Risk factors and biomarkers for Graves’ Disease and associated Graves’ Ophthalmopathy

Half-time review
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**Background:** Thyroid hormones tri-iodothyronine (T3) and thyroxine (T4) are produced in the thyroid follicles. Iodothyronine deiodinase II (DIO2) generates the active form of the thyroid hormone T3 by de-iodination of T4. Graves’ disease (GD) is an autoimmune disease caused by stimulating autoantibodies against the thyroid stimulating hormone receptor (TSHR) on thyroid follicular cells. GD is caused by interplay of genetic, environmental and endogeneous factors. Approximately 1/3 of the patients with GD develop symptoms and signs of Graves’ ophthalmopathy (GO). The strongest risk factor for developing GO is smoking. Suggested autoantigens in GO are TSHR and insulin-like growth factor-1 receptor (IGF-1R). The pathogenesis of GO includes inflammation and adipogenesis processes. Immediate early genes (IEGs) are mitogen responsive genes that rapidly, within 30-60 minutes, triggers the transcription cascade leading to the mature adipocytes. Cysteine-rich angiogenic inducer 61 (CYR61) is an IEG, which has been reported to be involved in inflammatory diseases. CYR61 is a multifunctional gene involved in many processes such as, inflammation, adipogenesis, cell proliferation and fibrosis. Hence several mechanisms by which it could be contributing to the pathogenesis of GO.

**Methods:** Study I: Seven SNPs in the DIO2 gene were studied to assess their association with GD and GO. Study II: Gene expression in intraorbital fat was studied in (n = 15) and nonsmokers (n = 12) with severe active GO using microarray and quantitative polymerase chain reaction (qPCR). Study III: 3T3-L1 preadipocytes and orbital fibroblasts were exposed to cigarette smoke extract (CSE) and treated with simvastatin. Gene expression in IEGs and late adipogenic genes was studied using qPCR.

**Results:** Study I: rs225011 in DIO2 was significantly associated with GD, no association with GO was found. Study II: IEGs were significantly higher expressed in smokers compared to nonsmokers. Study III: IEGs expression was induced by CSE alone, and could be downregulated by simvastatin. Late adipogenic genes were also downregulated by simvastatin.

**Conclusions:** Study I Further studies are necessary for an explanation on the mechanism behind the association. The findings in study II and study III underlines the importance of IEGs in the pathogenesis of GO and provides evidence for simvastatin as possible future treatment for GO.

**Published scientific articles:**


Shahida B, Planck T, Åsman P, Lantz M 2018, Study of Deiodinase Type 2 Polymorphisms in Graves’ Disease and Ophthalmopathy in a Swedish Population, European Thyroid Journal

**Manuscripts:**

B Shahida, P Sahlstrand Jonson, R Jain, H Brorson P Åsman, T Planck*, M Lantz*, Effects of simvastatin on cigarette smoke induced mRNA expression in 3T3-L1 preadipocytes and orbital fibroblasts from patients with Graves’ ophthalmopathy, Submitted August 2018, Thyroid: official journal of the American Thyroid Association