Rats Heterozygous for the MENX-Associated p27 Mutation Develop a MEN Phenotype

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Background: MENX is a spontaneous multiple endocrine neoplasia syndrome in the rat showing phenotypic overlap with both MEN1 and MEN2 human syndromes. MENX is caused by a biallelic germline mutation of the Cdkn1b (p27) gene and it was described as recessively inherited. CDKN1B alterations have been also identified in human patients with MEN1-like features but no MEN1 mutations (MEN4).

Aims: Since MEN4 patients present germline CDKN1B monoallelic mutations and mice with only one null Cdkn1b allele are predisposed to tumor formation, we performed a detailed phenotypic characterization of rats heterozygous for the germline Cdkn1b mutation causing MENX.

Methods: We determined the overall survival of wild-type (p27+/+) and heterozygous (p27+/m) rats and performed histological and immunohistochemical analysis of their tissues.

Results: We observed that p27+/m rats die earlier than p27+/+ rats (average 17 vs. 24 months) and develop tumors earlier. p27+/m animals show bilateral pheochromocytoma, paraganglioma, thyroid C-cell and endocrine pancreas hyperplasias, parathyroid and anterior pituitary adenomas, similarly to double-mutant rats (p27m/m). Interestingly, we could observe all the phases of progression of medullary thyroid carcinoma (MTC), from C-cell hyperplasia to carcinoma, often within the same gland.
**Conclusion:** Heterozygous rats develop a MEN phenotype, like the double mutant animals. They could be exploited to gain information about neuroendocrine tumor progression and, in particular, about MTC development.