Novel pathogenic mechanism suggested by ex vivo analysis of MCT8 (SLC16A2) mutations

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Monocarboxylate transporter 8 (MCT8; approved symbol SLC16A2) facilitates cellular uptake and efflux of 3,3?,5-triiodothyronine (T3). Mutations in MCT8 are associated with severe psychomotor retardation, high serum T3 and low 3,3?,5?-triiodothyronine (rT3) levels. Here we report three novel MCT8 mutations. Two subjects with the F501del mutation have mild psychomotor retardation with slightly elevated T3 and normal rT3 levels. T3 uptake was mildly affected in F501del fibroblasts and strongly decreased in fibroblasts from other MCT8 patients, while T3 efflux was always strongly reduced. Moreover, type 3 deiodinase activity was highly elevated in F501del fibroblasts, whereas it was reduced in fibroblasts from other MCT8 patients, probably reflecting parallel variation in cellular T3 content. Additionally, T3-responsive genes were markedly upregulated by T3 treatment in F501del fibroblasts but not in fibroblasts with other MCT8 mutations. In conclusion, mutations in MCT8 result in a decrea