# Parallel Neurochemical Alterations as measured by high field MRS in Patients and Mice with Spinocerebellar Ataxia Type 1 (SCA1)

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## Introduction

Spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of neurodegenerative diseases characterized by cerebellar Purkinje cell dysfunction and death which leads to loss of motor coordination (1). There are currently no treatments for these conditions. Successful development of such therapies will be facilitated by the availability of a faithful model of the human disease for pre-clinical trials. Spinocerebellar ataxia type 1 (SCA1) is an autosomal-dominant, polyglutamine disease for which a faithful mouse model exists. The *SCA1*[*82Q*] mice overexpress the mutant human ataxin-1 protein, reproduce the Purkinje cell pathology seen in patients and develop progressive ataxia similar to the human phenotype (2). Here we attempted to determine how similar neurochemical abnormalities as measured by high field MRS are in patients and model mice with the same genetic defect.

## Methods and Subjects

Eight patients with SCA1 (5 M / 3 F, average age ± SD: 54 ± 6 years) and 6 age-matched healthy volunteers (4 M / 2 F, 54 ± 8 years) were scanned at 4 tesla using a TEM volume coil (3). Spectra from the cerebellar hemispheres (4.9 mL volume) and vermis (6.2 mL volume) were acquired with an ultra-short echo STEAM (TE = 5 ms) sequence as described before (4). Subjects were also evaluated by a standardized ataxia rating scale, where a composite score of 117 denotes maximum deficit (5). For comparison to the patients, 7 *SCA1*[*82Q*] mice and 9 wild type controls (FVB background strain) were scanned at 9.4 tesla under 1.5 - 2% isoflurane anesthesia at 24 weeks of age with a quadrature surface coil. Spectra from the cerebellum (5 - 7 µL volumes) were acquired with a short echo (TE = 15 ms) localization by adiabatic selective refocusing (LASER) sequence (6). Metabolites were quantified with LCModel (7) using unsuppressed water as reference. Only results with Cramér-Rao lower bounds (CRLB) ≤ 50% were included in the analysis. Due to significant atrophy in patients, all concentrations were corrected for the amount of CSF present in each VOI.

## Results and Discussion

The higher spectral quality (SNR and resolution) achieved in the mice at 9.4T relative to humans at 4T (Fig. 1) enabled the reliable quantitation of a higher number of metabolites in mice. Eighteen metabolites were quantified reliably in mice and 11-12 metabolites in humans. Despite this difference, the alterations in some neurochemicals were remarkably similar in patients and the mutant mice. Namely, neuronal markers NAA and glutamate (Glu) were decreased and the putative gliosis marker *myo*-inositol (Ins) was increased in both mice and patients with SCA1 (Figs. 1, 2). These changes were even apparent in individual spectra (Fig. 1) and separated the patient and control groups with no overlap (Fig. 2). The scatter in the human data was higher as expected at the lower magnetic field strength, but also likely because the patients had more genetic and clinical variation. Thus, the polyglutamine repeat lengths of patients were in the range of 41 - 49 in the long allele (all mice had an 82 glutamine expansion) and their ataxia scores ranged from 18 - 47 (with 5 patients in the 34 - 36 range). Strikingly, the patient with the lowest ataxia score (18) also had NAA and Glu levels closest to controls (shown with an arrow in Fig. 2). On the other hand, the patient with the highest ataxia score (47) had one of the lowest NAA and Glu levels and the highest Ins level (marked with a star in Fig. 2).

These data demonstrate that findings regarding neurochemical changes as monitored by high field $^1$H MRS in future pre-clinical trials with SCA1 mice can be utilized for the design of clinical trials with patients. The data also emphasize the potential benefits of moving future human work to even higher magnetic fields.

### References

**1.** Taroni F & DiDonato S, *Nat Rev Neurosci*, 5: 641, 2004. **2**. Burright et al, *Cell*, 82: 937, 1995. **3.** Vaughan JT et al, *MRM*, 32: 206, 1994. **4.** Tkáč I et al., *Appl Magn Reson*, 29: 139, 2005. **5.** Subramony et al, *J Magn Reson*, 153: 155, 2001. **6.** Garwood & DelaBarre, *J Magn Reson*, 153: 155, 2001. **7.** Provencher SW, *MRM*, 30, 672, 1993.

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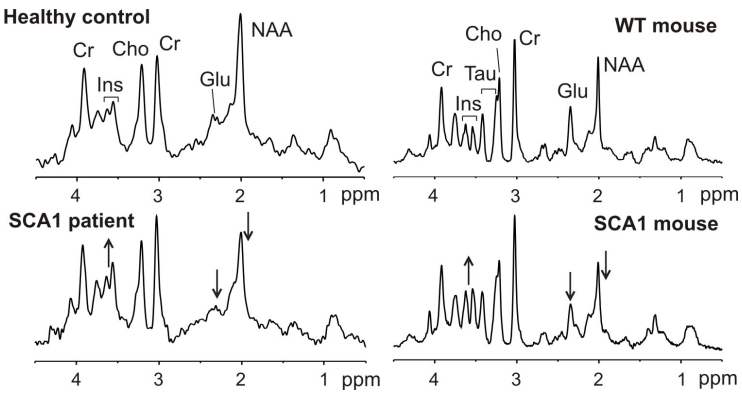


**Fig. 1.** $^1$H MRS spectra from an SCA1 patient, an SCA1 mouse and controls. Cr: creatine; Cho: choline; Tau: taurine; Glu: glutamate; NAA: N-acetylaspartate; Ins: *myo*-inositol. The changes in NAA, Ins and Glu with disease are marked with arrows. The human data were acquired from the cerebellar hemispheres.

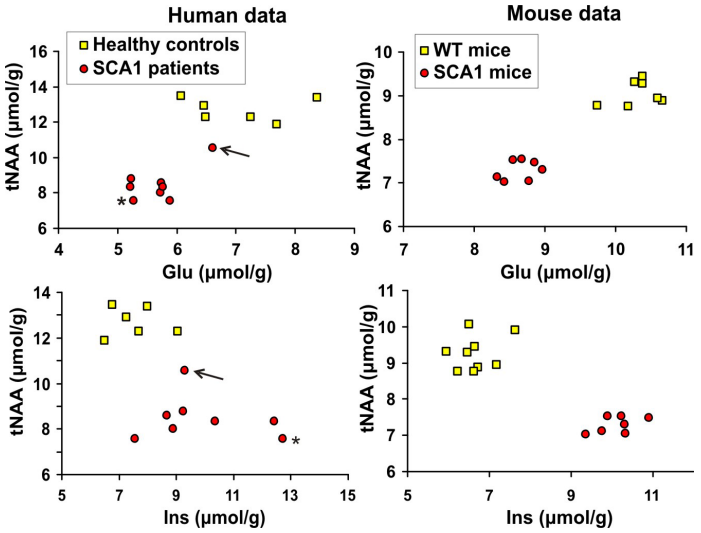


**Fig. 2.** Metabolite concentrations of human subjects (left) and mice (right). Each data point represents the neurochemical concentrations of an individual subject.