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Adult Leydig-cell tumors of the testis caused by germline fumarate hydratase mutations

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Leydig-cell tumors (LCTs) are the most common non-germ cell neoplasms of the testis. LCTs are often hormonally active and can result in precocious virilisation or in adult feminisation. We identified a LCT in an affected individual from a kindred with hereditary leiomyomatosis and renal cell cancer (HLRCC) and a germline fumarate hydratase (*FH*) mutation (N64T). To investigate the role of *FH* mutations in predisposition to LCTs, we tested for pathogenic effects of this mutation and screened a further 29 unselected LCTs for *FH* alterations. We also tested these LCTs for mutations in two genes, the luteinizing hormone/choriogonadotropin receptor (LHCGR) and the guanine nucleotide binding protein alpha (*GNAS*) that had been implicated in LCT tumorigenesis. No mutations were found in *GNAS* and one tumor had a *LHCGR* somatic substitution. In addition to the HLRCC case with the N64T germline *FH* mutation, we identified one other LCT with a previously unreported *FH* mutation (M411I). Both LCTs from these patients showed loss of the wildtype *FH* allele. Immunohistochemical and *in situ* hybridisation analyses demonstrated activation of the hypoxia/angiogenesis pathway not only in the tumors belonging to the *FH* mutation carriers, but also in several other mutation-negative LCTs. Our study represents one of the first reports of germline mutations in any type of adult testicular tumor.