Imaging Work-Up for Screening of Paraganglioma and Pheochromocytoma in *SDHx* Mutation Carriers: A Multicenter Prospective Study from the PGL.EVA Investigators

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Context: Recommendations have not been established concerning imaging to screen *SDHx* mutation carriers for paraganglioma and pheochromocytoma.

Objective: Our objective was to compare the performance of gadolinium-enhanced magnetic resonance angiography, contrast-enhanced computed tomography, and [^{123}I]metaiodo-benzylguanidine and somatostatin receptor scintigraphies for detecting head and neck and thoracic-abdominal-pelvic paragangliomas in *SDHx* mutation carriers.

Design and Setting: We conducted a prospective, multicenter study from June 2005 to December 2009 at 23 French medical centers.

Patients: A total of 238 index cases or relatives carrying mutations in *SDHD*, *SDHB*, or *SDHC* genes were included.

Intervention: Images obtained by each technique were analyzed blind, without knowledge of results from other tests, first in each local center and then centrally.

Main Outcome Measures: We evaluated sensitivity, specificity, and likelihood ratios for individual and combinations of tests, the gold standard being the consensus of an expert committee.

Results: Two hundred two tumors were diagnosed in 96 subjects. At local assessment, the sensitivity of anatomical imaging for detecting all tumors was higher (85.7%) than that of both scintigraphic techniques (42.7% for [^{123}I]metaiodo-benzylguanidine and 69.5% for somatostatin receptor scintigraphy), except for thoracic localizations where somatostatin receptor scintigraphy was more sensitive (61.5 *vs.* 46.2% for anatomical imaging and 30.8% for [^{123}I]metaiodo-benzylguanidine scintigraphy). The best diagnostic performance during local assessment was obtained by combining anatomical imaging tests and somatostatin receptor scintigraphy (sensitivity 91.7%). Central assessment significantly increased the sensitivity (98.6%) of tests in combination.

Conclusions: In routine practice, the imaging work-up for screening *SDHx* mutation carriers should include thoraco-abdomino-pelvic computed tomography, head and neck magnetic angiography, and somatostatin receptor scintigraphy. Expert centralized image assessment is recommended. **(*J Clin Endocrinol Metab* 98: E162–E173, 2013)**

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Abbreviations: CI, Confidence interval; CT, Computed tomography; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; FDOPA, fluorodihydroxyphenylalanine; FDG, fluorodeoxyglucose; HN, head and neck; mIBG, metaiodo-benzylguanidine; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission CT; SRS, somatostatin receptor scintigraphy; TAP, thoracic, abdominal, and pelvic.

Paraganglioma and pheochromocytoma are rare tumors; the incidence is two to eight cases per million inhabitants per year, and the estimated prevalence is one in 30,000 and one in 10,000, respectively (1–3). They develop from the paraganglia tissue in the head, neck, thorax, abdomen (pheochromocytoma are those that develop from adrenal medulla) and pelvis. They may secrete catecholamines and be revealed by secondary hypertension. The only curative therapy is complete surgical resection, which is a high-risk procedure. The incidence of nervous and vascular complications increases with the size of the tumor, and alternative strategies, such as external radiotherapy or monitoring of tumor growth, may be proposed (4–6). Approximately 35% of cases are caused by germline mutations in one of the 10 identified susceptibility genes (*RET*, *NF1*, *VHL*, *SDHD*, *SDHB*, *SDHC*, *TMEM127*, *SDHAF2*, *SDHA*, and *MAX*) (for review, see Ref. 7). Various familial diseases cause a predisposition to paraganglioma: hereditary paraganglioma is rare and includes five known different types (MIM 168000, 601650, 605373, 115310, and 614165). Germline mutations have been identified in patients affected by the disease in *SDHD* and *SDHC* in 2000 (8, 9), in *SDHB* in 2001 (10), and more recently, in 2010, in *SDHAF2* (11) and *SDHA* (12). The *SDHx* genes encode proteins forming the mitochondrial complex II or succinate dehydrogenase. The inactivation of succinate dehydrogenase in *SDHx*-related tumors induces, in normoxia, the activation of the hypoxia-angiogenesis pathway in the tumoral tissue, explaining the pathognomonic hypervascularization (13).

Large international cohorts of patients with hereditary paraganglioma have been reported (14–18). *SDHx* mutations carriers are predisposed to precocious, multiple, and sometimes malignant tumors (for review, see Ref. 19). More than 400 different *SDHx* mutations have been identified worldwide and are reported in the TCA Cycle Gene Mutation Database (20). Tumor detection at a presymptomatic stage should allow early management and decreased morbidity and mortality. Consequently, familial genetic testing is currently proposed to first-degree relatives of *SDHx* mutation carriers to identify at-risk subjects. However, recommendations have not been established for the initial imaging in genetically predisposed subjects in routine practice. The objective of the Paraganglioma Evaluation, or PGL.EVA, study was to assess the diagnostic performance of four routinely used imaging tests in a large prospective series of *SDHx* mutation carriers.

Patients and Methods

Design

The PGL.EVA study (http://clinicaltrials.gov/ct2/show/NCT00188019; registration number NCT00188019) was a French multicenter study designed to assess the sensitivity and specificity of the four screening methods usually available in routine practice in 2004. The study was approved by the appropriate ethics committee (Comité de Protection des Personnes, CPP Ouest II, Angers, France). Written informed consent was obtained from each patient for inclusion in the study. Two radiological and two nuclear medicine imaging techniques were evaluated. Head and neck (HN) gadolinium-enhanced magnetic resonance angiography (MRA) and thoracic, abdominal, and pelvic (TAP) contrast-enhanced computed tomography (CT) scan were compared with [^{123}I]metaiodobenzylguanidine (mIBG) scintigraphy and somatostatin receptor scintigraphy (SRS) with ^{111}In-labeled pentetreotide scintigraphy. Standardized protocols were used as described below.

Plasma catecholamine metabolites and chromogranin A were measured centrally. Blood samples were obtained in a supine position after a rest of at least 20 min. Plasma samples were stored at −80 C until assayed. Plasma methoxytyramine, normetanephrine, and metanephrine were measured by the Laboratory Medicine of University of Dresden as previously reported (21). Plasma chromogranin A concentration was measured in the Department of Physiology of Hôpital Européen Georges Pompidou by RIA with CgA-RIACT assay (CIS Bio International, Gif-sur-Yvette, France). Interfering therapies were stopped before the measurement or false-positive results were not considered.

The study involved 3 yr of follow-up (one medical consultation annually).

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Sites and patients

Subjects were enrolled consecutively from June 6, 2005, to December 22, 2009, in 23 centers (center 12 did not recruit) (Supplemental Fig. 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Two categories of subjects were recruited: 1) patients with a previous diagnosis of paraganglioma (index cases) and 2) apparently asymptomatic subjects identified by familial genetic testing as being at risk (relatives). They (men or women) were eligible if they were 6 yr old or older and had previously been informed of their positive genetic status (identification of a germline mutation in *SDHD*, *SDHB*, or *SDHC* genes, reported in Supplemental Table 1). Exclusion criteria were refusal or inability to understand and sign informed consent, children aged under 6 yr, pregnant and/or lactating women, and *SDHD* mutation inherited from the maternal branch. Patients with multiple bone and/or lymph node metastases were not recruited in the PGL.EVA study.

[^{123}I]mIBG scan

Examinations were performed after thyroid blockade (potassium iodide or Lugol 5%), standard intestinal preparation, and hyperhydration and with respect of possible pharmaceutical interactions (22–24). Adult patients received an iv injection of 200 MBq of [^{123}I]mIBG ([^{123}I]Iobenguane; Mallinckrodt/Covidien, Petten, The Netherlands). A dual-head large-field-of-view gamma-camera equipped with a low-energy high-resolution parallel-hole collimator provided anterior and posterior 256^2 matrix images at 18–24 h (early images at 4–6 h were also acquired). Data acquisition was performed using an energy window setting at 159 keV, with 20% of window width. Ten-minute spot images covered head and neck (including lateral views), thorax, abdomen, and pelvis. When possible, total body images were obtained by scanning at 5 cm/min. Single-photon emission CT (SPECT, or SPECT-CT for some adults) from relevant regions was performed at 24 h (60 projections of 60 sec acquired over 360° in a 128^2 matrix), reconstructed by iterative reconstruction (Ordered Subsets Expectation Maximization) or by filtered back-projection with dosimetric optimizations. A delay of 10 d was imposed between SRS and any subsequent mIBG scan.

Somatostatin receptor scintigraphy

Examinations were performed after standard intestinal preparation. Adults received an iv injection of 220 MBq of [^{111}In-]pentetreotide (Octreoscan; Mallinckrodt/Covidien) (25). For mIBG scan or SRS, the dose used for children was based on the recommendations of the European Association of Nuclear Medicine Pediatric Task Group (26). A dual-head large-field-of-view gamma-camera equipped with a medium-energy high-resolution parallel-hole collimator provided anterior and posterior 256^2 matrix images at 4–6 and 18–24 h. Data were acquired using an energy window setting at 173 and 245 keV, with 20% of window width. Ten-minute spot images covered head and neck (including lateral views), thorax, abdomen, and pelvis. Total body images were obtained scanning at 5 cm/min when possible. SPECT (or SPECT-CT for some adults) of relevant regions was performed at 24 h (60 projections of 45 sec acquired over 360° in a 128^2 matrix), reconstructed by iterative reconstruction (Ordered Subsets Expectation Maximization) or filtered back-projection with dosimetric optimizations. SRS was permitted immediately after the mIBG scan.

HN MRA scan

Magnetic resonance imaging (MRI) was used to detect head and neck paragangliomas. The volume explored was from the skull base (including petrous bone) to the lower neck, with a 4-mm slice thickness. MRI sequences included transverse and sagittal plane T1-weighted spin-echo images, T2-weighted fast spin-echo images, and T2-weighted fast spin-echo with fat saturation images. After iv contrast injection of gadolinium chelate (0.1 mmol/kg body weight, gadoteric acid; Dotarem Guerbet, Aulnay-sous-Bois, France), a fast spin-echo T1-weighted sequence with fat saturation and three-dimensional time-of-flight angiography projection images were obtained.

TAP CT scan

CT scan was used to determine thoracic and abdomino-pelvic paraganglioma localizations in adults. Exclusion criteria were renal failure (clearance under 30 ml/min calculated with the Cockroft or Modification of Diet in Renal Disease formula), known allergy to iodine contrast, or light-chain proteinuria. All imaging was performed with multidetector row CT scanners; the type and number of channels (at least four) differed between centers. The thoracic inlet to the pelvis was explored. To minimize the x-ray dose, only one postcontrast injection acquisition was performed and parameters were adapted to the subject's size and weight according to the ALARA (as low as reasonably achievable) rule. DLP (dose-length product) was registered for each study. One hundred to 120 ml of contrast agent (300 mg iodine/ml) was administered iv by a power injector at 2.5–3 ml/sec. To detect arterial hypervascularized lesions, dynamic contrast-enhanced images were obtained after a 25- to 30-sec scan delay on the chest and after a 40- to 50-sec scan delay on the subdiaphragmatic area. Gantry rotation time, table feed per gantry rotation, pitch, and section profile were adapted to obtain images reconstructed every 1.25–2.5 mm with a 512×512 matrix and a standard reconstruction algorithm. In case of exclusion criteria and/or for pediatric explorations, TAP MRI with 3- to 5-mm-thick axial images T2-weighted with fat saturation and T1-weighted with fat saturation before and after iv contrast injection (gadolinium chelate, 0.1 μmol/kg body weight) were performed.

Reading images

A three-step process was used. First, a blind local analysis was performed in the investigation center. After anonymization, examinations were archived on CD in DICOM format and sent to the coordinating center. Radiological images were reviewed on a workstation equipped with a diagnostic digital picture archiving and communication system (Impax RS 3000 1K review station; Agfa Technical Imaging Systems, Richfield Park, NJ). Nuclear medicine images were reviewed on a Xeleris 2 workstation (GE Medical Systems SCS/GE Healthcare, Velizy, France). Central blinded readings were performed by radiological (composed of radiologists, for HN MRA and TAP CT scans) and scintigraphical (composed of nuclear medicine physicians, for mIBG scan and SRS) working groups, both including at least two study-certified readers with fellowship training in body imaging and 20 yr experience. Central readers read the images blind to results of other tests and to clinical information. When the interpretations of the local and central readings were different, centralized reading with knowledge of the clinical information but blind to results of the first readings and results of other tests

was performed. Central readers did not read images from their own institution.

Gold standard

The gold standard status for the diagnosis or exclusion of paragangliomas or pheochromocytomas was defined by an expert committee for each enrolled subject. It was based on the results of the two (local and central readings without clinical data) or three (local and central readings without clinical data and central readings with clinical data) available image readings and also clinical, biological, and genetic data (source data were verified by clinical research associate during routine visits of all clinical centers) available in medical records. Each tumor detected by each exam was confirmed or not by the expert committee. Thus, each patient was classified as normal (tumor-free, no paraganglioma detected), positive (one or more paraganglioma detected), or doubtful.

Statistical analysis

Continuous variables are presented as means ± 1 SD. When not normally distributed, continuous variables are expressed as medians and interquartile range (25–75th range). Categorical variables are presented as numbers and percentages. We obtained exact 95% confidence intervals (CIs) for sensitivity and specificity from the binomial distribution. We calculated likelihood ratios for a positive test result as sensitivity divided by (1 − specificity) and likelihood ratios for negative result as (1 − sensitivity) divided by specificity (27). We calculated 95% CIs for likelihood ratios by using the normal distribution approximation. Because a doubtful status was a possible result for all exams, we calculated performance characteristics in two different ways: 1) calculation of the likelihood ratio for a doubtful result and 2) exclusion of doubtful results from calculations. Likelihood ratio for a doubtful result was calculated as [(number of doubtful exams with a positive gold standard status/number of exams with a positive gold standard status)/(number of doubtful exams with a negative gold standard status/number of exams with a negative gold standard status)]. Doubtful results were reclassified as negative when the likelihood ratio was less than or equal to 1, and as positive when the likelihood ratio was more than 1.

We determined sensitivity and specificity for a given exam alone and for various combinations of exams as single tests. The result of a combined test was the result of the either positive rule, using results of exams after reclassification of doubtful results; *i.e.* if one of the exams taking part of the combined test was positive, the result of the combined test was positive. $P < 0.05$ was considered to be significant. SAS software version 9.2 (SAS Inc., Cary, NC) was used for all statistical analysis. The results are reported according to the recommendations of the STARD (Standards for the Reporting of Diagnostic accuracy studies) statement (28).

Results

The PGL.EVA study

From June 6, 2005, to December 22, 2009, 258 subjects were recruited prospectively (Fig. 1). Eighteen patients were not enrolled: seven refused to participate, three were wrongly included after the identification of a nonfunctional *SDH* polymorphism, and for eight, the local investigation center was not able to organize the exams before the end of the recruitment period. Central reading was not possible for two subjects due to technical problems with CD writing. Thus, 238 subjects were included in the PGL.EVA study; 10 of the 23 centers enrolled at least 10 patients (Supplemental Fig. 1). Finally, the PGL.EVA cohort contained 124 *SDHB*, 96 *SDHD*, and 18 *SDHC* mutation carriers including 113 index cases and 125 relatives.

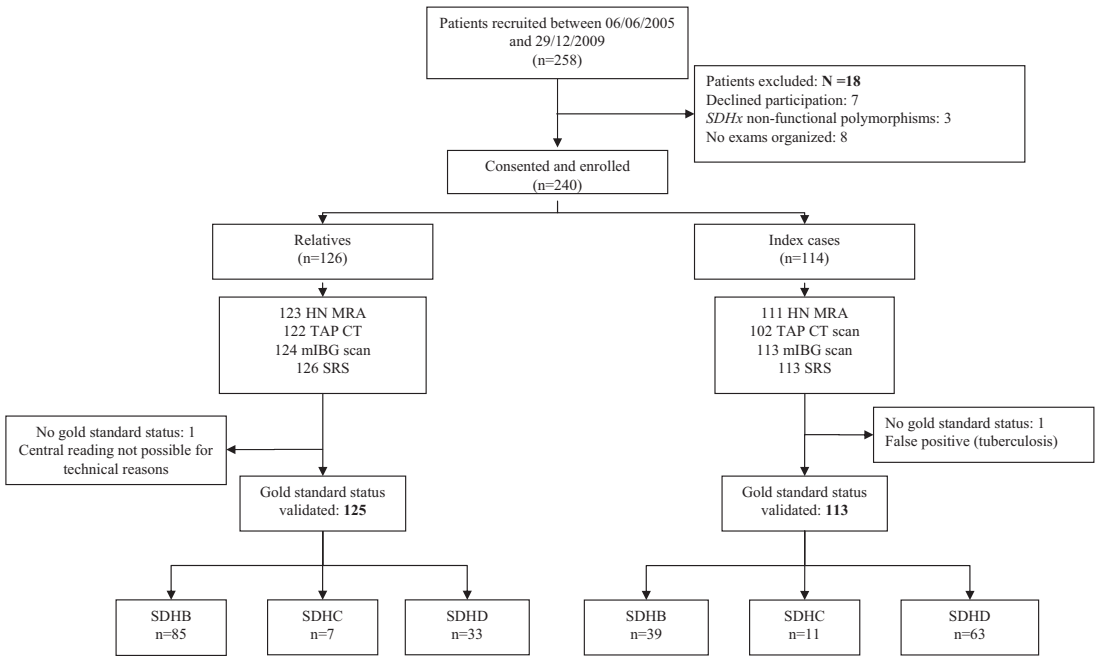

FIG. 1. Flowchart of the PGL.EVA study.

Patients and tumors

On inclusion, the relatives were younger than the index cases (39.0 *vs.* 46.6 yr) (Table 1). There were no differences between relatives and index cases concerning body mass index and blood pressure (Supplemental Table 2). According to the gold standard status established by the expert committee, a tumor-positive status was assigned to 96 (40.3%), a doubtful status to three (1.3%), and a tumor-free or normal status to 139 (58.4%) subjects (Supplemental Table 3). The PGL-.EVA study identified one, or several, paragangliomas in 21 (16.8%) relatives and in 75 (66.4%) index cases. A total of 202 tumors were diagnosed in 96 subjects: 185 paragangliomas (151 in the head and neck, 18 in the thorax, 16 in the pelvic area) and 17 pheochromocytomas (Table 2). There was no association between type of mutation and either gold standard status (33 positive gold standard status of 82 missense mutations, 40.2%, *vs.* 66 positive gold standards status of 156 non-missense mutations, 42.3%, $P = 0.76$). In relatives, 39 tumors were detected for the first time including 30 head and neck paragangliomas, five pheochromocytomas, and four abdominal or pelvic paragangliomas. In index cases, 163 tumors were detected, 89 for the first time and 74 previously known (29 had previously been treated by surgery or radiotherapy and 45 were followed medically). Among the 99 patients with a positive (n = 96) or a doubtful (n = 3) status, 46 of 79 (58.2%) produced an excess of plasma normetanephrine, 43 of 79 (54.4%) of 3-methoxytyramine, 18 of 85 (21.2%) of chromogranin A, and four of 78 (5.1%) of metanephrine (Supplemental Table 4).

Diagnostic performances of the four imaging tests

The diagnostic performances of the four tests are described in Table 3 and Supplemental Tables 5, 6, and 7. For detection of all paragangliomas or pheochromocytomas by local centers, HN MRA plus TAP CT scan had a higher sensitivity (85.4%) and specificity (96.4%) than mIBG scan or SRS (sensitivity, 42.7 and 69.5%; specificity, 89.8 and 97.1%, respectively). The expert central readings significantly increased the sensitivity of

TABLE 1. General characteristics of patients according to their status (index or relative) and their *SDHx* mutation

	SDHB	*SDHC*	*SDHD*	All
Index cases				
Number (n)	39	11	63	113
Mean age ± SD (yr)	47.1 ± 13.8	44.5 ± 13.4	46.6 ± 14.8	46.6 ± 14.3
Minor [n (%)]	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.9)
Women [n (%)]	18 (46.2)	8 (72.7)	35 (55.6)	61 (54.0)
Family history [n (%)]	13 (33.3)	2 (18.2)	44 (69.8)	59 (52.2)
Hypertension history [n (%)]	13 (33.3)	3 (27.3)	25 (39.7)	41 (36.3)
Mean age at first diagnosis ± SD (yr)	41.0 ± 13.0	38.8 ± 14.1	35.9 ± 14.9	37.9 ± 14.3
Diagnosis before inclusion [n (%)]				
Head and neck PGL only	22 (56.4)	9 (81.8)	49 (77.8)	80 (70.8)
Thoracic, abdominal, or pelvic PGL	12 (30.8)	2 (18.2)	0 (0.0)	14 (12.4)
Adrenal PGL or pheochromocytoma(s) only	3 (7.7)	0 (0.0)	3 (4.8)	6 (5.31)
Head and neck PGL and thoracic, abdominal, or pelvic PGL	1 (2.6)	0 (0.0)	5 (7.9)	6 (5.3)
Pheochromocytoma(s) and head and neck PGL	0 (0.0)	0 (0.0)	3 (4.8)	3 (2.7)
Pheochromocytoma(s) and thoracic, abdominal, or pelvic PGL	1 (2.6)	0 (0.0)	1 (1.6)	2 (1.8)
Pheochromocytoma(s); head and neck PGL; and thoracic, abdominal, or pelvic PGL	0 (0.0)	0 (0.0)	2 (3.2)	2 (1.8)
Relatives				
Number (n)	85	7	33	125
Mean age ± SD (yr)	40.6 ± 15.1	34.9 ± 15.3	35.9 ± 18.5	39.0 ± 16.1
Minor [n (%)]	5 (5.9)	0 (0.0)	6 (18.2)	11 (8.8)
Women [n (%)]	52 (61.2)	5 (71.4)	16 (48.5)	73 (58.4)
Hypertension history [n (%)]	14 (16.5)	2 (28.6)	5 (15.2)	21 (16.8)
All patients				
Number (n)	124	18	96	238
Mean age ± SD (yr)	42.6 ± 15.0	40.8 ± 14.5	42.9 ± 16.9	42.6 ± 15.7
Aged 6–18 [n (%)]	5 (4.0)	0 (0.0)	7 (7.3)	12 (5.0)
Women [n (%)]	70 (56.5)	13 (72.2)	51 (53.1)	134 (56.3)
Family history [n (%)]	98 (79.0)	9 (50.0)	77 (80.2)	184 (77.3)
Hypertension history [n (%)]	27 (21.8)	5 (27.8)	30 (31.3)	62 (26.1)

PGL, Paraganglioma.

TABLE 2. Number and localizations of diagnosed paraganglioma/pheochromocytoma

	***SDHB* mutation carriers**	***SDHC* mutation carriers**	***SDHD* mutation carriers**	**All *SDHx* mutation carriers**
Index cases				
All tumors (n)	24	7	132	163
All previously diagnosed tumors [n (SG/RT/UT)]	*12* (*5/2/5*)	*4* (*1/1/2*)	*58* (*9/11/38*)	*74* (*15/14/45*)
Head and neck PGL [n (%)]	15 (*62.5*)	7 (*100.0*)	99 (*75.0*)	121 (*74.2*)
Carotid (n)	6	1	40	47
Tympano-jugular (n)	6	3	23	32
Vagal (n)	3	1	33	37
Larynx (n)	0	2	3	5
Head and neck PGL previously diagnosed [n (SG/RT/UT)]	*9* (*3/1/5*)	*4* (*1/1/2*)	*51* (*9/11/31*)	*64* (*13/13/38*)
Thoracic PGL [n (%)]	3 (*12.5*)	0 (*0.0*)	15 (*11.4*)	18 (*11.0*)
Thoracic PGL previously diagnosed [n (SG/RT/UT)]	*1* (*0/1/0*)	*0* (*0/0/0*)	*1* (*0/0/1*)	*2* (*0/1/1*)
Abdominal or pelvic PGL [n (%)]	5 (*20.8*)	0 (*0.0*)	7 (*5.3*)	12 (*7.4*)
Abdominal or pelvic PGL previously diagnosed [n (SG/RT/UT)]	*2* (*2/0/0*)	*0* (*0/0/0*)	*2* (*0/0/2*)	*4* (*2/0/2*)
Adrenal PGL or pheochromocytoma [n (%)]	1 (*4.2*)	0 (*0.0*)	11 (*8.3*)	12 (*7.4*)
Pheochromocytoma previously diagnosed [n (SG/RT/UT)]	*0* (*0/0/0*)	*0* (*0/0/0*)	*4* (*0/0/4*)	*4* (*0/0/4*)
Relatives				
All tumors (n)	4	0	35	39
Head and neck PGL [n (%)]	3 (75.00)	0 (0.00)	27 (77.1)	30 (76.9)
Carotid (n)	3	0	17	20
Tympano-jugular (n)	0	0	0	0
Vagal (n)	0	0	10	10
Larynx (n)	0	0	0	0
Thoracic PGL [n (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.00)
Abdominal or pelvic PGL [n (%)]	0 (0.0)	0 (0.0)	4 (11.4)	4 (10.3)
Adrenal PGL or Pheochromocytoma [n (%)]	1 (25.0)	0 (0.0)	4 (11.4)	5 (12.8)
All patients				
All tumors (n)	28	7	167	202
Head and neck PGL [n (%)]	18 (64.3)	7 (100.0)	126 (75.5)	151 (74.8)
Thoracic PGL [n (%)]	3 (10.7)	0 (0.0)	15 (9.0)	18 (8.9)
Abdominal or pelvic PGL [n (%)]	5 (17.9)	0 (0.0)	11 (6.6)	16 (7.9)
Adrenal PGL or Pheochromocytoma [n (%)]	2 (7.1)	0 (0.0)	15 (9.0)	17 (8.4)

PGL, Paraganglioma; RT, radiotherapy; SG, surgery; UT, untreated. Previously diagnosed PGL are indicated in *italics*.

the HN MRA plus TAP CT scan to 91.7% (95% CI = 84.2–96.3) and that of the SRS to 82.4% (95% CI = 73.0–89.6), but this was not the case for the mIBG scan. Overall, the diagnostic performance of mIBG scan was less accurate; even for the diagnosis of the 17 pheochromocytomas detected by the PGL.EVA study, the sensitivity of TAP CT scan (100%) was higher than that of mIBG scan (72.7%).

The SRS had a higher sensitivity and specificity for head and neck and thoracic paraganglioma than for abdominal and pelvic paraganglioma or adrenal paraganglioma or pheochromocytoma. For head and neck paraganglioma, the sensitivity of HN MRA was higher (90.4–95.1 *vs.* 75–79%) than that of SRS whatever the reading. By contrast, for thoracic paraganglioma, the sensitivity of local reading of CT scans was lower (46.2%) than that of SRS (61.5%). This discrepancy disappeared after central reading with clinical data (sensitivity of 84.6% for CT scan and 83.3% for SRS).

Local reading of radiological imaging can fail to diagnose thoracic paraganglioma, so we tested the diagnostic performances of combinations of exams (Table 4). The best combination was HN MRA plus TAP CT scan plus SRS. For all localizations, this combination raised the sensitivity from 85.7 (95% CI = 76.4–92.4) to 91.7% (95% CI = 83.6–96.6) (Fig. 2).

Discussion

The recent work on paraganglioma and pheochromocytoma demonstrating that affected patients may carry a germline mutation in one paraganglioma susceptibility gene has dramatically changed the management of patients. In *SDHx* mutation carriers, multiple paragangliomas can emerge at sites distant from the first paraganglioma. Consequently, genetically predisposed patients required multiple investigations and multidisciplinary management. The PGL.EVA

TABLE 3. Diagnostic performances of the different exams for paraganglioma/pheochromocytoma diagnosis

	HN MRA + TAP CT scans	mIBG scan	SRS
n	235	236	237
All PGL			
Local reading			
Sensitivity (95% CI)	85.4 (76.7–91.8)	42.7 (32.7–53.2)	69.5 (59.2–78.5)
Specificity (95% CI)	96.4 (91.8–98.8)	89.8 (83.5–94.3)	97.1 (92.8–99.2)
Central reading without clinical data			
Sensitivity (95% CI)	86.5 (78.0–92.6)	43.8 (33.3–54.8)	72.5 (62.2–81.4)
Specificity (95% CI)	95.0 (89.9–98.0)	90.9 (84.7–95.2)	94.8 (89.6–97.9)
Central reading with clinical data			
Sensitivity (95% CI)	91.7 (84.2–96.3)	40.5 (30.2–51.4)	82.4 (73.0–89.6)
Specificity (95% CI)	96.4 (91.8–98.8)	93.2 (87.5–96.8)	92.6 (86.8–96.4)
Head and neck PGL			
Local reading			
Sensitivity (95% CI)	90.4 (81.9–95.8)	30.6 (21.1–41.5)	75.0 (64.4–83.8)
Specificity (95% CI)	92.0 (86.4–95.8)	96.0 (91.6–98.5)	94.1 (89.1–97.3)
Central reading without clinical data			
Sensitivity (95% CI)	91.5 (83.2–96.5)	34.2 (23.9–45.7)	72.8 (61.8–82.1)
Specificity (95% CI)	96.6 (92.1–98.9)	93.8 (88.5–97.1)	96.6 (92.2–98.9)
Central reading with clinical data			
Sensitivity (95% CI)	95.1 (88.0–98.7)	25.3 (16.2–36.4)	79.0 (68.5–87.3)
Specificity (95% CI)	99.3 (96.2–100.0)	94.5 (89.4–97.6)	95.2 (90.4–98.1)
Thoracic PGL			
Local reading			
Sensitivity (95% CI)	46.2 (19.2–74.9)	30.8 (9.1–61.4)	61.5 (31.6–86.1)
Specificity (95% CI)	100.0 (98.3–100.0)	98.7 (96.1–99.7)	94.2 (90.2–96.9)
Central reading without clinical data			
Sensitivity (95% CI)	76.9 (46.2–95.0)	33.3 (9.9–65.1)	75.0 (42.8–94.5)
Specificity (95% CI)	98.0 (95.0–99.5)	98.1 (95.2–99.5)	96.7 (93.4–98.7)
Central reading with clinical data			
Sensitivity (95% CI)	84.6 (54.6–98.1)	41.7 (15.2–72.3)	83.3 (51.6–97.9)
Specificity (95% CI)	100.0 (98.2–100.0)	98.1 (95.2–99.5)	96.7 (93.4–98.7)
Abdominal and pelvic PGL			
Local reading			
Sensitivity (95% CI)	53.9 (25.1–80.8)	53.9 (25.1–80.8)	38.5 (13.9–68.4)
Specificity (95% CI)	99.5 (97.4–100.0)	92.8 (88.6–95.8)	91.5 (87.0–94.8)
Central reading without clinical data			
Sensitivity (95% CI)	83.3 (51.6–97.9)	46.2 (19.2–74.9)	33.3 (9.9–65.1)
Specificity (95% CI)	98.5 (95.7–99.7)	96.2 (92.6–98.3)	97.2 (94.0–99.0)
Central reading with clinical data			
Sensitivity (95% CI)	83.3 (51.6–97.9)	30.8 (9.1–61.4)	33.3 (9.9–65.1)
Specificity (95% CI)	98.5 (95.7–99.7)	98.1 (95.2–99.5)	99.5 (97.4–100.0)
Adrenal PGL or pheochromocytoma			
Local reading			
Sensitivity (95% CI)	100.0 (76.8–100.0)	42.9 (17.7–71.1)	14.3 (1.8–42.8)
Specificity (95% CI)	95.7 (92.1–98.0)	100.0 (98.4–100.0)	100.0 (98.4–100.0)
Central reading without clinical data			
Sensitivity (95% CI)	100.0 (75.3–100.0)	72.7 (39.0–94.0)	0.0
Specificity (95% CI)	95.6 (91.8–98.0)	100.0 (98.3–100.0)	100.0 (98.3–100.0)
Central reading with clinical data			
Sensitivity (95% CI)	100.0 (75.3–100.0)	72.7 (39.0–94.0)	0.0
Specificity (95% CI)	97.5 (94.4–99.2)	100.0 (98.3–100.0)	100.0 (98.3–100.0)

PGL, Paraganglioma.

study aimed to establish recommendations and/or guidelines about the use of imaging for screening for paragangliomas and pheochromocytomas in *SDHx* mutation carriers. To our knowledge, our series of 238 *SDHx* mutation carriers, recruited prospectively, is the largest published cohort of *SDHx* subjects, who all underwent the same imaging exams by the same procedures analyzed by local and centralized readings. We demonstrate that the best combination of exams to detect paraganglioma in routine practice is HN MRA and TAP CT plus SRS. Clearly, [^{123}I]mIBG scintigraphy is of little value for screening for hereditary paraganglioma or pheochromocytoma but remains useful for

TABLE 4. Diagnostic performances of the exams tested in the PGL.EVA study in combination (only for the 213 patients who underwent all four exams)

	HN MRA + TAP CT + mIBG scan	HN MRA + TAP CT + SRS	mIBG scan + SRS	HN MRA + TAP CT + mIBG scan + SRS
n	213	213	213	213
All PGL				
Local reading				
Sensitivity (95% CI)	88.1 (79.2–94.1)	91.7 (83.6–96.6)	73.8 (63.1–82.8)	91.7 (83.6–96.6)
Specificity (95% CI)	88.4 (81.6–93.3)	95.4 (90.2–98.3)	87.6 (80.6–92.7)	86.8 (79.7–92.1)
Central reading without clinical data				
Sensitivity (95% CI)	91.4 (82.3–96.8)	95.7 (88.0–99.1)	85.7 (75.3–92.9)	95.7 (88.0–99.1)
Specificity (95% CI)	84.5 (76.6–90.5)	82.8 (74.6–89.1)	81.0 (72.7–87.7)	75.9 (67.0–83.3)
Central reading with clinical data				
Sensitivity (95% CI)	92.9 (84.1–97.6)	98.6 (92.3–100.0)	90.0 (80.5–95.9)	98.6 (92.3–100.0)
Specificity (95% CI)	89.7 (82.6–94.5)	89.7 (82.6–94.5)	87.1 (79.6–92.6)	84.5 (76.6–90.5)
Head and neck PGL				
Local reading				
Sensitivity (95% CI)	90.4 (81.2–96.1)	94.5 (86.6–98.5)	74.0 (62.4–83.6)	94.5 (86.6–98.5)
Specificity (95% CI)	91.4 (85.5–95.5)	90.0 (83.8–94.4)	91.4 (85.5–95.5)	87.9 (81.3–92.8)
Central reading without clinical data				
Sensitivity (95% CI)	95.2 (86.5–99.0)	96.8 (88.8–99.6)	75.8 (63.3–85.8)	96.8 (88.8–99.6)
Specificity (95% CI)	91.1 (84.7–95.5)	94.4 (88.7–97.7)	91.1 (84.7–95.5)	89.5 (82.7–94.3)
Central reading with clinical data				
Sensitivity (95% CI)	95.2 (86.5–99.0)	98.4 (91.3–100.0)	82.3 (70.5–90.8)	98.4 (91.3–100.0)
Specificity (95% CI)	93.6 (87.7–97.2)	94.4 (88.7–97.7)	90.3 (83.7–94.9)	90.3 (83.7–94.9)
Thoracic PGL				
Local reading				
Sensitivity (95% CI)	53.9 (25.1–80.8)	76.9 (46.2–95.0)	61.5 (31.6–86.1)	76.9 (46.2–95.0)
Specificity (95% CI)	98.5 (95.7–99.7)	94.0 (89.8–96.9)	94.0 (89.8–96.9)	94.0 (89.8–96.9)
Central reading without clinical data				
Sensitivity (95% CI)	83.3 (51.6–97.9)	100.0 (73.5–100.0)	75.0 (42.8–94.5)	100.0 (73.5–100.0)
Specificity (95% CI)	96.0 (91.9–98.4)	95.4 (91.1–98.0)	96.0 (91.9–98.4)	93.7 (89.0–96.8)
Central reading with clinical data				
Sensitivity (95% CI)	91.7 (61.5–99.8)	100.0 (73.5–100.0)	83.3 (51.6–97.9)	100.0 (73.5–100.0)
Specificity (95% CI)	99.4 (96.8–100.0)	97.7 (94.2–99.4)	97.1 (93.4–99.1)	97.1 (93.4–99.1)
Abdominal and pelvic PGL and adrenal PGL or pheochromocytoma				
Local reading				
Sensitivity (95% CI)	87.0 (66.4–97.2)	87.0 (66.4–97.2)	65.2 (42.7–83.6)	91.3 (72.0–98.9)
Specificity (95% CI)	87.4 (81.8–91.7)	85.3 (79.4–90.0)	87.4 (81.8–91.7)	82.1 (75.9–87.3)
Central reading without clinical data				
Sensitivity (95% CI)	93.3 (68.1–99.8)	100.0 (78.2–100.0)	66.7 (38.4–88.2)	100.0 (78.2–100.0)
Specificity (95% CI)	91.8 (86.6–95.5)	90.1 (84.6–94.1)	94.7 (90.2–97.6)	88.9 (83.2–93.2)
Central reading with clinical data				
Sensitivity (95% CI)	93.3 (68.1–99.8)	100.0 (78.2–100.0)	73.3 (44.9–92.2)	100.0 (78.2–100.0)
Specificity (95% CI)	94.7 (90.2–97.6)	94.7 (90.2–97.6)	95.9 (91.8–98.3)	93.0 (88.1–96.3)
Abdominal and pelvic PGL				
Local reading				
Sensitivity (95% CI)	76.9 (46.2–95.0)	69.2 (38.6–90.9)	61.5 (31.6–86.1)	84.6 (54.6–98.1)
Specificity (95% CI)	92.5 (87.9–95.7)	92.0 (87.3–95.4)	87.0 (81.5–91.3)	87.0 (81.5–91.3)
Central reading without clinical data				
Sensitivity (95% CI)	88.9 (51.8–99.7)	88.9 (51.8–99.7)	55.6 (21.2–86.3)	100.0 (66.4–100.0)
Specificity (95% CI)	94.9 (90.6–97.7)	94.9 (90.6–97.7)	93.2 (88.5–96.5)	92.1 (87.1–95.6)
Central reading with clinical data				
Sensitivity (95% CI)	88.9 (51.8–99.7)	88.9 (51.8–99.7)	44.4 (13.7–78.8)	100.0 (66.4–100.0)
Specificity (95% CI)	97.2 (93.5–99.1)	98.3 (95.1–99.7)	97.7 (94.3–99.4)	96.6 (92.8–98.8)
Adrenal PGL or pheochromocytoma				
Local reading				
Sensitivity (95% CI)	100.0 (75.3–100.0)	100.0 (75.3–100.0)	46.2 (19.2–74.9)	100.0 (75.3–100.0)
Specificity (95% CI)	95.5 (91.6–97.9)	95.5 (91.6–97.9)	100.0 (98.2–100.0)	95.5 (91.6–97.9)
Central reading without clinical data				
Sensitivity (95% CI)	100.0 (63.1–100.0)	100.0 (63.1–100.0)	75.0 (34.9–96.8)	100.0 (63.1–100.0)
Specificity (95% CI)	94.9 (90.6–97.7)	94.9 (90.6–97.7)	100.0 (98.0–100.0)	94.9 (90.6–97.7)
Central reading with clinical data				
Sensitivity (95% CI)	100.0 (63.1–100.0)	100.0 (63.1–100.0)	75.0 (34.9–96.8)	100.0 (63.1–100.0)
Specificity (95% CI)	97.2 (93.6–99.1)	97.2 (93.6–99.1)	100.0 (98.0–100.0)	97.2 (93.6–99.1)

PGL, Paraganglioma.

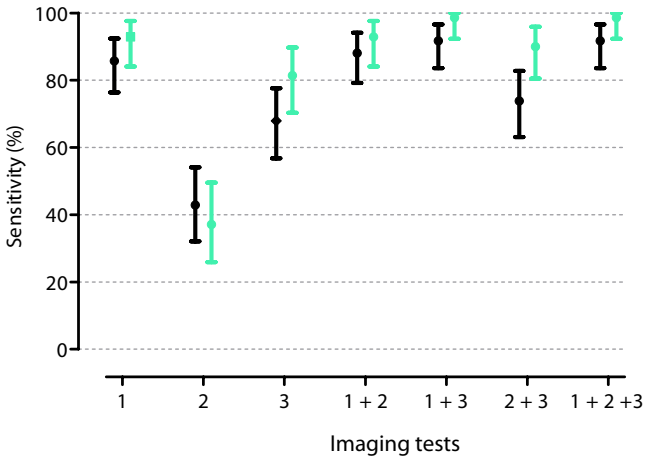

FIG. 2. Sensitivity of the screening methods tested in the PGL.EVA study to detect paragangliomas or pheochromocytomas in *SDHx* mutation carriers with assessment by local reading (*black*) and by central reading with clinical data (*green*). *Circles* and *bars* represent sensitivity values and 95% CIs, respectively, for HN MRA/TAP CT scan (1), [^{123}I]mIBG scintigraphy (2), or SRS (3), alone or in combination [HN MRA/TAP CT scans plus mIBG scan (1 + 2), HN MRA/TAP CT scans plus SRS (1 + 3), or HN MRA/TAP CT scans plus mIBG scan plus SRS (1 + 2+3)].

patients with metastatic paraganglioma because they may receive [^{131}I]mIBG therapy (29).

Overall, the phenotype-genotype correlations for patients included in the PGL.EVA cohort were consistent with those in other published studies (14–18, 30–32). However, systematic analysis of the head and neck area by RMA revealed that more than half of the *SDHB* mutation carriers (62.5%) also developed head and neck paragangliomas, confirming that the head and neck of *SDHx* patients, even *SDHB* mutation carriers, must always be screened. Our data support familial genetic testing in *SDHx*-related families; previously unidentified paragangliomas were diagnosed in 17.6% of relatives.

The strengths of our multicenter study include the large cohort, the large number of investigation centers, and the quality of the readings. The power of radiological exams for screening for head, neck, abdominal, and pelvic paraganglioma has been demonstrated. We show that screening for thoracic paraganglioma in routine practice requires a nuclear exam. We also clearly demonstrate the value of a centralized expert reading that may help avoid additional nuclear investigations for the detection of thoracic paraganglioma that may be missed by nonexpert radiologists. This argues for the establishment of expert referral centers, including in particular radiological experts, dedicated to the management of *SDHx* hereditary paraganglioma patients.

The diagnostic performance of nuclear medicine exams observed in the PGL.EVA study were poorer than those previously published probably because our series was large and involved different instruments and gamma-cameras in the 22 investigation centers (33–35). SPECT-CT, allowing the fusion of SPECT data with CT images, improves the sensitivity of exams but was available only in a few centers at the beginning of the study. We tested SRS and mIBG scans because they were widely available and useable in 2005. Since then, novel positron emission tomography (PET) tracers became available, such as 6-[^{18}F]fluorodopamine (only in the United States), 6-[^{18}F]fluorodihydroxyphenylalanine ([^{18}F]FDOPA), and 2-[^{18}F]fluorodeoxyglucose ([^{18}F]FDG) (36). Superior spatial resolution of PET studies allows the detection of small and metastatic lesions and whole-body scans. In a large prospective study (216 consecutive patients, 66 patients with *SDHB* and 12 with *SDHD* mutations), Timmers *et al.* (37) indicate that metastases are better detected by [^{18}F]FDG PET than by [^{123}I]mIBG SPECT with sensitivities of 80 and 49%, respectively, and was superior to detect bone metastases than whole-body CT and/or MRI (sensitivity 94 *vs.* 79%) and confirm that the sensitivity of [^{18}F]FDG PET is higher in *SDHB/D*-related than non-*SDHB/D*-related metastatic paragangliomas and pheochromocytomas. The role of [^{18}F]FDG among other imaging modalities (MRI, [^{18}F]FDOPA PET, SRS, *etc.*) remains to be determined for paraganglioma diagnosis (37). In a prospective study (30 patients, two *SDHB* and six *SDHD* mutation carriers), Fottner *et al.* (38) correlate functional imaging results with genetic and biochemical findings. [^{18}F]FDOPA PET is superior to [^{123}I]mIBG scintigraphy (sensitivity 98 *vs.* 53%) in patients with extraadrenal, noradrenaline-producing, hereditary paraganglioma, especially *SDHD* related (sensitivity 96 *vs.* 40%). In a recent meta-analysis (275 patients with suspected paraganglioma, 31 *SDHB* mutations), the pooled sensitivity of [^{18}F]FDOPA PET or PET/CT to paraganglioma detection was 91% and specificity was 95% (per patient). But, an unexplained significant increase of [^{18}F]FDOPA PET or PET/CT sensitivity was observed, when *SDHB* mutation carriers were excluded. Accuracy measured by area under the ROC curve was 0.95 and equal to 0.97 after exclusion of *SDHB* mutation carriers (39). Altogether, these recent data suggest that PET appears to be useful for paraganglioma diagnosis and should detect more lesions than SRS with [^{18}F]FDOPA and more metastases than SRS with [^{18}F]FDG, especially for *SDHB* carriers. Several compounds, the [^{68}Ga]DOTA 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-peptides (novel somatostatin-receptor-derived tracers for PET scanning), are suitable for PET-CT SRS. [^{68}Ga]DOTA-1-NaI3-octreotide has a wider spectrum of affinity for somatostatin receptor subtypes than [^{68}Ga]DOTA-Tyr3-octreotide acid. A recent prospective study showed the high sensitivity of [^{68}Ga]DOTA-1-NaI3-octreotide for both paragan-

glioma and pheochromocytoma. Most of the extraadrenal tumors were negative on [^{131}I]mIBG and new lesions compared with conventional imaging were detected (particularly, detection of multiple vertebral metastases for a patient with multiple head and neck paragangliomas, with isotopic therapeutic perspectives) (40). Similar results were obtained in a retrospective study with [^{68}Ga]DOTA-Tyr3-octreotide acid (41). However, all these studies were performed in monocentric series. Furthermore, the number of *SDHx* mutation carriers investigated was lower, and the reading procedures followed were not as robust as those used in the PGL.EVA study. New prospective studies, with a PGL.EVA-like design, should be initiated to assess the diagnostic performance of PET using all these novel tracers for screening *SDHx* mutation carriers.

Finally, the PGL.EVA study data clearly demonstrates that in routine practice, initial screening of *SDHx* mutation carriers should involve HN MRA plus TAP CT scan and SRS. The next step for *SDHx*-related hereditary paraganglioma families will be the validation of guidelines and/or recommendations for long-term follow-up, in particular the type and frequency of investigations.

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