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Looking beyond the thyroid: advances in the understanding of pheochromocytoma and hyperparathyroidism phenotypes in MEN2 and of non-MEN2 familial forms

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**ENDOCRINE-RELATED
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**OF MEN2 AND NON MEN2 FAMILIAL PHEOCHROMOCYTOMA
AND HYPERPARATHYROIDISM**

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1 **LOOKING BEYOND THE THYROID - ADVANCES IN UNDERSTANDING OF**
2 **PHEOCHROMOCYTOMA AND HYPERPARATHYROIDISM PHENOTYPES IN**
3 **MEN2 AND OF NON-MEN 2 FAMILIAL FORMS**

4

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25 **ABSTRACT**

26 Over the last years, the knowledge of MEN2 and non MEN2 familial forms of
27 pheochromocytoma (PHEO) has increased. In MEN2, PHEO is the second most
28 frequent disease: the penetrance and age at diagnosis depend on the mutation of
29 *RET*. Given the prevalence of bilateral PHEO (50% by age 50), adrenal sparing
30 surgery, aimed at sparing a part of the adrenal cortex to avoid adrenal insufficiency,
31 should be systematically considered in patients with bilateral PHEO. Non MEN2
32 familial forms of PHEO now include several new causative genes: however, only
33 small phenotypic series have been reported, and follow-up series are needed to
34 better understand the outcome of patients carrying mutations of these genes. The
35 first part of this review will mainly focus on these points.

36 In the second part, a focus will be given on MEN2 and non MEN2 familial forms of
37 hyperparathyroidism (HPTH). Again, the management of MEN2 HPTH should be
38 aimed at curing the disease while preserving an optimal quality of life by a tailored
39 parathyroidectomy. The phenotypes and outcome of MEN1, MEN4 and HRPT2
40 related HPTH are briefly described, with a focus on the most recent literature data,
41 and is compared with familial hypocalciuric hypercalcemia.

42

43

44 1. INTRODUCTION

45 The majority of the studies published on MEN2 focused on medullary thyroid cancer
46 (MTC), as it represents the first manifestation of the disease, and can lead to a fatal
47 outcome if undiagnosed or inappropriately treated (Wells, et al. 2013). However, in
48 familial cases with early genetic diagnosis, the guidelines recommend prophylactic
49 thyroidectomy leading to the absence of residual thyroid disease (Wells, et al. 2015).
50 Thus, the chronic disease risk of MEN2 is the development of pheochromocytoma
51 (PHEO), and less frequently of hyperparathyroidism (HPTH). The aim of this review
52 is first to detail the main characteristics and the management of MEN2 PHEO, and
53 then to define the main other etiologies of hereditary bilateral PHEO (table 1). A
54 similar review will be made for HPTH.

55

56 2. PHEOCHROMOCYTOMA IN MEN2 AND NON-MEN2 FAMILIAL FORMS

57 PHEO are neuroendocrine tumors arising from adrenal medulla cells.
58 Paragangliomas (PGL) originate from sympathetic or parasympathetic paraganglia;
59 they have rarely been reported in MEN2 patients (less than 1% in our series of 1210
60 patients with MEN2) (Castinetti, et al. 2014), but constitute a unique entity together
61 with PHEO in other hereditary forms.

62

63 a. MEN2 PHEO

64 Epidemiology and genetics

65 PHEO is the second most frequent disease in patients with MEN2. It is usually
66 diagnosed in the 3rd-4th decade (Nguyen, et al. 2001). Even if some reports
67 mentioned the possibility of PHEO first, with a delayed appearance of MTC, PHEO is
68 diagnosed concomitantly or after the diagnosis of MTC in the very large majority of

69 cases. Imai et al. reported that 17% of their 144 MEN2 patients were actually
70 diagnosed with PHEO before MTC (Imai, et al. 2013): however, calcitonin
71 measurement was not systematically performed, nor, obviously thyroidectomy, and it
72 is thus not sure that these patients indeed had normal C-cells at the time of PHEO
73 diagnosis.

74 The penetrance and age at diagnosis of PHEO in MEN2 seems to be dependent on
75 the *RET* mutation. For instance, Imai et al. reported that the penetrance of PHEO
76 was 52% by age 50 in codon 634 *RET* mutation carriers, while it was 36% at last
77 follow-up in patients with mutations other than codons 634 and 918 (Imai et al. 2013).

78 In our large series based on 563 individuals presenting with MEN2 PHEO, while 60%
79 patients with 634-*RET* mutations had at least one PHEO at last follow-up (median
80 age at first diagnosis, 35 years old), less than 20% of patients carrying with *RET*
81 *exon 10* mutations presented with PHEO at age 35 (Castinetti et al. 2014). A strong
82 genotype/phenotype correlation thus exists for PHEO penetrance in MEN2 patients.

83 However, we recently reported that the penetrance of PHEO in MEN2 was variable
84 depending on the geographic area, with an age at first diagnosis of PHEO
85 significantly higher in South America than in Europe (Castinetti, et al. 2017). The
86 American Thyroid Association (ATA) guidelines recommended screening for PHEO
87 beginning at 11 years for children in the ATA-high and highest risk (*RET* codons 634,
88 883 and 918) and 16 years in the ATA-moderate risk (all the other codons) (Wells et
89 al. 2015). Of note, one case report described the occurrence of PHEO in an 8-year
90 old boy carrying a 634 *RET* codon mutation (Rowland, et al. 2013).

91 Interestingly, in MEN2, patients within the same family, ie. carrying the same
92 mutation and theoretically exposed to the same environment, can present a different
93 penetrance of PHEO (absence, unilateral or bilateral): this might be due to modifying

94 genes as recently suggested to explain at least partly the difference of MTC
95 aggressiveness in patients with MEN2A compared to MEN2B (Oczko-
96 Wojciechowska, et al. 2017). Siqueira et al. had already shown that RET
97 polymorphisms had an influence on the prevalence of MEN2 PHEO. For instance,
98 the presence of two RET variants among *L769L*, *S836S*, and *G691S/S904S* was
99 associated with an increased risk for early PHEO development (Siqueira, et al.
100 2014).

101 The outcome of MEN2 PHEO is usually good in specialized MEN/endocrine referral
102 centers. Thosani et al. reported only 2 deaths out of 84 patients, because of PHEO
103 with hypertensive crises and autopsy diagnosis: however, the diagnostic procedure
104 had been performed in the 1960's, and such events now appear to be very rare in the
105 modern era of PHEO management (Thosani, et al. 2013). In our series, 5 deaths
106 (<1%) were due to PHEO, 4 because of hypertensive crises in undiagnosed patients,
107 and 1 because of diffuse PHEO metastases (Castinetti et al. 2014).

109 Diagnosis

110 Diagnosis follows the same procedure as sporadic PHEO. Of note, in our series, one
111 third of the patients were not symptomatic (hypertension, headaches, sweating) at
112 the time PHEO was diagnosed (Castinetti et al. 2014). Systematic screening should
113 thus be performed regularly even in the absence of clinical signs suggestive of
114 PHEO. From a pathophysiological viewpoint, adrenomedullary hyperplasia precedes
115 PHEO, and PHEO are frequently multifocal in the same adrenal gland (Korpershoek,
116 et al. 2014). Symptoms of catecholamine oversecretion can be already seen at the
117 stage of hyperplasia. The development of PHEO in MEN2 is usually progressive, and
118 bilateral PHEO are not always synchronous: metachronous PHEO have been

119 reported in up to 25% cases after a mean period of 5-10 years (Castinetti et al. 2014;
120 Thosani et al. 2013), requiring a prolonged follow-up after the first surgery. Positive
121 diagnosis is based on increased plasma or urinary free metanephrines and
122 normetanephrines (Bravo and Tagle 2003; Eisenhofer, et al. 2011). Imaging should
123 be performed only when biochemistry becomes positive.

124 Imaging

125 Once the biochemical diagnosis is established, the PHEO needs to be localized. The
126 commonest approach for localizing PHEO is to perform anatomical imaging studies.
127 Although CT is a radiation-ionizing diagnostic imaging, it provides a higher resolution
128 than MRI enabling detection of unique and multiple PHEO including those that can
129 coexist within the same glands. Most importantly, anatomical imaging may also
130 guides surgeons towards the most appropriate surgical strategy (total vs subtotal).
131 Therefore, the follow-up of MEN2-related PHEO should not be delayed beyond the
132 scheduled time for subtotal adrenalectomy (cortical-sparing surgery). Many of the
133 MEN2 patients do not need any specific functional imaging since the tumors are
134 almost always confined to the adrenal gland and the likelihood of metastasis is very
135 small. Currently, several specific radiopharmaceuticals (^{123}I -MIBG, ^{18}F -FDA, ^{18}F -
136 FDOPA PET and ^{68}Ga -DOTA-somatostatin analogs) are available. The main
137 advantage of ^{18}F -FDOPA compared to other radiopharmaceuticals is the absence or
138 faintly uptake by normal adrenal glands. On ^{18}F -FDOPA PET/CT, uptake should be
139 considered as pathological only in cases of adrenal uptake more intense than the
140 liver with concordant enlarged gland. ^{18}F -FDOPA PET/CT can also detect residual
141 MTC in patients with persistent hypercalcitoninemia (Taieb, et al. 2012).

142 Treatment

143 Adrenal surgery is the only available treatment: it should be done before thyroid
144 surgery in case of concomitant diagnosis of MTC and PHEO. Bilateral adrenalectomy
145 should only be performed when synchronous bilateral PHEO are diagnosed
146 (Lairmore, et al. 1993). Interestingly, despite the screening procedures usually
147 leading to smaller PHEO at the time of surgery (compared with sporadic PHEO), the
148 risk of hypertensive episodes during resection is identical: a similar pharmacological
149 preparation predominantly with alpha blockers should thus be performed before
150 surgery (Scholten, et al. 2011b).

151 The question remains on the role of adrenal sparing surgery when bilateral
152 adrenalectomy is required in such patients. We and others have reported the
153 excellent short-term outcomes of such an approach: the idea of adrenal-sparing
154 surgery is to take off the PHEO while maintaining 1/3rd-1/4th of the gland to allow
155 maintenance of a normal cortisol and aldosterone function. Out of 552 patients
156 operated, adrenal sparing surgery was performed in 114 (20.6%). Normal cortisol
157 function was reported in 57% of patients operated for bilateral PHEO with at least 1
158 sparing surgery (Castinetti et al. 2014). The results were quite the same for Grubbs
159 et al., with 58% of normal glucocorticoid function in 33 patients operated with adrenal
160 sparing surgery (Grubbs, et al. 2013). The main risk of adrenal sparing surgery is
161 PHEO recurrence: indeed, complete adrenal medulla resection is technically
162 impossible, and the risk of recurrence in this germinal disease is thus very high: while
163 we had 3% risk of recurrence after 10 years of follow-up, other series reported 1-11%
164 risk of recurrence after a mean follow-up of 6-10 years after surgery (review in
165 (Castinetti, et al. 2016)). It is likely that this risk will increase dramatically the longer
166 the duration of follow-up. Prolonged follow-up is thus required in these patients. As
167 there is only a very low 1-4% risk of malignancy for MEN2 PHEO (Lee, et al. 1996),

168 we suggest that this procedure should be systematically considered in all patients
169 with MEN2 PHEO. Of note, adrenal sparing surgery has an inherent limit due to the
170 pathophysiology of MEN2 as PHEO are frequently multifocal in the same gland,
171 which can make sparing surgery impossible, because of the impossibility to maintain
172 a sufficient amount of normal cortical tissue (Korpershoek et al. 2014). Recurrence
173 after adrenal sparing surgery will be mainly treated by total adrenalectomy, or in
174 some very experienced Centers, by another partial adrenalectomy (Brauckhoff, et al.
175 2004).

176 In summary, PHEO will become the most prevalent disease of MEN2 given the fact
177 that young familial cases are treated by prophylactic thyroidectomy. The majority of
178 the patients will be asymptomatic at the time of diagnosis, which implies a regular
179 biological follow-up in asymptomatic carriers. Being able to perform an early
180 diagnosis of PHEO is mandatory to allow the surgeon to get the possibility to perform
181 adrenal-sparing surgery, and avoid the risk of permanent post-surgical adrenal
182 insufficiency in patients with bilateral PHEO.

183

184 **b. Non MEN2 familial forms: the cluster 2 genes**

185 Transcriptomic studies performed over recent years established a clustered
186 classification for PHEO/PGL (review in (Gimenez-Roqueplo, et al. 2012; Vicha, et al.
187 2013)). Cluster 1 is characterized by activation of the hypoxia-angiogenesis pathway
188 despite normoxia: It includes SDH and VHL-related tumors. The hypoxia-inducible
189 factor (HIF) is abnormally stabilized due to an impairment in the VHL-mediated
190 degradation system, and induces angiogenesis, promoting the development of PHEO
191 and PGL. Cluster 2 includes genes which mutations lead to dysregulation of
192 intracellular signaling pathways (PI3K/AKT, MAPK/ERK kinase), triggering

193 tumorigenesis: RET and NF1 activate PI3K/AKT/mTOR and RAS/RAF/MAPK
194 signaling pathways; TMEM127 enhances mTOR activity; MAX modifies the MYC-
195 MAX-MXD1 network connected with mTOR pathway. Recently, based on mRNA
196 analysis, Fishbein et al. subdivided the whole group of PHEO/PGL in 4 different
197 entities: Wnt-altered pathway, kinase signaling pathway, pseudohypoxia pathway
198 and what they called cortical admixture. Interestingly, germline mutations in MAX
199 occurred in this specific subgroup and not in the Cluster 2 class (Fishbein, et al.
200 2017). The main pathways involved in PHEO pathogenesis are depicted in Figure 1
201 (adapted from (Dahia 2014)).

202 For this review, we will thus specifically focus on the genes classified in the Cluster 2,
203 but we will also include MAX. Cluster 1 genes will not be discussed. Of note, the
204 differential diagnosis with MEN2 for cluster 2 is mainly theoretical as normal
205 calcitonin level at the time of PHEO diagnosis will rule out the possibility of MEN2.

206 NF1

207 Neurofibromatosis type 1 (NF1 or Von Recklinghausen disease) is an autosomal
208 dominant disease due to mutations of *NF1*, a tumor suppressor gene. NF1 is mainly
209 characterized by neurofibromas, café au lait spots, optic pathway tumors, iris
210 hamartomas, bony lesions and skinfold freckling (review in (Gutmann, et al. 2017)).
211 PHEO occurs in only 0.1-10% of cases; it is however one the most frequent etiology
212 of hypertension in patients with NF1 (20-50% cases). This low prevalence explains
213 why only case reports and small series have been reported in the literature. Two
214 small studies suggested that NF1 PHEO size was usually smaller at the time of
215 diagnosis despite the fact that the diagnosis was made at a later age than sporadic
216 PHEO (Moramarco, et al. 2017; Shinall and Solorzano 2014). This likely explains
217 why Kepenekian et al. recently showed that the majority of the patients with NF1

218 PHEO were not symptomatic at the time of diagnosis, emphasizing the need for
219 systematic biological screening in patients with NF1 (Kepenekian, et al. 2016). In the
220 larger study ever published, 41 patients (out of 1415 admitted for PHEO, prevalence
221 2.9%) with NF1 PHEO were reported: the median age at diagnosis was 41 years
222 (range 14-67); the median size of PHEO at the time of diagnosis was 3.4 cm (range
223 0.8-9.5). Bilateral pheochromocytomas were identified in 17% of the patients, while
224 metastases were reported in 7%. The majority of patients (91%) had both
225 metanephrine and normetanephrine secretion at diagnosis (Gruber, et al. 2017).
226 PHEO screening in NF1 patients should be based on biology every 3 years
227 beginning at age 10-14. In contrast, systematic NF1 genetic screening in patients
228 with an apparently sporadic PHEO is not recommended, unless there are clinical
229 signs suggestive of neurofibromatosis (Bausch, et al. 2006). Optimal management of
230 NF1 PHEO is based on adrenalectomy (Gruber et al. 2017).

231 TMEM127

232 Germline *TMEM127* mutations were first identified as an etiology of PHEO seven
233 years ago (Qin, et al. 2010). *TMEM127* mutations prevalence is estimated to be
234 inferior to 2% (1.7% out of 1676 patients tested with PHEO and PGL) (Abermil, et al.
235 2012; Bausch, et al. 2017). *TMEM127* is a tumor suppressor, encoding a
236 transmembrane protein localized in several intracellular organelles (Jiang and Dahia
237 2011)). Mutations of *TMEM127* lead to a drastic decreased function of the protein
238 with an anarchic distribution into the cytoplasm, and dysregulate mTORC1 signaling
239 complex activation. In patients with *TMEM127* mutations, the age at diagnosis of
240 PHEO was highly variable from 20 to more than 65 years old (mean age at
241 diagnosis, 43 years, similar to the one of patients with sporadic PHEO). One third of
242 patients had bilateral tumors while only 1 had metastases at last follow-up. One third

243 of the patients with *TMEM127* mutations had a sporadic appearing benign PHEO.
244 Interestingly, a history of PHEO was observed in only a quarter of familial cases,
245 suggesting a low penetrance, even if the late age at first diagnosis of PHEO might
246 have biased these data because of an insufficient follow-up period (Qin et al. 2010;
247 Yao, et al. 2010). Neumann and coworkers expanded the phenotype one year later,
248 by describing the occurrence of PGL in 2 patients (1 with multiple head and neck
249 PGL, 1 with retroperitoneal extra-adrenal tumor), leading to a prevalence of PGL of
250 4% in this series of 48 patients. No patient had a malignant disease (Neumann, et al.
251 2011). Finally, Abermil and coworkers reported a prevalence of 0.9% (n=6 patients)
252 of *TMEM127* mutations in a large cohort of 642 unrelated patients with negative
253 testing for classical genes of PHEO and paraganglioma (Abermil et al. 2012). The
254 overall characteristics were comparable with a variable age at diagnosis, a sporadic
255 presentation in half of the patients, bilaterality in half of the patients, and the lack of
256 paraganglial tumor. In this series as in the previous one, all the 5 patients with data
257 available on secretion were presenting with higher metanephrines than
258 normetanephrines. Of note, large *TMEM127* gene deletions or duplications have
259 never been reported in any patient (Abermil et al. 2012). Optimal management of
260 *TMEM127* PHEO is based on adrenalectomy. For a detailed list of *TMEM127*
261 variants reported in the literature, please refer to supplemental table 1 (Abermil et al.
262 2012; Bausch et al. 2017; Curras-Freixes, et al. 2015; Elston, et al. 2013; Neumann
263 et al. 2011; Patocs, et al. 2016; Qin et al. 2010; Rattenberry, et al. 2013; Takeichi, et
264 al. 2012; Toledo, et al. 2015).

265 MYC Associated factor X (MAX)

266 *MAX* mutations were first identified as a cause of PHEO 6 years ago (Comino-
267 Mendez, et al. 2011). *MAX*, a tumor suppressor gene, is a component of the MYC-

268 MAX-MXD1 network of basic helix-loop-helix leucine zipper transcription factors,
269 regulating cell proliferation, differentiation and apoptosis. It is likely that MAX acts as
270 a negative regulator of the network: germline mutations of *MAX* disable its repressing
271 activity, and lead to *MYC* dysregulation and cancer predisposition (Cascon and
272 Robledo 2012). Twelve cases were reported by Comindo-Mendez et al.: age at
273 diagnosis ranged from 17 to 47 years old; the majority of the patients were
274 presenting with bilateral PHEO at diagnosis, and 3 patients had metastatic PHEO at
275 last follow-up (Comino-Mendez et al. 2011). These characteristics were confirmed by
276 a second prevalence study in a series of 1694 patients with PHEO and no mutation
277 in other susceptibility genes: 16 *MAX* mutations were identified in 23 index patients
278 (prevalence, 1.1%). The majority of them had bilateral PHEO, and 16% had
279 additional thoraco-abdominal PGL. Two patients were metastatic at last follow-up.
280 The secretion profile was mainly high secretion of normetanephrines with normal or
281 moderately increased metanephrines. Of note, 2 patients presented a renal
282 carcinoma and a renal oncocytoma (Burnichon, et al. 2012). This finding was recently
283 confirmed in the first study reporting a large genomic deletion of *MAX* in 3 siblings
284 presenting with bilateral PHEO (n=2) and a renal oncocytoma (n=1). This could
285 suggest that *MAX* also acts as a suppressor gene for renal oncocytomas
286 (Korpershoek, et al. 2016), and change the way to follow such patients (with a
287 systematic screening for renal cancers on a long-term basis?). Interestingly, the
288 association between pheochromocytoma/paraganglioma and renal tumors has also
289 been reported for *TMEM127* mutations (Hernandez, et al. 2015). For a detailed list of
290 cases of *MAX* variants reported in the literature, please refer to supplemental table 2
291 (Bausch et al. 2017; Burnichon et al. 2012; Comino-Mendez et al. 2011; Comino-

292 Mendez, et al. 2015; Peczkowska, et al. 2013; Romanet, et al. 2016; Welander, et al.
293 2014).

294

295 **3. HYPERPARATHYROIDISM IN MEN2 AND NON-MEN2 FAMILIAL FORMS**

296 Primary HPTH is a rather frequent disease, with an incidence of 1 per 1000, including
297 5-10% of hereditary etiology. These genetic etiologies include isolated primary
298 hyperparathyroidism (such as in familial hypocalciuric hypercalcemia) and syndromic
299 HPTH, among which *RET* mutations (table 4).

300

301 **a. MEN2 Hyperparathyroidism**

302 Epidemiology and genetics

303 HPTH penetrance is lower than MTC and PHEO in MEN2. The prevalence is
304 estimated to be 20% in MEN2A cases (while it is always absent in MEN2); some
305 series even reported a much lower prevalence of 5% in patients with *RET* mutations
306 (Elisei, et al. 2012; Frank-Raue, et al. 2011; Machens, et al. 2013). In MEN2A,
307 hyperparathyroidism seems to be more frequently associated with *634-RET*
308 mutations than other codons (Karga, et al. 1998; Kraimps, et al. 1996; Raue and
309 Frank-Raue 2009; Valdes, et al. 2015). Twenty years ago, Schuffenecker et al. had
310 reported that the prevalence of hyperparathyroidism did not differ between patients
311 with *C634R* or other *634* codon mutations; however, there was a wide intervariability
312 among families, with a prevalence varying from 9 to 40% (again suggesting the
313 involvement of modifying or environmental factors) (Schuffenecker, et al. 1998).

314 Parathyroid hyperplasia precedes the development of adenoma formation, but the
315 hyperplastic stage can lead to hypercalcemia (Mete and Asa 2013). Moreover,
316 hyperplasia and adenoma can coexist in several glands at the time of diagnosis, in

317 favor of an asynchronous development of the parathyroid disease in MEN2. This
318 means that at a given time point, some glands can still be normal, and recurrence will
319 happen after a more or less prolonged period of time after partial parathyroidectomy.
320 In contrast, parathyroid carcinoma has never been reported in MEN2. In sporadic
321 hyperparathyroidism, patients are usually older, with a mean age at diagnosis close
322 to 60, and they have only 1 pathologic parathyroid gland. In contrast, the mean age
323 at diagnosis of hyperparathyroidism in MEN2 is usually close to 40 years (Kraimps et
324 al. 1996; Machens et al. 2013; Schuffenecker et al. 1998).

325 MTC precedes hyperparathyroidism, even if some rare cases depicted early
326 diagnosis of hyperparathyroidism (Magalhaes, et al. 2011; Mian, et al. 2009). MEN2
327 diagnosis is thus rarely made after an isolated diagnosis of primary
328 hyperparathyroidism. The majority of the patients are asymptomatic at the time of
329 diagnosis (Carling and Udelsman 2005), emphasizing the need for a systematic
330 yearly calcium work-up in patients with MEN2, as stated by the ATA guidelines.

331 Diagnosis and screening

332 The ATA recommends to begin screening by age 8 in patients with MEN2A, and to
333 screen on a yearly basis for biology suggesting hyperparathyroidism in asymptomatic
334 carriers whatever the codon (Wells et al. 2015). The diagnosis procedure is the same
335 as the one performed in sporadic hyperparathyroidism, with at least calcium level and
336 albumin and then PTH, phosphate and urinary calcium (Elisei et al. 2012). In case of
337 positive diagnosis, imaging can be made to help the surgeon, even if multiglandular
338 disease is present in the majority of cases, and bilateral neck compartments
339 exploration is usually mandatory.

340 Imaging

341 When HPTH is diagnosed in a MTC patient, minimally invasive parathyroidectomy
342 approach is not a recommended surgical approach for HPTH since bilateral
343 cervicotomy is required for total thyroidectomy. In this situation, neck ultrasound
344 enables preoperative staging of MTC and localization of parathyroid lesions. The role
345 of radionuclide imaging is more limited since ectopic or supernumerary glands are
346 very rare and most of the lesions can be removed via the cervical route. By contrast,
347 when HPTH is diagnosed after thyroidectomy for MTC, preoperative localizing
348 studies are needed for directing focused approaches (concordance between neck
349 ultrasound and PS for the same abnormality). The optimal protocol should use the
350 $^{99m}\text{Tc-MIBI}/^{123}\text{I}$ subtraction protocol with pinhole acquisition (Hindie, et al. 2009;
351 Hindie, et al. 2015). The use of 4-dimensional computed tomography (4D-CT) for
352 parathyroid imaging has been reported but increases radiation exposure to the
353 patient (Philip, et al. 2008). ^{18}F -fluorocholine PET/CT was found to be very sensitive
354 and specific in patients with sporadic primary HPTH or renal HPTH and would need
355 to be evaluated in the setting of MEN2 patients, especially in cases with recurrent
356 HPTH and negative or discordant imaging findings.

357 Management

358 In MEN2, management raises the question of the extent of parathyroidectomy which
359 should be performed when HPTH is diagnosed in the preoperative workup of MTC:
360 total parathyroidectomy, total parathyroidectomy with autotransplantation, or
361 selective parathyroidectomy with removal of macroscopically abnormal glands
362 (Herfarth, et al. 1996; Scholten, et al. 2011a; Yoshida, et al. 2009). Total
363 parathyroidectomy without autotransplantation will lead to permanent
364 hypoparathyroidism, a condition not always easy to handle. Recently, Moley et al.
365 reported their experience of the management of parathyroid glands during preventive

366 thyroidectomy in patients with MEN2. They did not notice any difference between
367 preventive thyroidectomy, central neck dissection, total parathyroidectomy and
368 autotransplantation to the forearm or to the neck, compared to preventive
369 thyroidectomy attempting to preserve the parathyroid glands in situ with an intact
370 vascular pedicle (autotransplantation only if the parathyroid did not seem viable or
371 could not be preserved intact): permanent hypoparathyroidism was not significantly
372 different between both groups (6% vs 1%, $p=0.1$) (Moley, et al. 2015). Of note, it is
373 not recommended currently to perform systematic parathyroidectomy in patients with
374 MEN2 requiring thyroid surgery for MTC (either prophylactic or not), and still normal
375 PTH and calcium level. In contrast, when HPTH is diagnosed after thyroidectomy, a
376 tailored parathyroidectomy should be performed based, as previously stated, on an
377 exhaustive imaging workup.

378

379 **b. Non MEN2 hyperparathyroidism**

380 Multiple Endocrine Neoplasia type 1 (MEN1) Hyperparathyroidism

381 One objective of this review is to discuss novelties of non MEN2 familial forms of
382 hyperparathyroidism. We thus will not discuss in detail MEN1, but will specifically
383 focus on studies published during the last 3-4 years. Hyperparathyroidism is the
384 earliest and most common feature of MEN1, with a median age at diagnosis of 20-25
385 years, and a prevalence of almost 100% of cases by age 50-60. An epidemiological
386 overview of MEN1 patients diagnosed before 21 years old showed that only 56% of
387 the patients presented with primary hyperparathyroidism as the initial occurring
388 disease in MEN1. The first symptoms appeared before 10 years-old in 14% of cases,
389 and before 5 in 3% of cases. This emphasizes the need for genetic testing when any
390 of the disease listed as potentially due to MEN1 occurs in a young patient (Goudet, et

391 al. 2015). MEN1 genetic screening should be performed in any patient with primary
392 hyperparathyroidism manifestations occurring before age 30, or in any patient with
393 multiglandular disease whatever the age (Lassen, et al. 2014).

394 The natural history of hyperparathyroidism in MEN1 is similar to the one reported for
395 MEN2, with an asynchronous disease (adenoma, hyperplasia on one or several
396 glands) (Mete and Asa 2013). Interestingly, parathyroid carcinoma, though rare, has
397 been reported in patients with MEN1, without certainty that the carcinoma was
398 specific to the menin status. In a series of 348 patients with MEN1 followed in a
399 single tertiary care center (the Mayo Clinic), a prevalence of 0.28% (1 case) of
400 parathyroid carcinoma was reported (Singh Ospina, et al. 2014). In parallel, the MD
401 Anderson cancer Center also identified 2 patients in a series of 291, leading to a
402 prevalence of 0.8%. This may not be different from the prevalence of parathyroid
403 carcinoma in patients with sporadic primary hyperparathyroidism
404 (0.74) (Christakis, et al. 2016). The pathological diagnosis of parathyroid carcinoma
405 is usually difficult, and based on invasion of the thyroid, the laryngeal nerve or other
406 neck structures. Treatment is usually based on parathyroidectomy. The main risk is
407 biological recurrence, rather than systemic metastasis, requiring further surgery or
408 the use of cinacalcet (Sensipar®), which is marketed in this specific indication
409 (Christakis et al. 2016; Singh Ospina et al. 2014).

410 Initial surgery mostly relies on subtotal rather than total parathyroidectomy with
411 autotransplantation. In recurrent cases, parathyroid surgery should be repeated after
412 a complete imaging work-up to identify the cause (hyperplasia of the the parathyroid
413 remnant, supranumerary/ectopic glands) and allow to perform a tailored approach. in
414 experienced surgical hands, repeat surgery usually leads to normal calcium levels
415 (when a piece of parathyroid gland is maintained), or to hypoparathyroidism. When

416 surgery is impossible, an alternate medical treatment is possible. Giusti et al. recently
417 reported their experience with the use of cinacalcet therapy in patients with MEN1
418 (Giusti, et al. 2016). Cinacalcet is able to bind the calcium sensor receptor and
419 increases its sensitivity to extracellular calcium: this leads to decreased levels of
420 PTH, and calcium. In this 12 month-multicenter prospective, open label, non
421 comparative trial performed in 33 patients with MEN1 (22 with contra-indication or
422 refusal to surgery as a first line treatment, 11 with contra-indications to surgery in a
423 context of recurrent hyperparathyroidism), cinacalcet was able to normalize calcium
424 level in 89% of the patients at the end of the study, with 30 or 60 mg cinacalcet daily.
425 Five patients were excluded because of bad tolerance to the drug, not allowing to
426 adjust the dose of cinacalcet. Of note, no significant change was observed in terms
427 of PTH or urinary calcium at the end of the study (Giusti et al. 2016).

428

429 Multiple endocrine neoplasia type 4 (MEN4)

430 MEN1-like syndrome occurs in 5-10% patients without *menin* mutations. A subgroup
431 of these patients (roughly 2%) present with *CDKN1B* (p27) mutations. Identification
432 of *p27* mutations were based on a naturally occurring MEN1 rat model (MENX)
433 presenting with an 8 bp homozygous frameshift insertion leading to a premature stop
434 codon in *p27* (Pellegata, et al. 2006). A small number of patients with heterozygous
435 *p27* mutations have been reported since then, characterized by a wide variability in
436 all other diseases classically occurring in MEN1. Primary hyperparathyroidism, in
437 contrast, was present in all published cases, with an identical multiglandular
438 involvement (Agarwal, et al. 2009). Interestingly, the *V109G p27* variant has been
439 reported as responsible for modifying the natural history of parathyroid involvement in
440 MEN1, based on a cohort of 100 patients paired with 855 controls: V109G variant

441 was associated with a more frequent multiglandular involvement at diagnosis (3-4 vs
442 1-2 glandular disease) (Longuini, et al. 2014).

443

444 Hyperparathyroidism-Jaw tumor (HPT-JT) syndrome

445 HPT-JT is defined by the association of primary hyperparathyroidism, due to a single
446 or multiple parathyroid adenoma or a parathyroid carcinoma (30% cases), and a
447 fibro-osseous jaw tumor (30% cases). Uterine or kidney tumors have also been
448 described as associated with this syndrome. Of note, primary hyperparathyroidism
449 can be isolated at diagnosis, and the penetrance of other diseases is incomplete.
450 Differentiating between MEN1 and HPT-JT can thus be challenging in case of
451 isolated hyperparathyroidism, and should lead to genetic testing of both *menin* and
452 *CDC73*. HPT-JT is due to mutations of *CDC73* (*HRPT2*) tumor suppressor gene,
453 transmitted as an autosomal dominant trait (Carpten, et al. 2002). *CDC73* mutations
454 lead to the loss of expression of parafibromin, a nuclear protein involved in chromatin
455 remodeling and histone modification (review in (Thakker 2016)). Bricaire et al.
456 reported the characteristics of 20 index patients with a germinal *HRPT2* abnormality:
457 mean age at diagnosis was close to the one reported for MEN1 (23 years), but
458 calcium level at diagnosis was higher (mean, 3.19 mmol/l). Interestingly, a large
459 deletion of *HRPT2* was observed in a third of the cohort patients (Bricaire, et al.
460 2013). Management of HPTH in HPT-JT is based on parathyroidectomy with bilateral
461 neck compartments exploration, given the possible multiglandular and potential
462 malignant nature of the disease. In contrast with sporadic primary
463 hyperparathyroidism, follow-up should be prolonged on a long term basis to detect
464 recurrence (observed in up to 80% of operated patients) requiring a more aggressive
465 parathyroid surgery (Sarquis, et al. 2008). Interestingly, somatic *HRPT2* mutations

466 have also been detected in sporadic parathyroid carcinomas, arguing for a role of
467 *CDC73* mutations in the overall prognosis of parathyroid disease (Shattuck, et al.
468 2003).

469

470 c. The peculiar case of familial hypocalciuric hypercalcemia

471 Type 1, 2 and 3 familial hypocalciuric hypercalcemia (FHH) are due to an abnormal
472 inactivation of the calcium sensor receptor signaling pathway. Biological workup
473 usually shows hypercalcemia, unsuppressed PTH level (mostly normal), and not-
474 increased calciuria (low or normal). Basically, any biological phenotype can be seen
475 (Vargas-Poussou, et al. 2016). Calcium sensor receptor gene is located in 3q21.1,
476 encoding for the calcium sensor receptor, a transmembrane G protein coupled
477 receptor. FHH type 1 is due to inactivating mutations of CASr, FHH2 to inactivating
478 GNA11 mutations and FHH3 to mutations of AP2S1, involved in Calcium Sensor
479 endocytosis. FHH usually leads to parathyroid hyperplasia, even if some operated
480 patients actually presented a true parathyroid adenoma.

481

482 **4. PERSPECTIVES AND CONCLUSIONS**

483 MEN2 is now a well characterized disease; while original descriptions were almost
484 exclusively focusing on MTC, reports published over the last 10 years provide more
485 insights into the pathophysiology, diagnosis and management of PHEO, and to a
486 lower extent, HPTH. Both diseases are characterized by a usually benign tumor
487 profile preceded by a hyperplastic stage. Management of such tumors should thus be
488 aimed at curing the disease while preserving an optimal quality of life (partial
489 parathyroidectomy, partial adrenal surgery for instance, should be systematically
490 considered in such patients). Future studies should be aimed at better exploring the

491 phenotypes (with the help of large scale international networks) and understanding
492 the wide variability presented by the patients in terms of age at diagnosis,
493 asynchronous disease, as this individualized approach will help tailoring the
494 treatment for each patient.

495 In non MEN2 familial forms of PHEO and HPTH, the genetic spectrum has drastically
496 changed over the last 10 years, with an increasing rate of new identified genetic
497 etiologies (especially in PHEO). Interestingly, some of these etiologies have also
498 been linked to renal carcinogenesis, and this will be something to take into account
499 when following patients on a long term basis. In the future, next-generation
500 sequencing approaches will likely lead to focus on different issues, by questioning
501 about the pathogenicity of variants of unknown significance. Moreover, for new genes
502 such as *MAX* and *TMEM127*, only little is known about the natural history of PHEO
503 and extra-adrenal features. Large-scale follow-up studies will thus be necessary to
504 adapt the management. Despite the fact that MEN1 has been identified decades ago,
505 and HRPT2 roughly 15 years ago, there is still requirement for further studies, with
506 unresolved questions similar to what we reported for MEN2 (Castinetti et al. 2014):
507 little is known about the factors explaining the wide intra-familial variability of patients
508 carrying with such mutations: the hypotheses of modifying genes/factors or
509 epigenetics should thus pave the way for future research.

510

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516

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Table 1: Main characteristics of cluster 2 hereditary pheochromocytomas.

Disease	Multiple Endocrine Neoplasia type 2	Neurofibromatosis type 1	Familial PPGL with <i>TMEM127</i> gene mutation	Familial PPGL with <i>MAX</i> gene mutation
Gene	<i>RET</i>	<i>NF1</i>	<i>TMEM127</i>	<i>MAX</i>
Chromosomal locus	10q11.21	17q11.2	2q11.2	14q23.3
Gene function	proto-oncogene	tumor suppressor gene	tumor suppressor gene	tumor suppressor gene
Genetic Mechanism	activating mutation	inactivating mutation	inactivating mutation	inactivating mutation
Inheritance	AD	AD	AD	AD
Phenotype	Multiple Endocrine Neoplasia type 2A MTC (100%), PHEO (50%), primary HPTH (25%), notalgia	Multiple Endocrine Neoplasia type 2B MTC (100%), PHEO (50%), marfanoid habitus, mucosal neuromas	Neurofibromas (95%), café au lait spots (90%), iris hamartomas (90%), bony lesion, skinfold freckling (80%), optic pathway tumor (15%). PHEO (0, 1-10%).	Single or bilateral PHEO (30-50%); PGL (0-4%)
Secretion profile	Both metanephrins and normetanephrins	Both metanephrins and normetanephrins	Mainly metanephrins secretion	Mainly normetanephrins secretion
PHEO malignancy	Rare	<10%	Rare	<25 %

Legend: AD: autosomal dominant, HPTH: hyperparathyroidism, MTC: Medullary Thyroid Carcinoma, PHEO: pheochromocytoma, PGL: paraganglioma, PPGL: pheochromocytoma and paraganglioma

1 **Table 2: Main characteristics of hereditary primary hyperparathyroidism**

Disease	Multiple Endocrine Neoplasia type 1	HPTH - Jaw Tumor Syndrome	Multiple Endocrine Neoplasia type 4	Familial Isolated Primary HPTH with <i>GCM2</i> activating mutation
Gene	<i>MEN1</i>	<i>HRPT2</i>	<i>CDKN1B</i>	<i>GCM2</i>
Chromosomal locus	11q13.1	1q31.2	12p13.1	6p24.2
Gene function	Tumor suppressor gene	Tumor suppressor gene	Tumor suppressor gene	Proto-oncogene
Genetic Mechanism	Inactivating mutation	Inactivating mutation	Inactivating mutation	Activating mutation
Inheritance	AD	AD	AD	AD
Phenotype	Primary HPTH (90%), Neuroendocrine duodenopancreatic tumor (30 to 70%), pituitary adenoma (30 to 40%), adrenal tumor (40%)	Primary HPTH (95%), parathyroid carcinoma (21%), fibro-osseous tumour (30%), renal tumor (13%), uterine tumor (57% of females)	Primary HPTH (81%), pituitary adenoma (46%), gastric and bronchic carcinoid tumors, gastropancreatic tumor, adrenal tumor	Isolated primary HPTH
Prevalence	1/30 000	Unknown	Unknown	Unknown

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**Table 2
(continue)**

Disease	FHH1	Neonatal Severe HPTH	FHH2	FHH3
Gene	<i>CaSR</i>	<i>CaSR</i>	<i>GNA11</i>	<i>AP2S1</i>
Chromosomal locus	3q21.1	3q21.1	19p13.3	19q13.3
Gene function	CaSR signalling pathway	CaSR signalling pathway	CaSR signalling pathway	CaSR signalling pathway
Genetic Mechanism	Inactivating mutation	Inactivating mutation	Inactivating mutation	Inactivating mutation
Inheritance	AD	AR or AD	AD	AD
Phenotype	Longlife hypercalcemia, relative hypocalciuria, normal or mild elevated PTH	Severe hypercalcemia, letal without parathyroidectomy	Longlife hypercalcemia, relative hypocalciuria, normal or mild elevated PTH	Longlife hypercalcemia, relative hypocalciuria, normal or mild elevated PTH
Prevalence	1/10 000 to 1/100 000	Unknown	Unknown	Unknown

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6 Legend: HPTH: hyperparathyroidism, FHH: Familial hypocalciuric hypercalcemia,

7 AD: autosomal dominant, AR: autosomal recessive

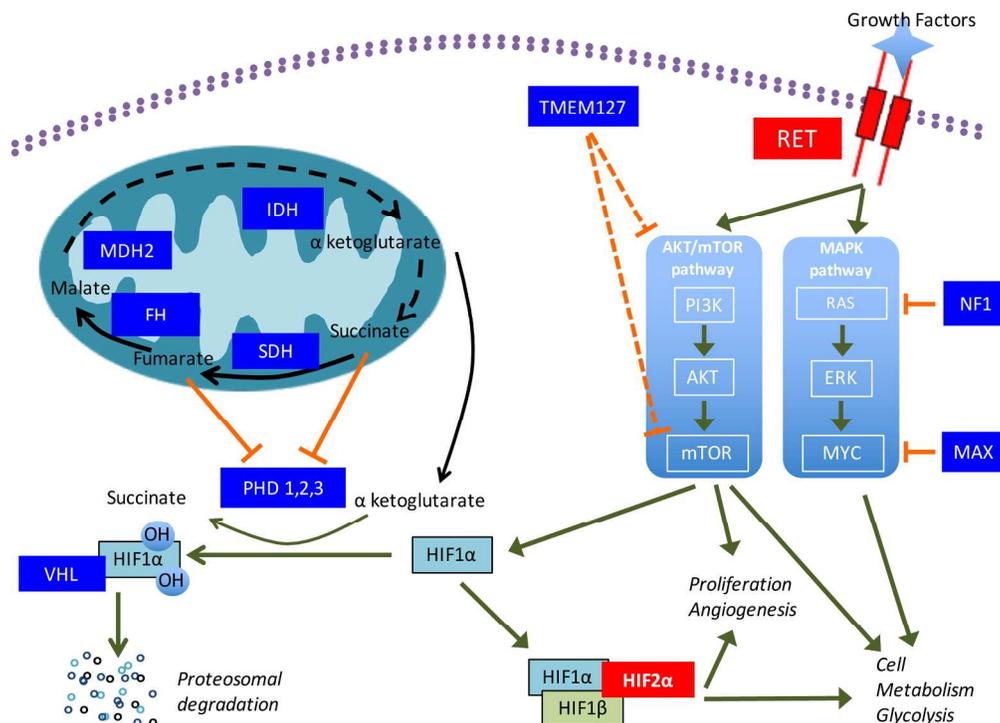
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Legend to Figure 1

Simplified overview of main genes and pathways involved in PHEO/PGL.

Blue boxes: tumor suppressor genes involved in hereditary PHEO/PGL; Red boxes: proto-oncogenes involved in hereditary PHEO/PGL; Black arrows: simplified Krebs cycle; Orange arrows: inhibition effect; dotted arrows: not well established mechanism; green arrow: stimulating effect. AKT: RAC-alpha serine/threonine-protein kinase, ERK/MAPK1: Mitogen-activated protein kinase 1, FH: Fumarate Hydratase, HIF1 α : Hypoxia-inducible factor 1 alpha subunit, HIF1 β : Hypoxia-inducible factor 1 beta subunit, HIF2 α /EPAS1: Endothelial PAS domain protein 1, IDH: Isocitrate DeHydrogenase, MAPK pathway: Mitogen-Activated Protein Kinase pathway, MAX: MYC-associated factor X, MDH2: Malate DesHydrogenase 2, mTOR: mammalian Target Of Rapamycin, MYC: MYC proto-oncogene, NF1: Neurofibromin 1, PHD/EGLN 1, 2, 3: Prolyl Hydroxylase Domain protein/egl-9 family hypoxia inducible factor 1, 2, 3, PI3K: Phosphatidylinositol-4,5-bisphosphate 3-Kinase RAS: Rat Sarcome oncogene, RET: REarranged during Transfection proto-oncogene, SDH: Succinate DeHydrogenase complex, TMEM127: TransMEMbrane protein 127, VHL: Von Hippel-Lindau tumor suppressor.

Adapted from (Dahia 2014)



Simplified overview of main genes and pathways involved in PHEO/PGL. Blue boxes: tumor suppressor genes involved in hereditary PHEO/PGL; Red boxes: proto-oncogenes involved in hereditary PHEO/PGL; Black arrows : simplified Krebs cycle; Orange arrows: inhibition effect ; dotted arrows : not well established mechanism; green arrow : stimulating effect. AKT: RAC-alpha serine/threonine-protein kinase, ERK/MAPK1:

Mitogen-activated protein kinase 1, FH: Fumarate Hydratase, HIF1 α : Hypoxia-inducible factor 1 alpha subunit, HIF1 β : Hypoxia-inducible factor 1 beta subunit, HIF2 α /EPAS1: Endothelial PAS domain protein 1, IDH: Isocitrate DeHydrogenase, MAPK pathway: Mitogen-Activated Protein Kinase pathway, MAX: MYC-associated factor X, MDH2: Malate DesHydrogenase 2, mTOR: mammalian Target Of Rapamycin, MYC: MYC proto-oncogene, NF1: Neurofibromin 1, PHD/EGLN 1, 2, 3: Prolyl Hydroxylase Domain protein/egl-9 family hypoxia inducible factor 1, 2, 3, PI3K: PhosphatidyInositol-4,5-bisphosphate 3-Kinase RAS: Rat Sarcome oncogene, RET: REarranged during Transfection proto-oncogene, SDH: Succinate DeHydrogenase complex, TMEM127: TransMEMbrane protein 127, VHL: Von Hippel-Lindau tumor suppressor.

Adapted from (Dahia 2014)

209x150mm (300 x 300 DPI)

Supplemental Table 1: Listing of the *TMEM127* gene mutations (NM_017849.3) reported in literature and phenotypic description of the patients.

Exon	Mutation	Predicted effect	Clinical manifestations	Malignancy	Age at diagnosis	Sex	Reference
2	c.3G>A	Start loss	unilateral PHEO	no	35	M	Bausch, 2017
2	c.3G>A	Start loss	unilateral PHEO	no	58	F	Bausch, 2017
2	c.73A>T	p.Lys25*	unilateral PHEO	no	68	M	Bausch, 2017
2	c.117_120del	p.Ile41Argfs*39	PHEO	no	26	F	Curras-Freixes, 2015
2	c.117_120del	p.Ile41Argfs*39	bilateral PHEO	no	40	M	Takeichi, 2012
2	c.117_120del	p.Ile41Argfs*39	bilateral PHEO	no	48	M	Takeichi, 2012
2	c.131T>G*	p.Leu44Arg	bilateral PHEO	no	43	F	Bausch, 2017
2	c.140C>A	p.Ala47Asp	bilateral PHEO	NA	45	F	Abermil, 2012
2	c.150insA	p.Pro51Thrfs*57	unilateral PHEO	NA	25	NA	Qin, 2010
2	c.190_191dup	p.Gln64Hisfs*18	unilateral PHEO	NA	28	F	Abermil, 2012
2	c.202del	p.Val68Serfs*13	unilateral PHEO	NA	56	F	Abermil, 2012
2	c.215T>A	p.Leu72*	unilateral PHEO	no	58	F	Bausch, 2017
2	c.221A>C	p.Tyr74Ser	PHEO	no	35	M	Curras-Freixes, 2015
3	c.245-1G>T	splicing alteration	bilateral PHEO	NA	54, 66	NA	Qin, 2010
3	c.265_268del	p.Thr89Cysfs*34	bilateral PHEO	NA	46	NA	Qin, 2010
3	c.325T>C*	p.Ser109Pro	carotid PGL	no	34	F	Bausch, 2017, & Neumann, 2011
4	c.410-1G>C	splicing alteration	bilateral PHEO	no	45	M	Bausch, 2017
4	c.410-2A>C	splicing alteration	PHEO, bilateral for 3/9	NA	34 to 66 (9 cases from 2 Families)	NA	Qin, 2010

4	c.410-2A>C	splicing alteration	bilateral PHEO and multiple retroperitoneal PGL	no	33	F	Toledo, 2015
4	c.413T>G*	p.Leu138Arg	unilateral PHEO	no	66	M	Bausch, 2017
4	c.415C>T	p.Gln139*	bilateral PHEO	no	33	M	Elston, 2013
4	c.419G>A	p.Cys140Tyr	unilateral PHEO	no	22	F	Bausch, 2017
4	c.419G>A	p.Cys140Tyr	unilateral PHEO	no	22	NA	9
4	c.462C>G*	p.Ile154Met	unilateral PHEO	no	76	M	Bausch, 2017
4	c.464T>A	p.Leu155*	bilateral PHEO and retroperitoneal PGL	yes	51	F	Bausch, 2017
4	c.464T>A	p.Leu155*	bilateral PHEO, retroperitoneal PGLs and in the neck/head	no	51	NA	Patocs, 2016
4	c.469C>T	p.Gln157*	unilateral PHEO	NA	42	M	Abermil, 2012
4	c.475C>T	p.Gln159*	bilateral PHEO	NA	48 and 72	NA	Qin, 2010
4	c.492C>G	p.Tyr164*	unilateral PHEO	NA	35	F	Abermil, 2012
4	c.512delinsGCC	p.Val171Glyfs*137	Neck/head PGL	NA	NA	NA	Rattenberry, 2013
4	c.518T>C	p.Phe173Ser	unilateral PHEO	no	26	F	Bausch, 2017
4	c.532dup	p.Tyr178Leufs*48	unilateral PHEO	no	25	F	Bausch, 2017
4	c.553G>A*	p.Gly185Arg	bilateral PHEO and retroperitoneal PGL	no	51	F	Bausch, 2017 & Neumann, 2011
4	c.543_555dup	p.Ala186Argfs*44	bilateral PHEO	no	33	F	Bausch, 2017
4	c.568G>A*	p.Ala190Thr	tympanic PGL	no	50	F	Bausch, 2017
4	c.572del	p.Thr191Argfs*116	unilateral PHEO	no	26	F	Bausch, 2017
4	c.572del	p.Thr191Argfs*116	bilateral PHEO	no	47	F	Bausch, 2017
4	c.572del	p.Thr191Argfs*116	bilateral PHEO	no	47	NA	Patocs, 2016

NA: Not available, PHEO: pheochromocytoma, PGL: paraganglioma, *: likely pathogenic variant.

For Review Only

Supplemental table 2: Listing of the *MAX* gene mutations (NM_002382) reported in literature and phenotypic description of the patients.

Exon	Mutation	Predicted effect	Presentation	Malignancy	Age at diagnosis	sex	Reference
1	c.1A>G	Start loss	bilateral PHEO	yes	46	F	Comino-Mendez, 2011
1	c.1A>G	Start loss	unilateral PHEO	NA	29	M	Comino-Mendez, 2011
1	c.2T>A	Start loss	bilateral PHEO and TA PGL	NA	46	F	Burnichon, 2012
3	c.73C>T	p.Arg25Trp	unilateral PHEO	no	36	F	Bausch, 2017
3	c.73C>T	p.Arg25Trp	bilateral PHEO	NA	43	F	Burnichon, 2012, & Comino-Mendez, 2015
3	c.97C>T	p.Arg33*	bilateral PHEO	NA	23	M	Burnichon, 2012
3	c.97C>T	p.Arg33*	bilateral PHEO	NA	34	M	Burnichon, 2012
3	c.97C>T	p.Arg33*	multiple PHEO in the same gland	NA	58	F	Burnichon, 2012
3	c.97C>T	p.Arg33*	unilateral PHEO	NA	26	F	Burnichon, 2012
3	c.97C>T	p.Arg33*	unilateral PHEO	NA	38	M	Burnichon, 2012
3	c.97C>T	p.Arg33*	bilateral PHEO	NA	24	M	Burnichon, 2012
3	c.97C>T	p.Arg33*	unilateral PHEO and TA PGL	NA	43	F	Burnichon, 2012
3	c.97C>T	p.Arg33*	bilateral PHEO	no	17, 20	M	Comino-Mendez, 2011
3	c.97C>T	p.Arg33*	bilateral PHEO	no	17, 20	M	Comino-Mendez, 2011
3	c.97C>T	p.Arg33*	bilateral PHEO and multiple, hyperplasia	no	25	M	Romanet, 2016
3	c.97C>T	p.Arg33*	unilateral	NA	NA	NA	Welander,

3	c.146C>G	p.Ser49*	PHEO unilateral PHEO	no	23	F	2014 Bausch, 2017
3	c.171+1G>A	splicing alteration	bilateral PHEO	no	18	F	Burnichon, 2012 Burnichon, 2012, & Comino- Mendez, 2015
4	c.178C>T	p.Arg60Trp	bilateral PHEO	NA	55	F	Comino- Mendez, 2011
4	c.186_187	p.Gln62Hisfs*24	bilateral PHEO	no	47	F	Comino- Mendez, 2011,4 Burnichon, 2012, & Comino- Mendez, 2015
4	c.281T>C	p.Leu94Pro	unilateral PHEO	no	41	F	Bausch, 2017
4	c.212T>G	p.Ile71Ser	bilateral PHEO	NA	34	F	Bausch, 2017
4	c.223C>T	p.Arg75*	unilateral PHEO	no	32	M	Burnichon, 2012
4	c.223C>T	p.Arg75*	bilateral PHEO	no	38	F	Burnichon, 2012
4	c.223C>T	p.Arg75*	bilateral PHEO	NA	18	M	Burnichon, 2012
4	c.223C>T	p.Arg75*	bilateral PHEO	NA	18	M	Comino- Mendez, 2011
4	c.223C>T	p.Arg75*	bilateral PHEO	yes	29	M	Comino- Mendez, 2011
4	c.223C>T	p.Arg75*	bilateral PHEO	no	35	M	Comino- Mendez, 2011
4	c.223C>T	p.Arg75*	bilateral PHEO	no	34	F	Comino- Mendez, 2011
4	c.223C>T	p.Arg75*	bilateral PHEO	no	28	F	Comino- Mendez, 2011
4	c.223C>T	p.Arg75*	bilateral PHEO and mutiple	no	36	M	Peczowska, 2013
4	c.242_243	p.His81Profs*5	bilateral PHEO	no	50	F	Bausch, 2017
4	c.244C>T	p.Gln82*	unilateral PHEO	yes	18	F	Burnichon, 2012
4	c.295+1G>T	splicing alteration	bilateral PHEO	Yes	40	F	Burnichon, 2012

4	c.295+1G>T	splicing alteration	bilateral PHEO	yes	32	M	Comino-Mendez, 2011
4	c.295+1G>A	splicing alteration	bilateral PHEO	yes	32	M	Comino-Mendez, 2011
4	c.292dup	p.Gln98Profs*48	unilateral PHEO	no	21	M	Bausch, 2017
5	c.305T>C	p.Leu102Pro	unilateral PHEO	NA	13	M	Burnichon, 2012, & Comino-Mendez, 2015
5	c.307G>T	p.Glu103*	bilateral PHEO	no	26	M	Bausch, 2017

NA: Not available, PHEO: pheochromocytoma, PGL: paraganglioma, TA: Thoraco-abdominal