

**Conclusion:** HNF4A gene encodes hepatocyte nuclear factor-4-alpha that regulates hepatic gluconeogenesis and lipid metabolism. Dominant inactivating variants in HNF4A gene associated with familial HI, are typically associated with increased size for gestational age, mild diazoxide-responsive hypoglycemia (which may be transient) and monogenic diabetes during adolescence. HNF4A mutations were described as one of the most common genetic cause of diazoxide-responsive congenital hyperinsulinism and are associated with MODY1. It is important to consider genetic evaluation in diazoxide responsive HI cases. Identifying children with HNF4A variant early on will impact their long-term follow-up leading to earlier diagnosis and treatment of MODY-1 and potentially improve long-term outcomes.

## Thyroid

### THYROID NEOPLASIA AND CANCER

#### *Influence of Lymphocytic Thyroiditis at Histology and Serum Thyroglobulin Autoantibodies on the Course of Papillary Thyroid Carcinoma*

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#### MON-495

**PURPOSE** Papillary thyroid carcinoma (PTC) is frequently associated with diffuse lymphocytic thyroiditis (LT) at histology and serum autoantibodies to thyroglobulin (TgAb) and to thyroperoxidase (TPOAb). The influence of LT and thyroid autoantibodies on the prognosis of PTC is debated. We evaluated the clinical course of a large group of PTC patients according to the presence or absence of LT (LT+ and LT-) and thyroid autoantibodies. **METHODS** We evaluated 194 consecutive and non-selected PTC patients treated with total thyroidectomy plus <sup>131</sup>I ablation between 2007 and 2009, followed for 7.2 years (mean). 72 patients had follicular variant of PTC, 97 classic, 16 tall cells and the remaining 9 others variants (solid or oxyphilic cells). LT was diagnosed in presence of >10 lymphocytes/field (40x). At the time of ablation, all patients underwent measurement of Tg, TgAb and TPOAb, neck ultrasound and whole body scan. After ablation, patients underwent Tg (Beckman Coulter), TgAb and TPOAb (Tosoh) measurement and neck ultrasound (associated with other imaging if required) every 6-12 months. PTC was considered in remission according to the following criteria: un-stimulated Tg <0.2 ng/mL or stimulated Tg <1 ng/mL with TgAb <8 IU/mL and no evidence of structural disease. PTC was considered as persistent when un-stimulated Tg was ≥0.2 ng/mL or stimulated Tg was ≥1 ng/mL, or when TgAb were ≥8 IU/mL, or there was evidence of structural disease. **RESULTS** LT was found in 47% of patients, with a F/M ratio of 6.6/1, and

was associated with a hypoechoic pattern at thyroid ultrasound (p = 0.05). At the end of follow-up 44/194 (22.7%) had persistent disease. Among them, 17/72 (23.6%) were follicular, 19/97 (19.6%) classic, 6/16 (37.5%) tall cells and 2/9 (22.2%) other variants. The time to remission was longer in the LT+ compared to the LT- patients (19.5 vs 7.5 months) (median) (p <0.001), in TgAb positive compared to TgAb negative patients (28.5 vs 7.5 months) (p <0.001) and in TPOAb positive compared to TPOAb negative patients (28.0 vs 8.0 months) (p = 0.005). At multivariate analysis TgAb were the only independent factor influencing the time to remission (0.54; 0.35-0.83; HR and confidence interval) (p = 0.001). However, evaluating only the 111 TgAb negative patients, the time to remission (undetectable un-stimulated or stimulated Tg and no evidence of structural disease) was similar in the LT+ and LT- groups (8.0 months for both). At variance, in 83 TgAb positive patients the time to remission was longer in LT+ than in LT- patients (29.3 vs 13.0 months) (p=0.01). **CONCLUSIONS** The time to remission is longer in LT+ compared to LT- PTC patients treated with total thyroidectomy plus <sup>131</sup>I ablation. This is due to the frequent association of LT with TgAb, because undetectable TgAb is required to define the remission of PTC. Indeed, coexistent LT does not influence the time to remission when the analysis is restricted to TgAb negative patients.

## Thyroid

### THYROID NEOPLASIA AND CANCER

#### *Polygenic Susceptibility to Papillary Thyroid Cancer in Italian Subjects*

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#### MON-486

Polygenic Susceptibility to Papillary Thyroid Cancer in Italian Subjects

**INTRODUCTION AND AIM.** Thyroid cancer is the most common endocrine neoplasia, with an estimated age-standardized incidence rate of 6.7 per 100000 worldwide in 2018 [1]. This rate is rapidly increasing and papillary thyroid carcinoma (PTC) is the main histotype. PTC susceptibility is the result of genetic predisposition, environmental factors and lifestyle. We studied the genetic combination that characterizes PTC affected subjects, differentiating them from healthy controls.

**METHODS AND RESULTS.** We considered the genetic variants (SNPs) significantly associated with PTC on the PubMed database. 184 informative SNPs were selected, considering linkage disequilibrium. Then, SNPs data were extracted from the online 1000 Genomes database,

comprising genome of 2504 unselected individuals collected worldwide. The combination of 184 SNPs associated with PTC was used to group individuals in different risk-clusters according to their genetic structure, calculated by Bayesian statistics, as previously performed for polycystic ovary syndrome [2]. Individuals were distributed among 7 groups worldwide, indicating different degree of genetic predisposition to PTC. We then considered genetic data from about 1200 individuals (697 PTC *versus* 497 healthy controls) of Central/South Italian origin registered in a GWAS, specific for PTC [3]. This first analysis was refined using the 33 SNPs reasonably most causative of genetic clustering (26 with  $p < 0.05$  at trend test in GWAS and 7 with  $p < 0.05$  in the model of recessive inheritance). At multivariate logistic regression analysis, PTC and healthy controls resulted genetically different (ODDS RATIO 188.6, 95%CI 64.35-552.8), revealing diverse predisposition to develop cancer. Afterwards, these results have been confirmed in an independent cohort of Italian subjects (234 PTC and 100 controls). Then, the genetic structure of each subject was indicated as a percentage of affinity to each risk-cluster and re-analyzed together with other risk factors: sex, body-mass index, area of origin and familiarity (quantified in a growing score as the degree of kinship increases). These data were analyzed together by principal component analysis and clustering of the two groups was even more pronounced. The most contributive factors to the diversity between PTC and healthy controls were genetics and familiarity.

**CONCLUSION.** We demonstrated that PTC affected subjects are genetically different from healthy controls, and that the difference is identifiable in a peculiar combination of genetic variants.

#### REFERENCES

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## Neuroendocrinology and Pituitary PITUITARY TUMORS II

### *AIP Gene Germline Mutations in Non-Selected Patients with Apparently Sporadic Pituitary Macroadenomas*

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#### MON-300

Up to 5% of all pituitary tumors are hereditary (e.g. due to *menin* or *AIP* genes germline mutations). *AIP* gene mutations are more common in subjects with acromegaly, less than 30 years old at the onset of disease, and with *FIPA* family history.

The study was aimed at the assessment of the frequency and characteristics of *AIP*-mutation related tumors in non-selected patients with pituitary macroadenomas.

**Material and methods.** The study included subsequent 131 patients (57 males, 74 females; median age 42 years (IQR 25 years) diagnosed with pituitary macroadenomas, and with a negative family history of *FIPA* or *MEN1* syndromes. The following tumors were identified: 11 ACTH-secreting, 49 GH-secreting (including 7 pluri-hormonal ones), 6 gonadotropinomas, 23 prolactinomas, 1 TSH-oma, and 43 non-secreting adenomas. Sanger sequencing was used for the assessment of *AIP* gene variants. The study was approved by the Ethics Board of JUMC.

**Results.** An *AIP* mutation was identified in five of 131 included subjects (3.8%): one diagnosed with Cushing's disease, two with acromegaly, and two with non-secreting adenomas. In two patients, the identified mutation usually predisposes to ACTH-secreting adenomas, in two patients - mutations of unknown clinical significance were found (usually connected with pituitary adenomas), and the mutation detected in one patient was described as benign. Patients harboring hereditary *AIP* gene variations did not differ from the rest of the study group in median age at diagnosis (41 vs. 42.5 years,  $p=0.8$ ), median largest tumor diameter (25 vs. 24 mm,  $p=0.6$ ), gender distribution (60% of females vs. 56.3%,  $p=0.8$ ), secreting tumor frequency (60% vs. 67.5%,  $p=0.7$ ), or acromegaly diagnosis frequency (40% vs. 37.3%,  $p=0.9$ ). 2 of the 5 patients with identified *AIP* gene mutations agreed for their families to be offered *AIP* genetic testing: (1) An *AIP* mutation was found in the asymptomatic mother of one acromegalic female patient. (2) The *AIP* mutation of unknown clinical significance was detected in the son of a male acromegalic patient with acromegaly, clinically unscreened yet.

**Conclusions.** In our series of apparently sporadic pituitary macroadenomas, *AIP* gene mutation carriers did not differ substantially from patients with negative genetic testing. A risk factor-centered approach to *AIP* genetic screening may result in missing germline mutations, therefore, there is a need to establish if such a situation negatively impacts a patient's and his/her family outcomes.

## Diabetes Mellitus and Glucose Metabolism

### CLINICAL AND TRANSLATIONAL GLUCOSE METABOLISM AND DIABETES

#### *Frequency and Associated Factors with Multidrug-Resistant Organism Infection in Diabetic Foot Ulcers in a Peruvian Public Hospital*

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#### MON-626

**Objective:** To determine the frequency and associated factors with multidrug-resistant organism (MDRO) infection among patients with diabetic foot ulcers in a Peruvian Public Hospital.

**Materials and methods.** Cross-sectional survey was conducted from January 2017 -December 2018 at National