Germ-line mutations in nonsyndromic pheochromocytoma

Hartmut P H Neumann, Birke Bausch, Sarah R McWhinney, Bernhard U Bender, Oliver Gimm, Gerlind Franke, Joerg Schipper, Joachim Klisch, Carsten Altehoefer, Klaus Zerres, Andrzej Januszewicz, Charis Eng, Wendy M Smith, Robin Munk, Tanja Manz, Sven Glaesker, Thomas W Apel, Markus Treier, Martin Reineke, Martin K Walz, Cuong Hoang-Vu, Michael Brauckhoff, Andreas Klein-Franke, Peter Klose, Heinrich Schmidt, Mariola Peçzkowska, Cesary Szmigielski & Freiburg-Warsaw-Columbus Pheochromocytoma Study Group

BACKGROUND: The group of susceptibility genes for pheochromocytoma that included the proto-oncogene RET (associated with multiple endocrine neoplasia type 2 [MEN-2]) and the tumor-suppressor gene VHL (associated with von Hippel-Lindau disease) now also encompasses the newly identified genes for succinate dehydrogenase subunit D (SDHD) and succinate dehydrogenase subunit B (SDHB), which predispose carriers to pheochromocytomas and glomus tumors. We used molecular tools to classify a large cohort of patients with pheochromocytoma with respect to the presence or absence of mutations of one of these four genes and to investigate the relevance of genetic analyses to clinical practice. METHODS: Peripheral blood from unrelated, consenting registry patients with pheochromocytoma was tested for mutations of RET, VHL, SDHD, and SDHB. Clinical data at first presentation and follow-up were evaluated. RESULTS: Among 271 patients who presented with nonsyndromic pheochromocytoma and without a family history of the disease, 66 (24 percent) were found to have mutations (mean age, 25 years; 32 men and 34 women). Of these 66, 30 had mutations of VHL, 13 of RET, 11 of SDHD, and 12 of SDHB. Younger age, multifocal tumors, and extraadrenal tumors were significantly associated with the presence of a mutation. However, among the 66 patients who were positive for mutations, only 21 had multifocal pheochromocytoma. Twenty-three (35 percent) presented after the age of 30 years, and 17 (8 percent) after the age of 40. Sixty-one (92 percent) of the patients with mutations were identified solely by molecular testing of VHL, RET, SDHD, and SDHB; these patients had no associated signs and symptoms at presentation. CONCLUSIONS: Almost one fourth of patients with apparently sporadic pheochromocytoma may be carriers of mutations; routine analysis for mutations of RET, VHL, SDHD, and SDHB is indicated to identify pheochromocytoma-associated syndromes that would otherwise be missed.
type: journal paper/review (English)
date of publishing: 9-5-2002
journal title: N Engl J Med (346/19)
ISSN electronic: 1533-4406
pages: 1459-66