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Inherited defects of thyroid hormone metabolism

Altérations héréditaires du métabolisme des hormones thyroïdiennes

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Résumé

Le métabolisme intracellulaire des hormones thyroïdiennes et la disponibilité en l'hormone active, la triiodothyronine, sont régulés par trois sélénoprotéines iodothyronine désiodases (Ds). Alors que les modifications acquises de l'activité des désiodases sont courantes, leurs altérations héréditaires n'ont pas encore été identifiées chez les humains. Le sélénium (Se) est un oligoélément essentiel indispensable pour la biosynthèse des sélénoprotéines et la *selenocysteine insertion sequence* (SECIS) *binding proteine* 2 (SBP2) représente un facteur clé de transactivation pour l'insertion de la sélénocystéine au sein des sélénoprotéines. En 2005, nous avons rapporté les premières mutations du gène *SBP2* dans les familles où les probants présentaient un retard de croissance transitoire, associé à des altérations des tests de la fonction thyroïdienne : baisse de triiodothyronine (T_3), augmentation de thyroxine (T_4) et de T3 inverse (rT_3) et léger accroissement de TSH. Les enfants atteints étaient soit homozygotes, soit hétérozygotes composites pour la mutation du gène *SBP2*; le phénotype relativement discret était lié à un déficit partiel de la protéine SBP2 affectant l'expression d'une sous-population de sélénoprotéines. Les études in vivo de ces sujets ont exploré les effets de la supplémentation en sélénoprotéines et en hormones thyroïdiennes. Les expérimentations in vitro ont apporté des informations nouvelles sur les effets des mutations de *SBP2*. Un phénotype plus large et plus complexe a été mis en lumière par l'identification ultérieure de trois nouveaux cas issus de différentes familles porteuses de mutations du gène *SBP2*. Ces mutations sont responsables d'un déficit sévère de SBP2 résultant d'une réduction de la synthèse de la plupart des 25 sélénoprotéines humaines identifiées. Dans cette revue, nous synthétisons la présentation clinique des mutations *SBP2*, leur effet sur la fonction de SBP2 et leurs conséquences délétères pour la synthèse et la fonction de la sélénoprotéine.

Mots clés : Désiodase ; Sélénoprotéine ; SBP2 ; Hormones thyroïdiennes ; Myopathie ; Retard de croissance ; Infertilité

Abstract

Intracellular metabolism of thyroid hormone and availability of the active hormone, triiodothyronine is regulated by three selenoprotein iodothyronine deiodinases (Ds). While acquired changes in D activities are common, inherited defects in humans have not been identified. Selenium (Se) is an essential trace element required for the biosynthesis of selenoproteins, and selenocysteine insertion sequence (SECIS) binding protein 2 (SBP2) represents a key trans-acting factor for the cotranslational insertion of selenocysteine into selenoproteins. In 2005 we reported the first mutations in the *SBP2* gene in two families in which the probands presented with transient growth retardation associated with abnormal thyroid function tests, low triiodothyronine (T_3), high thyroxine (T_4) and reverse T_3, and slightly elevated thyrotropin. Affected children were either homozygous or compound heterozygous for *SBP2* gene mutations and the relatively mild phenotype was due to partial SBP2 deficiency, affecting the expression of a subset of selenoproteins. In vivo studies of these subjects have explored the effects of Se and thyroid hormone supplementation. In vitro experiments have provided new insights into the effect of *SBP2* mutations. A broader and more complex phenotype was brought to light by the subsequent identification of three new cases from different families with *SBP2* gene mutations. These mutations caused a severe SBP2 deficiency resulting in reduced synthesis of most of the 25 known human selenoproteins. Here we summarize the clinical presentation of *SBP2* mutations, their effect on SBP2 function and downstream consequences for selenoprotein synthesis and function.

Keywords: Deiodinase; Selenoprotein; SBP2; Thyroid hormone; Myopathy; Growth delay; Infertility

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1. Selenoprotein synthesis

Selenoproteins contain the rare aminoacid selenocysteine (Sec) in their active center. Several factors are required for Sec incorporation: cis-acting sequences present in the mRNA of a selenoprotein (UGA codon and Sec insertion sequence, SECIS), and trans-acting factors (Sec-specific elongation factor [eEF^{Sec}]), Sec-specific tRNA^{Sec} and SECIS-binding protein (SECISBP2 or SBP2) [1]. However, the list of factors involved in this mechanism is constantly growing, the most recent members being the ribosomal protein L30 [2], the 43 KDa RNA binding protein (Secp43) and the soluble liver antigen protein (SLA) [3–5]. Using the SECIS element as bait, the rat SECIS binding protein, SBP2 was purified and cloned in 2000 [6].

The human selenoproteome comprises at least 25 individual selenoproteins [4,7]. Although the precise function of most selenoproteins is unknown, some characterized mammalian selenoproteins were found to serve as antioxidants or oxido-reductases (glutathione peroxidases [GPx] and thioredoxin reductases), in thyroid hormone metabolism (deiodinases, [Dio or D]), selenium transport and storage (selenoprotein P, SePP) and potential protein folding (Sep15, SelN, SelM, SelS). Some selenoproteins must have a crucial function as supported by the observation that removal of the tRNA^{Sec} gene is lethal to the embryo [8].

A distinct hierarchy exists in the synthesis of selenoproteins as the expression of individual selenoproteins is differentially affected by the cellular content in Se [3]. This may be due to changes in the distribution of the two isoforms of tRNA^{Sec} [3], mRNA degradation by nonsense-mediated decay [9] and preferential SECIS recognition by SBP2 [10,11].

2. Clinical presentation

A total of six families have been identified to harbor recessive *SBP2* gene mutations [12–15]. The probands of the initial three families were brought to clinical attention because of growth delay [12,13]. All three were boys ranging in age from six to 14.5 years. The proband of a fourth family was a 12-yr-old girl who presented with delayed bone maturation, congenital myopathy, impaired mental and motor coordination development and bilateral sensorineural loss [14]. In a fifth family, a male child, presented at age two years with progressive failure to thrive in infancy, followed by global developmental delay and short stature that prompted further investigation. Other features in this patient are an early diagnosis of eosinophilic colitis, fasting nonketotic hypoglycemia with low insulin levels requiring supplemental enteral nutrition, muscle weakness and mild bilateral high-frequency hearing loss [15].

The only adult with SBP2 deficiency is the proband of the sixth family, who presented at age 35 years with primary infertility, skin photosensitivity, fatigue, muscle weakness, and severe Raynaud disease (digital vasospasm), impaired hearing, and rotatory vertigo [15]. In childhood, both motor and speech developmental milestones were delayed, requiring speech therapy. Hearing problems persisted despite myringotomies for secretory otitis media at six years of age. Multiple additional features became obvious as he was advancing in age. He had difficulty walking and running in adolescence, with genu valgus and external rotation of the hip requiring orthotic footwear. At the age of 13 years, marked sun photosensitivity was noted with abnormal UV responses on phototesting. Pubertal development was normal, but at the age of 15 years, he developed unilateral testicular torsion requiring orchiectomy and fixation of the remaining testis. His final stature (1.67 m), though close to the mean parental height of 1.69 m, was in the ninth centile. The ethnic origins of the first three families are Bedouin from Saudi Arabia, Irish/Kenyan, and African from Ghana [12,13]. The three more recent families are one from Brazil and two from the UK [14,15].

Table 1
Reported *SBP2* mutations.

Family	SBP2 gene	SBP2 protein
A	R540Q homozygous	R540Q homozygous
B	K438X	Truncated, missing C-terminus
	IVS8ds+29G−>A	Alternative transcripts
C	R128X homozygous	Smaller SBP2 isoforms from downstream ATGs
Brazil	120 X	Smaller SBP2 isoforms from downstream ATGs
	R770X	Truncated, disrupted C-terminus
UK 1	c.668delT fs223 255X	Truncation and smaller SBP2 isoforms from downstream ATGs
	Intron 6–155 del C	Abnormal splicing, truncated, missing C-terminus
UK2	C691R	Increased proteasomal degradation
	? (intronic SNPs)	Transcripts lacking exons 2-4 or 3 and 4, smaller SBP2 isoforms from downstream ATGs

Some of the clinical features, in particular delayed growth and bone age, prompted thyroid function testing. All affected subjects were found to have unusual thyroid function test abnormalities, characterized by high serum thyroxine (T_4), low 3,3′, 5-triiodothyronine (T_3), high 3,3′, 5′-triiodothyronine (reverse T_3 or rT_3) and normal or slightly elevated thyrotropin (TSH) concentrations (Fig. 1). None of the subjects had an enlarged thyroid gland confirmed by ultrasound examinations.

3. *SBP2* mutations

Extensive in vivo and in vitro studies on the initial family allowed the identification of this new genetic defect [12]. This family of Bedouin origin from Saudi Arabia had seven children three of them being affected. Affected individuals required larger doses of levothyroxine (L-T_4) but not liothyronine (L-T_3) to suppress their serum TSH concentration, indicating a defect in iodothyronine metabolism. However co-segregation of the phenotype with the three deiodinases was excluded.

Skin fibroblasts demonstrated low deiodinase D2 enzymatic activity but normal mRNA content, reflecting a defect in this selenoenzyme synthesis. Affected subjects shared homozygous haplotypes at the *SBP2* locus and were found to be homozygous for R540Q mutation. Table 1 summarizes the ten *SBP2* gene defects identified so far.