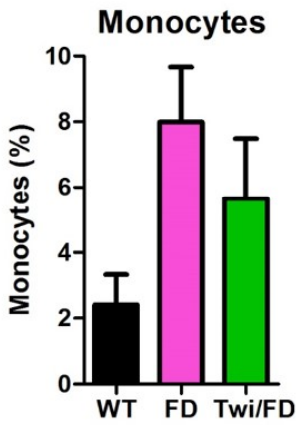

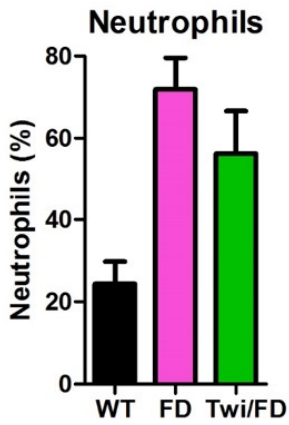

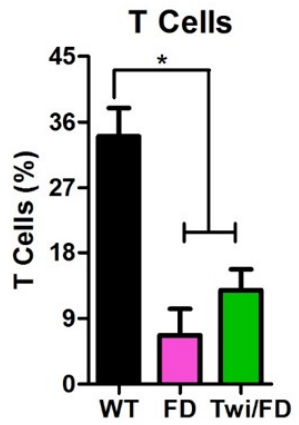

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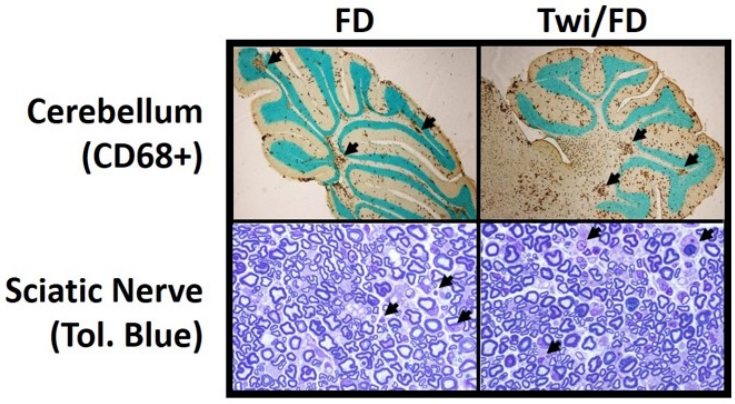
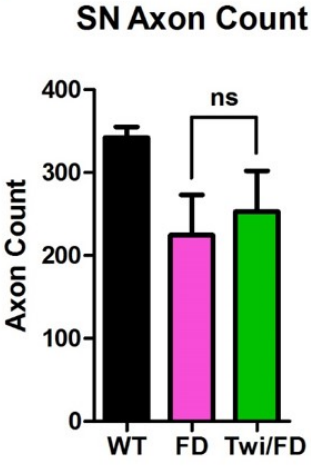
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