Cyclin-dependent kinase inhibitor 1B (CDKN1B) gene variants in AIP mutation-negative familial isolated pituitary adenoma kindreds

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Résumé en anglais	Familial isolated pituitary adenoma (FIPA) occurs in families and is unrelated to multiple endocrine neoplasia type 1 and Carney complex. Mutations in AIP account only for 15-25% of FIPA families. CDKN1B mutations cause MEN4 in which affected patients can suffer from pituitary adenomas. With this study, we wanted to assess whether mutations in CDKN1B occur among a large cohort of AIP mutation-negative FIPA kindreds. Eighty-eight AIP mutation-negative FIPA families were studied and 124 affected subjects underwent sequencing of CDKN1B. Functional analysis of putative CDKN1B mutations was performed using in silico and in vitro approaches. Germline CDKN1B analysis revealed two nucleotide changes: c.286A>C (p.K96Q) and c.356T>C (p.I119T). In vitro, the K96Q change decreased p27 affinity for Grb2 but did not segregate with pituitary adenoma in the FIPA kindred. The I119T substitution occurred in a female patient with acromegaly. p27(I119T) shows an abnormal migration pattern by SDS-PAGE. Three variants (p.S56T, p.T142T, and c.605+36C>T) are likely nonpathogenic because In vitro effects were not seen. In conclusion, two patients had germline sequence changes in CDKN1B, which led to functional alterations in the encoded p27 proteins in vitro. Such rare CDKN1B variants may contribute to the development of pituitary adenomas, but their low incidence and lack of clear segregation with affected patients make CDKN1B sequencing unlikely to be of use in routine genetic investigation of FIPA kindreds. However, further characterization of the role of CDKN1B in pituitary tumorigenesis in these and other cases could help clarify the clinicopathological profile of MEN4.
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