Mutations of the Thyroxine-Binding Globulin Gene in Japanese

Thyroxine-binding globulin (TBG) is the major transport protein for thyroid hormones in circulation. It is synthesized in liver parenchymal cells as a 54-kDa glycoprotein containing 395 amino acids and 4 N-linked oligosaccharide residues. A single TBG gene is located on the long arm of X-chromosome, Xq22.2 (1, 2).

Inherited TBG variants have been divided into three major groups based on the concentration of TBG: excess, partial and complete deficiency. Analysis of TBG gene enabled clarification of the molecular basis for inherited TBG variants. In the Japanese population, complete TBG deficiency seems to be associated with only one mutation in the fifth exon of the TBG gene (3–6). The mutation is a single nucleotide deletion of the first base in the codon for amino acid 352 of the common type TBG (TBG-C), leading to a frame shift and premature termination. TBG partial deficiency in Japanese is also likely to be caused by only one mutation (3). The mutation is a single nucleotide substitution of the second base in the codon for amino acid 363 of the TBG-C, leading to the replacement of Pro with Leu (7). In vitro experiments expressing the cDNAs for TBG-C and TBG-PDJ revealed that the impairment of the intracellular transport of the variant TBGs was the main cause of the lack or reduced concentration (8, 9). The molecular mechanism leading to TBG excess has been clarified recently by Mori et al (10). They elegantly demonstrated that gene amplification is the cause for the excess in two Japanese families (10).

See also p 266.

Despite the detailed information on the molecular nature of variant TBGs in the Japanese population, the gene frequency for each TBG-variant has not been studied. Noguchi et al in this issue screened 1,589 male subjects undergoing a comprehensive health examination to evaluate the gene frequency for complete TBG deficiency (11). First screening was based on the high T3 resin uptake in subjects with complete TBG deficiency. The screening was followed by the direct determination of TBG concentration in serum together with detection of the TBG-CDJ mutation using primer-directed mutagenesis. It was demonstrated that three subjects with a TBG concentration of less than 5 mg/l harbored the mutation. The frequency of TBG-CDJ in Japanese was calculated to be 0.09% which was equivalent to that found in neonatal screening of the Japanese (1:1,200 to 1:1,900) (12, 13). Albeit small in number, this was the first gene screening of TBG-CDJ in the Japanese population.

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References