

Progress Report: NTSAD/CTSF Grant: Platt, Platt and Cerundolo - February 2012

The double knock out mice have been analysed and are surviving longer than the untreated Sandhoff mice. Deaths in the Sandhoff colony occurred from 13 weeks of age onwards where as no deaths in the SH/IL-1R $-/-$ mice occurred before 15 weeks of age. We have consolidated these findings and this observation has been reproducible following the analysis of more mice and both sexes. Functionally, the double knock out mice have improved coat condition and activity levels and reduced tremor (see Fig. 1).

We are currently building up the analysis of sufficient numbers of hexb $^{-/-}$ IL-1R $+/-$ mice (the main control group) to determine whether the benefits are due to loss of IL-1R or genetic background influences from the IL-1R deficient strain.

To date we have not had enough of these animals generated to allow robust statistical analysis and so we cannot draw definitive conclusions at the current time. However, we have now got permission from the Home Office to use affected young Sandhoff males in the breeding program so we should be able to get some litters with a high frequency of the control genotype we need (our breeding protocol prior to this amendment did not permit this).

Immunological and biochemical analysis of the double knock out mice is in progress. This and the analysis of the control genotype group (hexb $^{-/-}$ IL-1R $+/-$ mice) will run into the period beyond the official end of the grant and we therefore propose a no-cost extension of 6 months to complete the study. We will then submit a final report.

We are currently finalising an MTA to obtain an approved IL-1R antagonist mimetic that crosses the blood-brain barrier and will be trialled in the mice as a prelude to potential clinical trials in Tay-Sachs and Sandhoff disease patients. We are delighted to report that we have just received a one-year pump-priming grant from the John Fell Fund (University of Oxford) to trial the IL-1R antagonist mimetic in Sandhoff mice as a direct result of this NTSAD/ CTSF funded project.

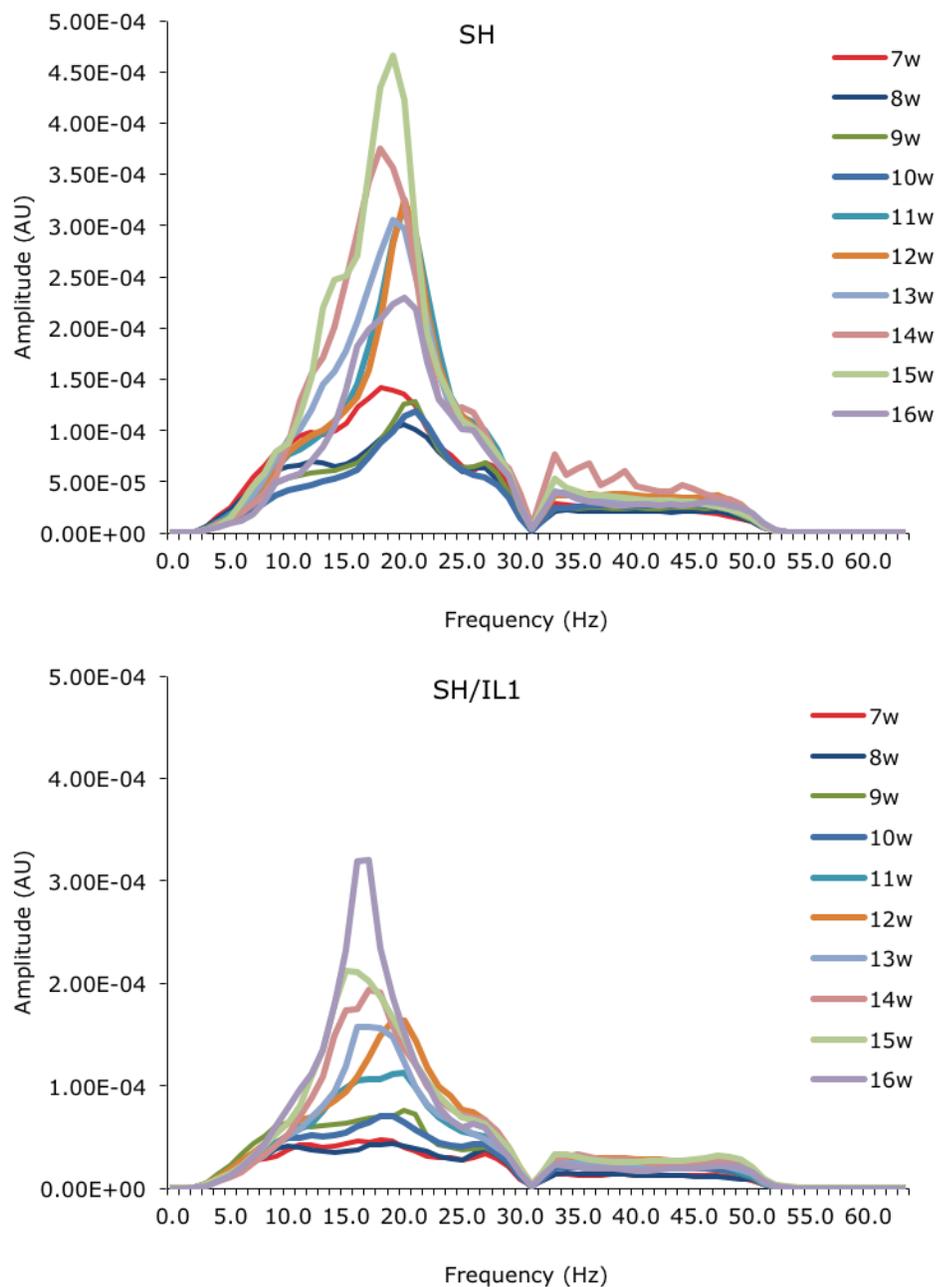


Fig. 1

Reduced Tremor amplitude in SH/Il-1R (SH/IL-1 lower panel) mice relative to Sandhoff mice (SH) (upper panel) from 7-16 weeks of age, monitored weekly using a commercial tremor monitor (San Diego Instruments)