

## Familial Gastrointestinal Stromal Tumors and Germ-Line Mutations

**TO THE EDITOR:** Gastrointestinal stromal tumors may be sporadic or inherited in an autosomal dominant manner, alone or as a component of a syndrome associated with other tumors, such as in the context of neurofibromatosis type 1.<sup>1</sup> We have described seven male and five female patients (median age, 23 years) from five unrelated families who had both gastrointestinal stromal tumors and paragangliomas. Susceptibility to the tumors was inherited in an apparently autosomal dominant manner, with incomplete penetrance.<sup>2</sup> This condition has been referred to as “the dyad of paraganglioma and gastrointestinal stromal tumors” or the “Carney–Stratakis syndrome” (or “Carney–Stratakis dyad”).<sup>3</sup>

Germ-line mutations of the genes encoding succinate dehydrogenase subunits B, C, and D (*SDHB*, *SDHC*, and *SDHD*) have been described in inherited paraganglioma and pheochromocytoma<sup>4</sup> but not in familial gastrointestinal tumors. The family history of a kindred with multiple paragangliomas and a germ-line *SDHB* mutation included a person with a gastrointestinal stromal tumor,<sup>5</sup> but neither blood nor tissue specimens from this patient were studied for *SDHB* abnormalities.

We identified six germ-line *SDHB*, *SDHC*, and *SDHD* mutations in patients with the dyad (Fig. 1). Gastrointestinal stromal tumors from the patients showed allelic losses around the chromosomal loci of the succinate dehydrogenase subunit. The patients did not have mutations of *KIT* or the gene for platelet-derived growth factor receptor alpha (*PDGFRA*), which have been associated with gastrointestinal tumors.<sup>1</sup> We conclude that familial gastrointestinal stromal tumors may be caused by mutations of the succinate dehydrogenase subunit genes *SDHB*, *SDHC*, and *SDHD*, and abdominal paragangliomas associated with gastrointestinal tumors may be caused uniquely by *SDHC* mutations.

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### Figure 1 (facing page). Families with the Carney–Stratakis Syndrome and Findings from Their Tumors.

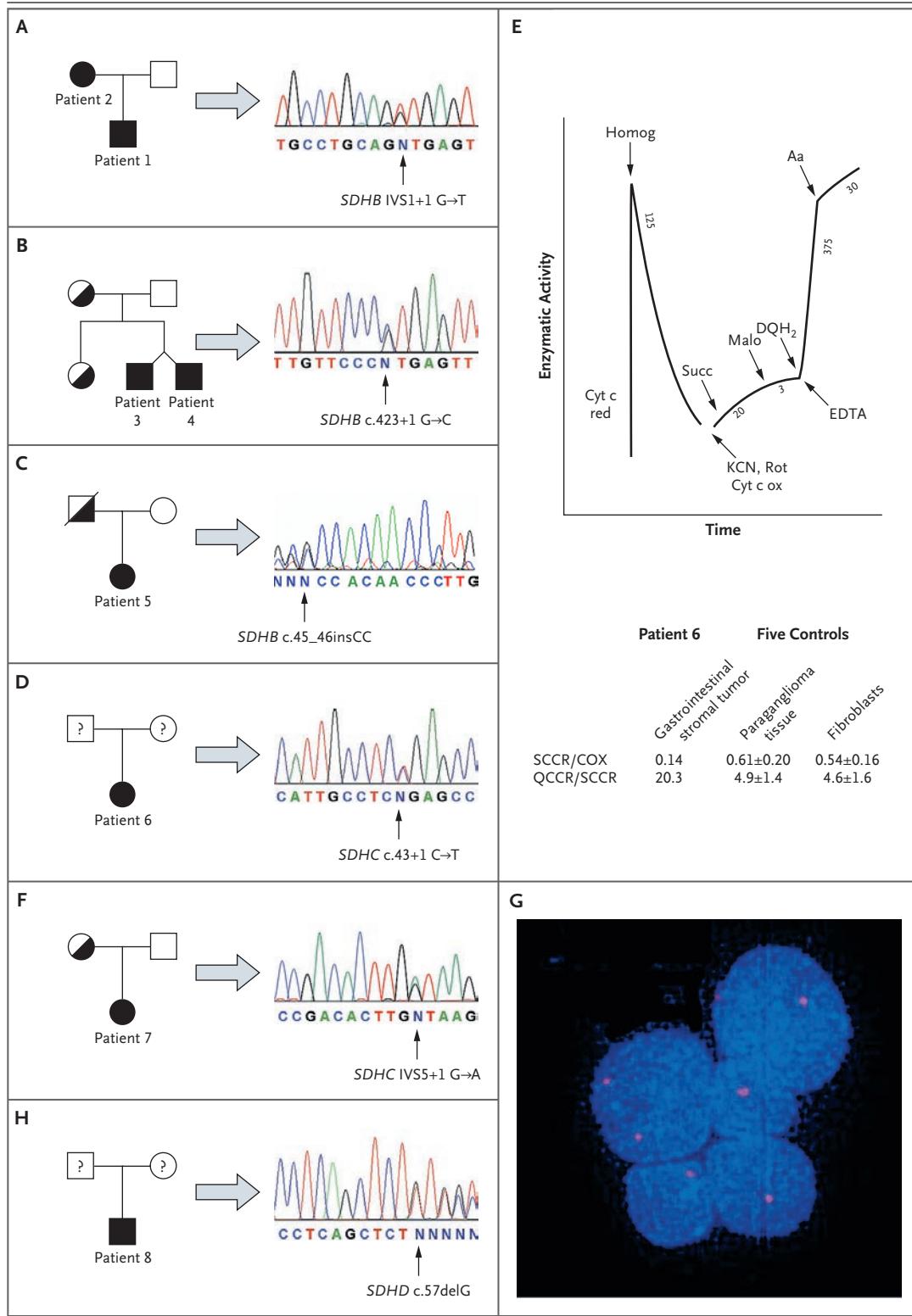
Circles represent female family members, squares male family members, open symbols members without the dyad, solid symbols members with the dyad, and half-solid symbols unaffected carriers. A question mark indicates that the person was not tested clinically or genetically. A slash indicates a deceased person. Panels A, B, and C show mutations in the succinate dehydrogenase subunit gene *SDHB*, Panels D and F show mutations in the succinate dehydrogenase subunit gene *SDHC*, and Panel H shows mutations in the succinate dehydrogenase subunit gene *SDHD*. Panel E shows the results of mitochondrial respiratory-chain function studies in the gastrointestinal stromal tumor of a patient with the *SDHC*-inactivating mutation (Patient 6, shown in Panel D). The upper part of the panel shows a spectrophotometric recording of respiratory-chain enzyme activities in the *SDHC*-related gastrointestinal stromal tumor. Cyt c red denotes 10  $\mu$ M reduced cytochrome *c*, Homog gastrointestinal-stromal-tumor homogenate, KCN 0.3 mM potassium cyanide, Rot 8  $\mu$ M rotenone, Cyt c ox 10  $\mu$ M oxidized cytochrome *c*, Succ 5 mM succinate, Malo 5 mM malonate, DQH<sub>2</sub> 50  $\mu$ M decylubiquinol, and Aa 1  $\mu$ M antimycin. Values for enzyme activity (numbers along the tracing) are expressed as nanomoles per minute per milligram of protein when substances such as EDTA are added in the assay. The enzyme activities in Patient 6 and in specimens of paraganglioma tissue and fibroblasts from 5 patients without succinate dehydrogenase subunit gene mutations (controls) are shown in the lower part of Panel E. SCCR denotes malonate-sensitive succinate cytochrome *c* reductase activity (complexes II and III), COX cytochrome oxidase (complex IV), and QCCR quinol cytochrome *c* reductase (complex III). Panel G shows deletion of the 1q21 region in a touch preparation from a gastrointestinal stromal tumor in Patient 7 (shown in Panel F). Hybridization of nuclei in interphase with the RP11-991L1 probe containing the *SDHC* gene showed one signal (red dots) in more than 75% of the cells; in Panel G, three of the five cells show one signal of the 1q-located *SDHC* gene.

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## A Comparison of Three Initial Antiretroviral AIDS Regimens

**TO THE EDITOR:** Study A5095 by the AIDS Clinical Trials Group (ACTG) was a randomized, double-blind, placebo-controlled, comparative study of three antiretroviral regimens for the initial treatment of human immunodeficiency virus (HIV) infection. The three regimens were zidovudine, lamivudine, and abacavir (the triple-nucleoside regimen), the triple-nucleoside regimen plus efavirenz (the four-drug regimen), and zidovudine, lamivudine, and efavirenz (the three-drug, standard-of-care regimen). The study was designed to follow patients for 120 weeks after randomization. The primary study end point was the time to virologic failure, which was defined as a confirmed HIV RNA level of more than 200 copies per milliliter at or after week 16 of the study.

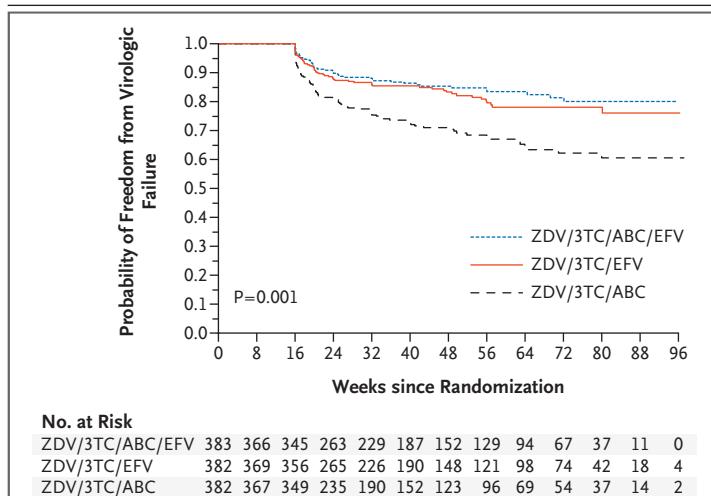
At the second review of the data and safety monitoring board in February 2003, with a median of 32 weeks of study follow-up, pairwise

comparisons among the three study groups showed differences that met prespecified stopping guidelines: the triple-nucleoside regimen was virologically inferior to the other two regimens. As a result, the board recommended that the triple-nucleoside regimen be stopped. They also recommended continued double-blind follow-up of the other two groups and that pooled data from these groups be presented with data from the triple-nucleoside group. These data were published in March 2004.<sup>1</sup>

Follow-up for the two blinded groups receiving efavirenz was completed in March 2005 and showed no significant differences between the groups with respect to virologic or immunologic responses, adverse events, adherence to treatment, or drug-resistant mutations at the time of virologic failure.<sup>2</sup>

With the study completed, we feel that it is appropriate to present the unpooled data comparing the triple-nucleoside regimen with each of the efavirenz-containing regimens through the closure of blinded follow-up of the triple-nucleoside group in February 2003. Hazard ratios are presented for the triple-nucleoside group; 97.5% adjusted confidence intervals are based on an O'Brien-Fleming<sup>3</sup> and Lan and DeMets<sup>4</sup> group sequential-monitoring boundary.

With a median of 48 weeks of follow-up, 98 of 382 patients in the triple-nucleoside group had virologic failure, as compared with 50 of 383 patients in the four-drug group (hazard ratio, 2.21; 97.5% confidence interval [CI], 1.32 to 3.7) and with 60 of 382 in the three-drug, standard-of-care group (hazard ratio, 1.85; 97.5% CI, 1.14 to 3.01) (Fig. 1). We conclude that this analysis confirms the findings of the review board and clearly shows that the triple-nucleoside regimen was inferior virologically to both the four-drug regimen and the three-drug, standard-of-care regimen.



**Figure 1. Time to Virologic Failure for Three Initial Antiretroviral Regimens.**

Data are from study A5095 of the AIDS Clinical Trials Group. Virologic failure was defined as a confirmed HIV RNA level of more than 200 copies per milliliter at or after week 16 of the study. ZDV denotes zidovudine, 3TC lamivudine, ABC abacavir, and EFV efavirenz.