FURTHER EVIDENCE THAT BOREALIN/CDCA8 IS INVOLVED IN THYROID MORPHOGENESIS AND AGING

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INTRODUCTION

We found BOREALIN/CDCA8 mutations in patients with Congenital Hypothyroidism and Thyroid Dysgenesis, varying from asymmetric lobes to athyreosis[1]. Borealin is a major component of the Chromosomal Passenger Complex, an essential regulator of mitosis. We demonstrated a new feature of BOREALIN: involvement in the adhesion and the migration of the thyrocytes.

AIM

Further understand the role of Borealin in thyroid development and function.

METHOD

Borealin+/- mice were studied during development, at the adult stage and during old age.

Borealin-/- mice were not available because they die at E5.5.

We documented thyroid morphology, performed immunohistology with thyroid markers (Nkx2-1, Thyroglobulin, T4) and we analyzed the thyroid function. Thyroid surface area were normalized for weight of each embryo. We used a well-established model with antithyroid drug induced hypothyroidism which was applied to the Borealin+/- and wild-type mice.

All data were statistically evaluated (*P<0.05, ** P>0.01).

CONCLUSIONS

Summary: Thyroid development is altered in Borealin+/- mice. Goiter do develop in adult Borealin+/- mice and they are more prone to hypothyroidism when treated with anti-thyroid drugs.

Conclusion: Borealin is involved during crucial steps of the thyroid lifetime cycle. These data demonstrated the involvement of Borealin in the structural organization of the thyroid gland. The role of Borealin in thyroid development and function was strengthened here and supports its involvement in thyroid dysgenesis of patients with congenital hypothyroidism.

RESULTS

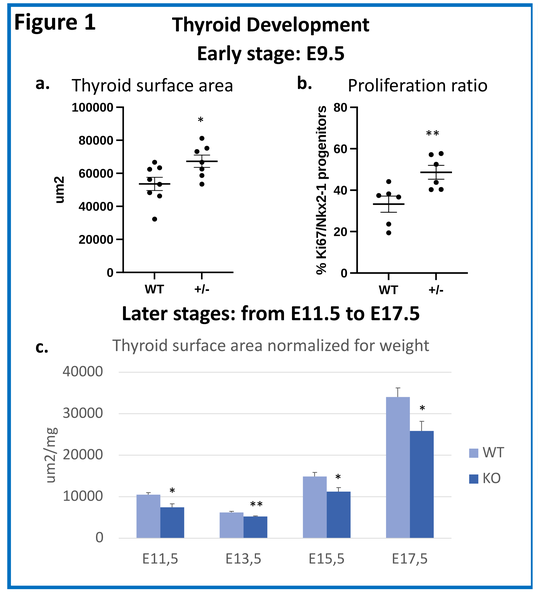

Figure 1:

We found that thyroids of Borealin+/- (+/-) were significantly hyperplastic at E9.5 in comparison with wild-type (WT- (**a**.) with higher proliferation of thyroid progenitors (**b**.), and hypoplastic from E11.5 to E17.5 (P<0.05) (**c**.).

Thyroid development was abnormal in Borealin+/- compared to wild-type from E9.5.

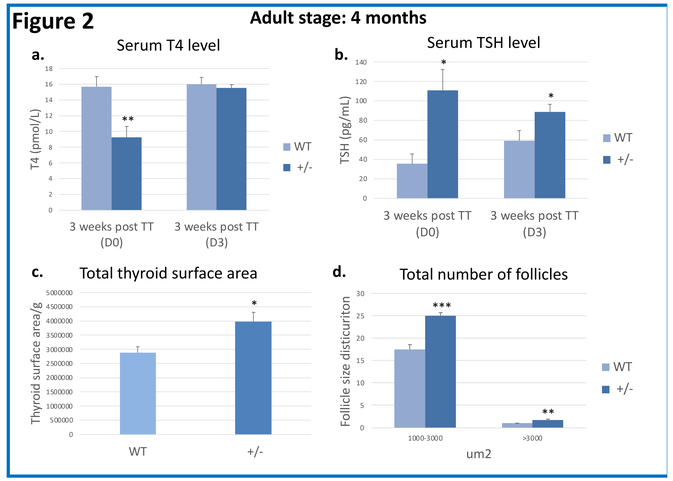

Figure 2:

Borealin+/- mice had no hypothyroidism at the adult stage (4-month-old) but they were significantly more sensitive with a more profound hypothyroidism than wild-type when treated with antithyroid drugs (at D0: **a**: T4: 41% less for Borealin+/- vs wild-type, P<0.01; **b**: TSH: 214% more Borealin+/- vs wild-type and more 51% at D3 for TSH). A4 months, male mice were treated during 3 weeks with methimazole 0.02% and sodium perchlorate 0.05% to induce hypothyroid. Serum T4 and TSH levels were determined three weeks after treatment (D0) and three days (D3) after withdrawal the treatment.

Thyroids of Borealin +/- mice were significantly hyperplastic (**c**.) with larger follicles surfaces in comparison with wild-type (P<0.05) (**d**.). Follicles were divided into size categories (lumen area, 1000–3000 um2 , and >3000 um2).

At 4 months, the Borealin+/- mice remain euthyroid because they developed a goiter with large follicles.

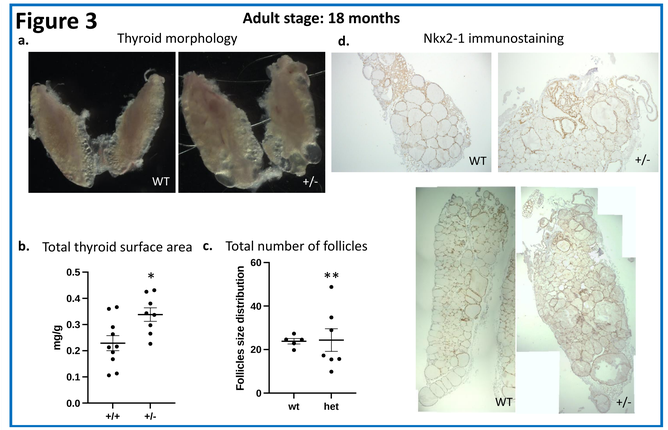

Figure 3:

Thyroid morphology of Borealin+/- was altered (**a**.) with heterogeneity in size of follicles with predominantly very large follicles and thyroids that were significantly hyperplastic compared with wild-type (**b**, **c** and **d**). **c**. Distribution of follicles size was significantly heterogeneous in the Borealin+/- group in comparison with wild-type (lumen area, >3000 um2). **d**. Nkx2-1 (in brown) immunostaining of adult thyroid tissue at 18 months. Note the disorganization of the thyroid tissue in Borealin+/- versus wild-type mice. Top: magnification x10. Bottom: Overview of a thyroid lobe in each Borealin+/- and wild-type.

At 18 months, hyperplastic thyroid gland of Borealin+/- mice do not age properly with larger follicles and disorganized morphological structure.

REFERENCES

1. Carré A, et al. Mutations in BOREALIN cause thyroid dysgenesis. Hum Mol Genet. 2017 Feb 1;26(3):599-610.

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