

## **NaS1 sulfate transporter, hyposulfataemia and autism**

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Sulfate is involved in many metabolic and cellular processes, and is essential for normal growth and development. Circulating sulfate levels are maintained by the NaS1 sulfate transporter, which is expressed in the kidney where it facilitates renal sulfate reabsorption. We generated NaS1 knock out (Nas1<sup>-/-</sup>) mice, which exhibit hyposulfataemia, reduced sulfonation capacity, seizures, gastrointestinal disturbances and behavioural abnormalities. A consistent autistic disorder (AD) susceptibility locus is on chromosome 7q31-33, which contains the NaS1 gene that we have cloned. Some AD patients have sulfonation defects, for which the aetiology is yet unknown. Due to phenotypic similarities between AD individuals and our Nas1<sup>-/-</sup> mice, the aims of this study were to explore the involvement of NaS1 and sulfate homeostasis in AD. We developed a highly specific assay for measuring sulfate, which we used to calculate the fractional excretion index (FEI) for sulfate (normal range 0.32-0.47) in a selected clinical cohort of children meeting autism diagnostic observation schedule (ADOS) criteria. FEI sulfate levels were increased (>0.50) in some of the autistic individuals, indicating reduced renal sulfate reabsorption. Sequence analysis of the NaS1 gene in these AD individuals revealed 2 single nucleotide polymorphisms, R12X and N174S, which lead to 100% and 60% loss of NaS1 function, respectively. These findings demonstrate that loss of NaS1 function is associated with hyposulfataemia in some autistic individuals. The significance of this study is relevant to humans with hyposulfataemia and prompts future assessment of autistic individuals with altered sulfate homeostasis.