An investigation into the D727E polymorphism in the TSH receptor gene in patients with congenital hypothyroidism

Maslinda Musa, Fatimah Harun and Sarni Mat Junit

Departments of 1Molecular Medicine and 2Paediatrics, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur.

Received 31 Jan 2008 / Accepted 28 July 2008

Abstract. We had recently detected the germline D727E polymorphism of the thyroid-stimulating receptor (TSHR) gene in a cohort of patients with congenital hypothyroidism (CH). The role of TSHR genetic variants in CH has not been well studied. This study investigated the possible relationship between the polymorphism and CH in these patients. We studied 104 normal subjects as control and 33 patients with CH. A PCR-RFLP analysis was used to identify the mutation. There was no significant difference in either the genotype distribution or allelic frequencies between total CH and total controls for the D727E polymorphism (P=0.348 and 0.222 respectively). The controls and the patients with CH were further subdivided into 3 groups according to their ethnicities: Malay, Chinese and Indian. There were no significant differences in the D727E polymorphism genotype distribution between 1) the Malay patients with CH and the Malay normal healthy controls (P=0.442); 2) the Chinese patients with CH and the Chinese healthy controls (P=0.410) and 3) the Indian patients with CH and the Indian healthy controls (P=0.433). In addition, there were also no significant differences of the frequency of the C allele between 1) the Malay patients with CH and the Malay healthy controls (P=0.251) the Chinese patients with CH and the Chinese healthy controls (P=0.251). However, we found that the C allele for the D727E polymorphism was significantly more common in the Indian patients with CH as compared to the Indian healthy controls (P=0.03). These findings suggest that in this cohort of CH patients, the D727E polymorphism of the TSHR gene is a predisposing genetic factor for the development of CH in the Indian but not in the Malay and Chinese.

Keywords: D727E polymorphism, Congenital hypothyroidism, TSH receptor, Asian population

INTRODUCTION

Thyroid gland synthesizes and secretes 2 main hormones, thyroxine (T4) and triiodothyronine (T3). The amount of the thyroid hormones synthesized by the thyroid gland is dependent on a sufficient intake of iodine and on stimulation of the gland by thyroid stimulating hormone (TSH) from the pituitary gland. TSH binds to its receptor, the thyroid stimulating hormone receptor (TSHR). This interaction leads to activation of second messenger pathways involving cAMP, inositol 1, 4, 5-triphosphate and diacylglycerol (DG) (Jackson, 1982; Saladinski et al., 2002) leading to production and secretion of T3 and T4.

Deficiency in T4 production results in hypothyroidism. Hypothyroidism in the neonates is known as congenital hypothyroidism (CH). Primary hypothyroidism refers to disorders of the thyroid gland whereas that due to disorders of the hypothalamus as secondary hypothyroidism. Excessive production of T3 leads to hyperthyroidism. The most common cause is Grave's disease, an autoimmune disorder that may be accompanied by enlargement of the thyroid gland (goiter) (Whitley, 1999). Others include toxic multinodular goiter.

Primary CH affects approximately 1 in 3500 newborns (Toublanc, 1992). Babies born with CH have low thyroid hormones primarily due to thyroid gland dysgenesis (absence/abnormal location) or thyroid dyshormonogenesis. Babies born with CH appear normal at birth but if they are not treated early, within the first few weeks of life, they may develop irreversible mental retardation.

Mutation in the TSHR gene is the most frequently reported cause of CH in patients with either thyroid dysgenesis (Biebermann et al., 1997; Tonascera et al., 2000; Nagashima et al., 2001; Abramowicz et al., 1997; Alberti et al., 2002; Toscano et al., 1999; Gagne et al., 1998) and dyshormonogenesis (de Roux et al., 1996; Clifton-Bligh et al., 1997; Sunthornthepvanakul et al., 1995; Onigata et al., 2003; Jordan et al., 2003). The presence of the germline polymorphism

*Author for Correspondence.
Mailing address: Department of Molecular Medicine, University of Malaya 50603, Kuala Lumpur, Malaysia. Tel: 603-79674718/7535; Fax: 603-79674957; Email: sarni@um.edu.my