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The *HABP2* G534E variant is an unlikely cause of familial non-medullary thyroid cancer

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ABSTRACT

Context: A recent study reported the non-synonymous G534E (rs7080536, allele A) variant in the *HABP2* gene as causal in familial non-medullary thyroid cancer (NMTC).

Objective: The objective of this study was to evaluate the causality of *HABP2* G534E in the TCUKIN study, a multi-center population based study of NMTC cases from the British Isles.

Design and setting: A case-control analysis of rs7080536 genotypes was performed using 2,105 TCUKIN cases and 5,172 UK controls.

Participants: Cases comprised 2,105 NMTC cases. Patients sub-groups with papillary (N=1,056), follicular (N=691) and Hurthle cell (N=86) TC cases were studied separately. Controls comprised 5,172 individuals from the 1958 Birth Cohort (58C) and the National Blood Donor Service (NBS) study. The controls had previously been genotyped using genome-wide SNP arrays by the Wellcome Trust Case Control Consortium study.

Outcome Measures: Association between *HABP2* G534E (rs7080536A) and NMTC risk was evaluated using logistic regression.

Results: The frequency of *HABP2* G534E was 4.2% in cases and 4.6% in controls. We did not detect an association between this variant and NMTC risk (OR=0.896, 95% CI: 0.746-1.071, P=0.233). We also failed to detect an association between *HABP2* G534E and cases with papillary (1056 cases, G534E frequency= 3.5%, OR=0.74, P=0.017), follicular (691 cases, G534E frequency= 4.7%, OR=1.00, P=1.000) or Hurthle cell (86 cases, G534E frequency= 6.3%, OR=1.40, P=0.279) histology.

Conclusions: We found that *HABP2* G534E is a low-to-moderate frequency variant in the British Isles and failed to detect an association with NMTC risk, independent of histological type. Hence, our study does not implicate *HABP2* G534E or a correlated polymorphism in familial NMTC and additional data are required before using this variant in NMTC risk assessment.

INTRODUCTION

Non-medullary thyroid cancer (NMTC) is the most common endocrine malignancy. As incidence rates are growing at an annual 5% in the U.S. (1), this malignancy will soon become the third most commonly diagnosed cancer among American women and is now the second most common cancer among U.S. Hispanic women (1-3). NMTC is also one of the few cancer types for which a genetic risk is higher than the risk conferred by lifestyle and environmental exposures (4). Genome-wide association (GWA) and candidate studies have identified low penetrance NMTC variants on chromosomes 9q22, 14q13, 2q35, 8p12, 8q24 and 14q13 (5-8) while linkage studies of familial NMTC have suggested that genomic regions on 1q21, 2q21 and 19p13 harbor highly penetrant variants (9-11), although no causal mutations have been identified conclusively in the latter regions.

In a recent study, Gara *et al (12)* identified a missense variant (G534E or rs7080536 allele A, rs7080536A) in the *HABP2* gene, on chromosome 10q25, that showed complete co-segregation in an kindred of seven affected NMTC cases from unknown ethnicity including six with a papillary histology and one with a follicular adenoma. After several functional experiments, which included enhanced colony formation and increased cell migration and reporting a significant frequency difference, at $p<0.001$ between the data from the thyroid cancer TCGA study and a "multi-ethnic" database, the authors concluded that *HABP2* G534E was causal of familial NMTC. The *HABP2* gene was identified as a plasma-hyaluronan-binding protein with serine protease activity that plays a role in coagulation and fibrinolysis (13-15). The *HABP2* G534E variant is also known as Marburgh I polymorphism, which has shown to reduce *HABP2* activity (16) and which has been implicated as a risk factor in cardiovascular diseases (17), in progression of carotid stenosis (18) and in venous thromboembolism in some but not all studies (19,20). Gara *et al* thus suggested a new role for *HABP2* as a familial NMTC gene, a finding that could be of potential great importance for risk assessment and for personalized prevention and treatment of this increasingly common malignancy. Intrigued by the potential importance of *HABP2* G534E for NMTC risk, we decided to investigate this variant in a large multi-center population-based study of NMTC in the British Isles (21,22).

MATERIALS AND METHODS

Study Samples

2,105 NMTC cases were recruited through a multi-center Thyroid Cancer genetics UK and Ireland (TCUKIN) study (21,22). All cases had histologically confirmed NMTC and were of northern European ancestry. After completion of a brief questionnaire, cases donated ~10ml of blood for DNA isolation. The Southampton and South West Hampshire Research Ethics Committee approved the TCUKIN research protocol. For the present study, we also used previously published genotype data from 5,172 UK population controls, which included 2,673 participants in the 1958 Birth Cohort and (58C) and 2,499 donors of the National Blood Donor Service (NBS) (21).

Genotyping

All cases were genotyped for *HABP2* G534E/rs7080536A using KASP chemistry (LGC genomics, UK) following the manufacturer's protocol (genotyping probes are shown in Supplemental Table 1). Two of the *HABP2* G534E homozygous and two of the heterozygous cases detected by KASP genotyping were verified by Sanger sequencing (Supplemental Figure 1). Call rates for genotyping were >99%; concordance between KASP genotyping and Sanger sequencing was 100% and the visual inspection of the genotype clusters did not reveal obvious technical issue. *HABP2* G534E/rs7080536A was in Hardy Weinberg equilibrium in both cases and controls (data not shown).

Statistical analysis

Association testing: Logistic regression methods implemented in PLINK (23) and R (24) were used to obtain association statistics (odd ratios, ORs, and two sided P-values) as reported previously (21,22). We also carried out case-control and case-only analyses between *HABP2* G534E and clinical characteristics

including age of onset and histological subtype (available in 1,833 cases). These analyses were carried out using the chi-square test and R.

Haplotype analysis In order to investigate the origin of the *HABP2* G534E variant, we genotyped four *HABP2* G534E homozygous and 18 heterozygous carriers at four closely linked SNPs (rs10787491, rs932650, rs10885478 and rs1885434), which covered a 6kb region (chr10:113,584,808-113,590,838) centered around *HABP2* G534E. Haplotype reconstruction was carried out using Haploview (25).

RESULTS

Association between *HABP2* G534E and NMTC risk

We genotyped 2,105 cases from the British Isles for the *HABP2* G534E variant and used publically available genotype data from 5,172 population matched controls as reported before (21,22,26-28). Allele counts, odds ratios and two sided allelic P values are shown in Table 1. The population frequency of *HABP2* G534E was found to be 4.6%, which suggest that this is a low-to-moderate frequency variation in the general population of the British Isles. As shown in Table 1, *HABP2* G534E was more common in controls than in cases and we failed to detect a significant association between this variant and NMTC risk in our study (OR=0.896, 95% CI: 0.746-1.071, P=0.233, Table 1) despite having considerable statistical power to detect variants associated with the expected familial effect of *HABP2* G534E (not shown).

Association between *HABP2* G534E and histological subtype and age of diagnosis

Histologically, NMTC can be divided into main subtypes: Papillary TC (PTC), the most common subtype which accounts for ~80% of all the cases and follicular TC (FTC), which accounts ~10-20% of cases (29,30) and also includes cases with follicular variant histology (30). Hurthle cell carcinoma is also a rare histological subtype commonly found in NMTC families (31). In our study, we evaluated the association

between the *HABP2* G534E and these three NMTC subtypes. As shown in Table 2, we failed to detect significant associations between *HABP2* G534E and increased risk of any of the three NMTC subtypes tested in our study. Unexpectedly, we detected a protective effect of this variant in PTC (P=0.017, OR=0.74, Table 2) which further disagrees with Gara *et al* findings. Next, we examined if the *HABP2* G534E heterozygotes or homozygotes had an earlier age of onset as the expectation for highly penetrant mutations is an anticipation of the disease. We did not detect differences in *HABP2* G534E carriers and non-carriers in our study (average age for heterozygous = 48.3years, G534E homozygous = 46.2years, non-carriers = 46.7years, P>0.273 for all comparisons, Table 3). Therefore, the stratification of our study by histological type and age of onset also failed to detect an effect of *HABP2* G534E on NMTC risk.

Haplotype analysis

An intriguing possibility that could explain our failure to replicate Gara *et al's* findings is that *HABP2* G534 could have multiple independent origins and that one of the *HABP2* G534 bearing haplotypes could have a second cryptic casual mutation in a second gene in the same region for NMTC. To assess whether *HABP2* G534 had single or multiple origins, we evaluated closely linked markers in the region. Table 4 shows the haplotypes reconstructed in the 22 individuals (4 homozygous and 18 heterozygous) with this variant in our study. We found that all *HABP2* G534E carriers shared the same 2.5kb core haplotype defined by three markers (*HABP2* G534E/rs7080536A, rs10885478G, rs1885434G, Table 4). This finding is important because it suggests that the G534E allele has a single origin as it only happens in a unique haplotype.

DISCUSSION

NMTC is the most common endocrine malignancy and one of the few cancers where the variance in the risk explained by a genetic predisposition (53%) is more important than the risk explained by lifestyle, the environment or chance (32). Although several regions harboring highly penetrant NMTC variants have

been identified so far, no mutated genes have been conclusively found in such regions (5-11). Only the recent study by Gara *et al* reported *HABP2* G534E as a causal variant in an NMTC family. As these findings can have potentially important implications in NMTC risk assessment and management, we investigated the role of this *HABP2* variant in our large population-based study but failed to confirm a causal role of *HABP2* G534E in NMTC.

The frequency of *HABP2* G534E has been reported to range from 1.6% to 4.3% in European populations (33). Our study confirmed these previous findings as we observed a population frequency of 4.6% in the British Isles controls. Our data are also consistent with a previous British study on cardiovascular disease where *HABP2* G534E population frequency was found to be 4.3% (17). We can therefore conclude that *HABP2* G534E is a low-to-moderate frequency variant that segregates in populations of European ancestry. This finding may explain why Gara *et al* reported a frequency of ~4% in cases from the NMTC TCGA study, most of whom were likely to be white/European Americans (30). As a control group, Gara *et al* used data from a "multi-ethnic database" where *HABP2* G534E frequency was ~0.07%. This database was most likely the 1000 Genomes Study, which contains populations of both European and non-European ancestry and where *HABP2* G534E frequencies are affected by the very different ancestries in the sample. Thus, the significant P-value reported by Gara *et al* could have been the result of population stratification rather than that of an association with the disease. The population frequency analyses from our study therefore suggest that *HABP2* G534E is a low-to-moderate frequency variant that is highly unlikely to be a highly penetrant, cancer-causing mutation. This conclusion is further supported by our association analyses, where we failed to detect associations between *HABP2* G534E and increased NMTC risk using both case-control and cases-only analyses, showing that it is not even a low-penetrance thyroid cancer gene. Although we cannot exclude the possibility that the G534E variant reported as causal in the Gara *et al* study resides in a very rare haplotype harboring additional cryptic mutations that cause NMTC, our haplotype analyses suggested a single origin of this variant in populations of European

ancestry. While further haplotype analyses should also be carried out in Gara *et al*'s family, our finding of a single haplotype does not support the notion of multiple independent origins of G534E.

In summary, our study suggests that *HABP2* G534E is very unlikely to cause familial NMTC. At the population level, we also found that this variant does not increase NMTC risk. We therefore suggest that careful replication studies should be performed and great caution should be taken when assessing NMTC risk among carriers of any *HABP2* variant.

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