LETTER TO THE EDITORS

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Are We Overestimating the Penetrance of Mutations in *SDHB*?

Francesca Schiavi,[1†] Roger L. Milne,[2†] Emma Anda,[3] Pilar Blay,[4] Maurizio Castellano,[5] Giuseppe Opocher,[1,6] Mercedes Robledo,[7,8] and Alberto Cascón[7,8*]

[1]*Familial Cancer Clinic, Veneto Institute of Oncology, Padua, Italy;* [2]*Genetic and Molecular Epidemiology Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain;* [3]*Department of Endocrinology, Hospital de Navarra, Pamplona, Spain;* [4]*Medical Oncology Service, Hospital Central de Asturias, Oviedo, Spain;* [5]*Internal Medicine and Endocrinology Unit, Department of Medical and Surgical Sciences, University of Brescia, Brescia, Italy;* [6]*Department of Medical and Surgical Sciences, University of Padova, Padova, Italy;* [7]*Hereditary Endocrine Cancer Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain;* [8]*ISCIII Center for Biomedical Research on Rare Diseases (CIBERER), Spain*

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We recently read with interest the article by Ricketts and colleagues [2010] based on a genotype–phenotype association study performed in a very large number of germline *SDHB* or *SDHD* mutation carriers. Genetic variants in three of the four succinate dehydrogenase genes (*SDHB*, *SDHC*, and *SDHD*) are known to cause hereditary susceptibility to three closely related paraganglioma syndromes: PGL4 (MIM 115310), PGL3 (MIM 605373), and PGL1 (MIM 168000), respectively. Although the development of extra-adrenal paragangliomas is the main clinical feature common to these three syndromes, the presence of extra-paraganglial manifestations and metastases in PGL4 highlights the need for improved understanding of *SDHB*-mutation-associated characteristics. In this regard, it should be noted that *SDHB*-related paragangliomas usually appear as isolated masses in elderly patients with no familial antecedents [Cascon et al., 2009a], which strongly indicates that mutations in this gene have a low penetrance (age-specific cumulative risk of cancer). Ricketts and colleagues [2010] estimated an average penetrance of 50% by age 50 years using 295 affected and unaffected *SDHB* mutation carriers from 125 families. This estimate was lower than that previously reported by Neumann and colleagues [2004] (75% by 50 years), but was more consistent with that found by Benn and colleagues [2006] (~55% by 50 years). These three studies estimated the penetrance using standard Kaplan-Meier methods applied to tested mutation carriers. These methods overestimate the average penetrance because no correction is made for the ascertainment of mutation carriers. All mutation carriers are identified via index cases that have both the mutation and the disease, and this should be taken into consideration in the analysis.

To estimate the penetrance of mutations in *SDHB*, we carried out a similar family-based study of 446 people from 33 mutation-carrier families from Italy and Spain. Families were identified via a consecutive series of paraganglioma patients who were tested for mutations regardless of family history (Fig. 1). Information was collected for index patients and their relatives on relationship, sex, current age or age at death, paraganglioma diagnosis, and age at diagnosis. We estimated the age-specific average cumulative risk of paraganglioma via a maximum likelihood method using modified segregation analysis implemented in the pedigree analysis software, MENDEL. This method has been previously described in detail [Antoniou et al., 2003; Lange et al., 1988]. For each family, we maximized the conditional likelihood of observing all genotypes and disease phenotypes in the family, given the phenotype of the first individual to test positive. The incidence rates for mutation carriers were assumed to follow a Cox proportional hazards model, under which the incidence in mutation carriers is a constant multiple of the age-specific incidence in the general population. Individuals were followed from birth, and were censored at the first of paraganglioma diagnosis, death, age last follow-up, or age 80 years. The incidence in the general population was assumed to increase linearly with age, corresponding to a cumulative lifetime risk (to age 80 years) of 1/10,000. We assumed that the allele frequency for all deleterious mutations in *SDHB* combined was 0.0001. Our results were highly consistent when varying these assumptions.

We considered uninformative, and therefore excluded, nine families for which information was available for the proband only, leaving 437 people from 24 families in the final analysis. These included 135 carriers of deleterious mutations in *SDHB*. There was a median of nine members per family (range: 4–182), one affected per family 1 (1–6) and four mutation carriers (2–37). We estimated the average penetrance to age 50 years to be 13% (95% confidence interval [CI] = 7–18%) and the average lifetime penetrance (to age 80) to be 30% (95% CI = 17–41%). These are substantially lower than previously reported estimates (Table 1). This is at least partly due to the adjustment for ascertainment. When the same retrospective likelihood method was applied, but without conditioning on the affectation status of the proband, the corresponding estimates were 31% (95% CI = 23–39%) and 63% (95% CI = 51–72%), confirming that failure to account for ascertainment results in overestimation of penetrance.

In the context of a severe inherited disease with a complex follow-up protocol, genetic counselling is an integral component of the appropriate clinical management of both patients and relatives. PGL4-related paragangliomas are characterized by a high risk of malignancy (~35%) [Cascon et al., 2009b; Neumann et al., 2004], so in this setting it is essential that accurate estimates of the age-dependent penetrance of *SDHB* mutations are used. This is further complicated by the varying phenotypes that *SDHB*

†Francesca Schiavi and Roger L. Milne are contributed equally to this work.

*Correspondence to: Alberto Cascón, Hereditary Endocrine Cancer Group, Human Cancer Genetics Programme, Centro Nacional de Investigaciones Oncológicas, Melchor Fernández Almagro 3, 28029 Madrid, Spain. E-mail: acascon@cnio.es

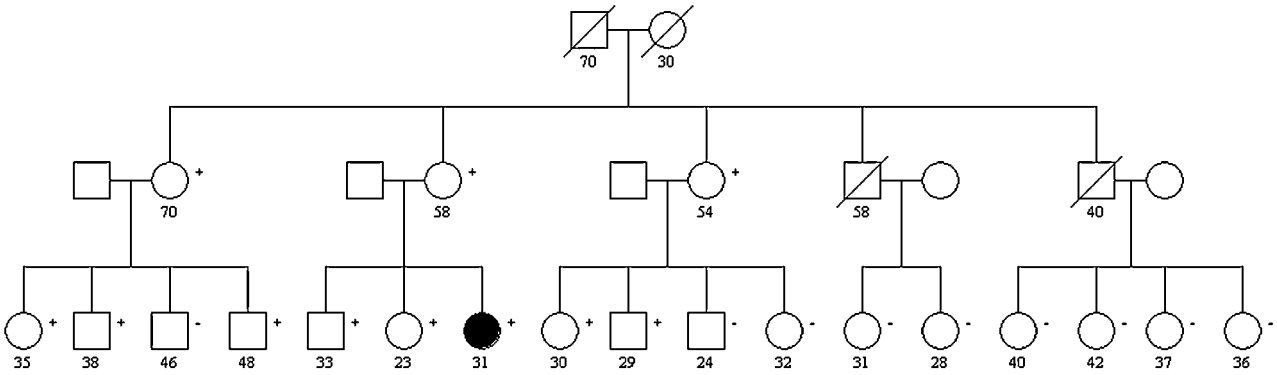

Figure 1. Pedigree corresponding to a typical family included in the analysis. The symptomatic proband of the family, diagnosed with both adrenal pheochromocytoma and abdominal paraganglioma, is shown with a full black circle. There were no other affected individuals in the family. Carriers and noncarriers of the *SDHB* mutation (c.1−10413_73−3866del) are denoted by a + and a−sign, respectively.

Table 1. Estimates of the Penetrance of Mutations in SDHB to Ages 20, 40, 60 and 80 Years from the Present and Previous Studies

Age	Neumann et al.[a]	Benn et al.[a]	Ricketts et al.[a]	Present study: estimate (95% CI)
20 years	30%	10%	20%	1% (0.6–2%)
40 years	55%	45%	40%	8% (4–11%)
60 years	95%	75%	70%	18% (10–26%)
80 years	100%	80%	–	30% (17–41%)

[a]Extrapolated from the graphs provided in the respective publications.
CI, confidence interval.

mutation carriers may exhibit [Ricketts et al., 2008, 2010; Solis et al., 2009]. We therefore encourage a collaborative effort to combine data from different series to both provide a more accurate measure of the average penetrance of all mutations, and to allow for analyses specific to different malignant phenotypes of this challenging cancer syndrome.

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