A novel succinate dehydrogenase subunit B gene mutation, H132P, causes familial malignant sympathetic extraadrenal paragangliomas

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We report a family with malignant sympathetic paragangliomas (PGL) exhibiting a new type of germline mutation in the succinate dehydrogenase subunit B (SDHB) gene. Two affected brothers, presenting with symptoms at the ages of 25 and 52 yr, suffered from malignant abdominal extraadrenal sympathetic PGL. They died of their disease at ages 43 and 61 yr. Their mother had the same history of signs and symptoms, suggesting a catecholamine-producing tumor at the age of 55 yr. Analysis of the germline DNA from these three patients revealed a novel mutation in exon 4 (H132P) of the SDHB gene. This mutation was absent in 160 control chromosomes. Loss of heterozygosity analysis of the tumors showed a loss of one SDHB allele, and RT-PCR-based expression analysis confirmed the exclusive expression of the mutated allele in both tumors. A review of the published PGL families revealed malignant tumors in seven of 12 well-documented families with SDHB mutation-associated extraadrenal PGL. These findings, as well as findings of the family reported here, suggest a strong causal relationship of SDHB germline mutations with malignant extraadrenal abdominal PGL and imply the necessity of a close follow-up of affected individuals and family members.