ABSTRACT

Contribution of thyroid biosynthesis pathway genes in the etiology of Down syndrome

Trisomy of the human chromosome 21, detected in patients with Down syndrome (DS), is the most frequent cause for intellectual disability, although trisomy 21 does not answer all the DS related phenotypic attributes. Subjects with DS frequently have thyroid dysfunction while being at a greater risk of developing leukemia. On the other hand, solid tumors especially breast cancer (BC) is rare. Proper thyroid function is essential for normal growth, brain development, basal metabolic rate, neuronal activity etc. and BC patients often exhibit altered thyroid functions. Based on these observations, it was hypothesized that lower occurrence of BC in DS could be influenced by the thyroid hormone (TH) and role of SNPs in thyroid biosynthesis pathway genes (TRH, TSHB, TSHR, NIS, TPO & TG) were investigated in 183 unrelated nuclear families with DS probands, 100 BC patients and 225 ethnically matched healthy individuals after obtaining informed written consent for participation. Genomic DNA was isolated from the peripheral blood and genotyping was done using RFLP/DNA sequencing techniques. Out of 111 SNPs studied, only 11 functional SNPs were found to be polymorphic in the studied population. Data obtained was subjected to population-based as well as family-based statistical analysis. TRH rs13097335 ‘G’ allele showed significant lower occurrence in the BC population as compared to the female control and was paternally over transmitted to the female DS probands, thus indicating a possible role in conferring protection to BC. TSHR variants, rs2075178 & rs2075179 showed significant association in the male DS probands and BC. These sites were revealed to be splicing modulators of TSH receptor and thus could play important role in DS related thyroid abnormalities as well as BC. TPO rs1126799 ‘C’ allele was preferentially transmitted from parents to DS probands and was present in the best interactive models of different study groups. Significant synergistic interactions between the studied variants were absent, except in the father of DS. It may be inferred that the TH biosynthesis pathway genes, mainly TRH and TSHR, regulating level of TH, have a sexually dimorphic regulatory role in the etiology of DS and BC, warranting further in depth investigation.