Abstract:

Incorporation of selenocysteine (Sec), through recoding of the UGA stop codon, creates a unique class of proteins. Mice lacking tRNA(Sec) die in utero, but the in vivo role of other components involved in selenoprotein synthesis is unknown, and Sec incorporation defects have not been described in humans. Deiodinases (DIOs) are selenoproteins involved in thyroid hormone metabolism. We identified three of seven siblings with clinical evidence of abnormal thyroid hormone metabolism. Their fibroblasts showed decreased DIO2 enzymatic activity not linked to the DIO2 locus. Systematic linkage analysis of genes involved in DIO2 synthesis and degradation led to the identification of an inherited Sec incorporation defect, caused by a homozygous missense mutation in SECISBP2 (also called SBP2). An unrelated child with a similar phenotype was compound heterozygous with respect to mutations in SECISBP2. Because SBP2 is epistatic to selenoprotein synthesis, these defects had a generalized effect on selenoproteins. Incomplete loss of SBP2 function probably causes the mild phenotype.