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Camille Gosseaume, Thierry Fournier, Isabelle Jéru, Marie-Léone Vignaud,  
Isabelle Missotte, Françoise Archambeaud, Xavier Debussche, Céline  
Droumaguet, Bruno Fève, Sophie Grillot, et al.

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1 **Perinatal, Metabolic and Reproductive Features in *PPARG*-related Lipodystrophy**

2 Camille Gosseaume<sup>1\*</sup>, Thierry Fournier<sup>2\*</sup>, Isabelle Jéru<sup>1,3</sup>, Marie-Léone Vignaud<sup>2</sup>, Isabelle  
3 Missotte<sup>4</sup>, Françoise Archambeaud<sup>5</sup>, Xavier Debussche<sup>6</sup>, Céline Droumaguet<sup>7</sup>, Bruno  
4 Fève<sup>1,8</sup>, Sophie Grillo<sup>9</sup>, Bruno Guerci<sup>10</sup>, Sylvie Hieronimus<sup>11</sup>, Yves Horsmans<sup>12</sup>, Estelle  
5 Nobecourt<sup>13</sup>, Catherine Pienkowski<sup>14</sup>, Christine Poitou<sup>15</sup>, Jean-Paul Thissen<sup>12</sup>, Olivier  
6 Lascols<sup>1,3</sup>, Séverine Degrelle<sup>2,16</sup>, Vassilis Tsatsaris<sup>2</sup>, Corinne Vigouroux<sup>1,3,8\*</sup>, Camille  
7 Vatier<sup>1,8\*</sup>

8

9 <sup>1</sup> Sorbonne University, Inserm U938, Saint-Antoine Research Centre, Institute of  
10 Cardiometabolism and Nutrition, Paris, France

11 <sup>2</sup> Université Paris Cité, Inserm, 3PHM, "Pathophysiology and Pharmacotoxicology of the  
12 Human Placenta, pre & post natal Microbiota, Paris, F-75006, France

13 <sup>3</sup> Assistance Publique-Hôpitaux de Paris, Saint-Antoine University Hospital, Department of  
14 Molecular Biology and Genetics, Paris, France

15 <sup>4</sup> Department of Pediatrics, Territorial Hospital Center, Nouméa, New Caledonia, France

16 <sup>5</sup> Department of Endocrinology, Limoges University Hospital, Limoges, France

17 <sup>6</sup> Clinical Investigation and Clinical Epidemiology Center (CIC-EC  
18 INSERM/CHU/University), Reunion Island University Hospital, Saint-Denis de la Réunion,  
19 France

20 <sup>7</sup> Assistance Publique-Hôpitaux de Paris, Henri-Mondor Hospital, Department of Intern  
21 Medicine, Créteil, France

22 <sup>8</sup> Assistance Publique-Hôpitaux de Paris, Saint-Antoine University Hospital, National  
23 Reference Center for Rare Diseases of Insulin Secretion and Insulin Sensitivity (PRISIS),  
24 Department of Endocrinology, Diabetology and Reproductive Endocrinology, Paris, France

25 <sup>9</sup> Department of Endocrinology and Diabetology, Pays du Mont Blanc Hospital, Sallanches,  
26 France

27 <sup>10</sup> Department of Endocrinology, Diabetology and Nutrition, Brabois Hospital, University of  
28 Lorraine, Vandoeuvre Lès Nancy, France

29 <sup>11</sup> Department of Diabetology and Nutrition, Nice University Hospital, Nice, France,

30 <sup>12</sup> Department of Hepatogastroenterology, Clinical and Experimental Research Institute  
31 Louvain Catholic University, Saint-Luc University Hospital, Bruxelles, Belgium

32 <sup>13</sup> Department of Endocrinology, Metabolism and Nutrition, Saint-Pierre Hospital, Reunion  
33 Island University Hospital, Saint-Denis de la Réunion, France

34 <sup>14</sup> Reference Center for Rare Gynecologic Diseases, Endocrinology and Medical Gynecology  
35 Unit, Toulouse University Hospital, France

36 <sup>15</sup> Assistance Publique-Hôpitaux de Paris, Pitié-Salpêtrière University Hospital, Reference  
37 Center for Rare Diseases PRADORT (PRADer-Willi Syndrome and other Rare Obesity  
38 with Eating Disorders), Nutrition Department, Paris, France, Sorbonne University, Inserm

39 <sup>16</sup> Inovarion, Paris, France

40 \*equal contribution

41 ORCID numbers : **Camille Vatier** 0000-0001-8342-1596, Corinne Vigouroux 0000-0002-  
42 8181-4721

43 **Corresponding authors:** Camille Vatier and Corinne Vigouroux, Sorbonne Université  
44 Médecine, Site Saint-Antoine, 27, rue Chaligny, 75571 Paris Cedex 12, France ; E-mail :  
45 [camille.vatier@aphp.fr](mailto:camille.vatier@aphp.fr), [corinne.vigouroux@inserm.fr](mailto:corinne.vigouroux@inserm.fr)

46

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48 **Keywords:** diabetes mellitus, lipodystrophy, placenta, *PPARG*, pregnancy complications

49 **Short title :** Perinatal consequences of *PPARG* variants

50

51 **Abstract**

52 **Objective:** The adipogenic *PPARG*-encoded PPAR $\gamma$  nuclear receptor also displays essential  
53 placental functions. We evaluated metabolic, reproductive and perinatal features of patients  
54 with *PPARG*-related lipodystrophy.

55 **Methods:** Current and retrospective data were collected in patients referred to a National  
56 Rare Diseases Reference Centre.

57 **Results:** 26 patients from 15 unrelated families were studied (18 women, median age 43  
58 years). They carried monoallelic *PPARG* variants except a homozygous patient with  
59 congenital generalized lipodystrophy. Among heterozygous patients aged 16 or more (n=24),  
60 92% had diabetes, 96% partial lipodystrophy (median age at diagnosis 24 and 37 years,  
61 respectively), 78% hypertriglyceridemia, 71% liver steatosis and 58% hypertension. Mean  
62 BMI was  $26 \pm 5.0$  kg/m<sup>2</sup>. Women (n=16) were frequently affected by acute pancreatitis (n=6)  
63 and/or polycystic ovary syndrome (n=12). Eleven women obtained one or several  
64 pregnancies, all complicated by diabetes (n=8), hypertension (n=4) and/or  
65 hypertriglyceridemia (n=10). We analysed perinatal data of patients according to the presence  
66 (n=8) or absence (n=9) of maternal dysmetabolic environment. The median gestational age at  
67 birth was low in both groups (37 and 36 weeks of amenorrhea, respectively). As expected,  
68 birth weight was higher in patients exposed to a fetal dysmetabolic environment of maternal  
69 origin. In contrast, 85.7% of non-exposed patients, in whom the variant is, or is very likely to  
70 be, paternally-inherited, were small for gestational age.

71 **Conclusions:** Lipodystrophy-related *PPARG* variants induce early metabolic complications.  
72 Our results suggest that placental expression of *PPARG* pathogenic variants carried by  
73 affected fetuses could impair prenatal growth and parturition. This justifies careful pregnancy  
74 monitoring in affected families.

75

76 **Significance Statement**

77 *PPARG*-related lipodystrophy is a rare disease due to variants in *PPARG* encoding a major  
78 regulator of adipocyte differentiation, also involved in placenta formation.

79 We show, in the largest cohort of patients with *PPARG*-related lipodystrophy reported to date  
80 (n=26), that the disease is associated with early and severe metabolic complications and  
81 decreased gestational age at birth. In affected women, metabolic complications during  
82 pregnancy lead to increased newborns' birth weight. However, 85.7% of patients not exposed  
83 to fetal dysmetabolic environment (with a very likely paternally-inherited disease), were born  
84 small-for-gestational age. Placental *PPARG* variants originating from the fetus may thus  
85 impair fetal growth and parturition. Close metabolic follow-up of patients and monitoring of  
86 fetal growth in their descendants, are needed in *PPARG*-related lipodystrophy.

87

88 **INTRODUCTION**

89

90 Peroxisome proliferator-activated receptor gamma ( $PPAR\gamma$ ) is a nuclear receptor that controls  
91 the expression of genes involved in numerous physiological pathways.  $PPAR\gamma$  modulates  
92 adipocyte differentiation and function, energy homeostasis and insulin sensitivity, and is the  
93 target of the antidiabetic drugs such as thiazolidinediones (1). Pathogenic variants of *PPARG*  
94 are responsible for familial partial lipodystrophy type 3 (FPLD3), an autosomal dominant rare  
95 disease characterized by a limited capacity of peripheral adipose tissue to store excess energy  
96 as triglycerides, leading to the progressive development of severe insulin resistance,  
97 hypertriglyceridemia, non-alcoholic fatty liver disease, and frequent hypertension (2, 3).  
98 Nevertheless, the natural history of the disease, regarding metabolic complications and  
99 reproductive consequences of insulin resistance, remains largely unknown, since large cohorts  
100 of patients have not been described.

101

102 Besides its well-known role in adipogenesis, PPAR $\gamma$  has been shown to play an essential role  
103 in the formation of the placenta, a transitional organ essential for embryo implantation,  
104 pregnancy maintenance and outcome, and fetal development and growth. The placenta is a  
105 post-zygotic organ, and is therefore genetically identical to the fetus. *PPARG*, the human  
106 PPAR $\gamma$ -encoding gene, is expressed by both the villous and extravillous cytotrophoblasts of  
107 the chorionic villi, *i.e.* the structural and functional unit of the placenta (4). PPAR $\gamma$  is  
108 activated during the differentiation of villous cytotrophoblasts into syncytiotrophoblasts (5,  
109 6), which ensure placental endocrine functions. PPAR $\gamma$  also controls the migration and  
110 invasion of extravillous cytotrophoblasts and is therefore essential for the anchorage of  
111 chorionic villi into the uterine wall (7) - a major pre-requisite for embryo implantation and  
112 growth -, remodeling of uterine spiral arteries, and immune tolerance during pregnancy.  
113 However, only a few and conflicting results are available regarding the pathophysiological  
114 role of *PPARG* in pregnancy outcomes in humans (8, 9, 10).

115 Two case reports of pregnancies complicated by premature birth and placental anomalies  
116 were reported in women with FPLD3 (11, 12), but whether this could be due to severe  
117 maternal lipodystrophy-linked metabolic complications and/or to the effects of placental  
118 expression of *PPARG* variants carried by the fetus remains unknown.

119

120 The cohort of patients and families referred to our reference centre provides a unique  
121 opportunity to study the consequences of FPLD3-related *PPARG* variants on metabolic  
122 characteristics, reproductive phenotype of affected women, and perinatal features. In addition  
123 to the characterisation of the FPLD3 phenotype in an important cohort of patients, our results  
124 bring data in favor of a deleterious role of placental expression of lipodystrophy-associated  
125 *PPARG* variants on the course of pregnancy and on fetal growth.

126

## 127 **METHODS**

128 This study includes 26 patients from 15 unrelated families referred in our French Reference  
129 Centre for Rare Diseases of Insulin Secretion and Insulin Sensitivity (PRISIS) for  
130 lipodystrophy and/or insulin resistance, and diagnosed with *PPARG*-related lipodystrophy.  
131 *PPARG* variants were identified using a lipodystrophy-dedicated diagnostic gene panel.  
132 Capture (SeqCapEZ enrichment protocol, Roche NimbleGen) of exons and flanking intronic  
133 sequences of 23 genes was followed by massively parallel sequencing on a MiSeq platform  
134 (Illumina Inc, San Diego, CA, USA). Data were analysed using the Sophia Genetics DDM  
135 pipeline®. *PPARG* variants were confirmed by Sanger sequencing and described based on the  
136 isoform NM\_015869.4. Written informed consents were collected according to legal  
137 procedures for molecular investigations. This study was approved by the Comité de  
138 Protection des Personnes Ile-de-France 5 (Paris, France) and conducted in accordance with  
139 the Declaration of Helsinki and the Guideline for Good Clinical Practice.

140

141 Current metabolic data, as well as obstetrical and neonatal retrospective data, were collected  
142 through analysis of medical records and patient interviews after written informed consent.  
143 Collected data included gender and age, age at clinical and molecular diagnosis of  
144 lipodystrophy and at diagnosis of complications, type and parental origin of the variant when  
145 available, physical characteristics (clinical lipodystrophy and body fat distribution, presence  
146 of muscle hypertrophy, acanthosis nigricans and hyperandrogenism in women). Weight,  
147 height, triglyceride, aspartate transaminase, alanine transaminase, and leptin serum levels,  
148 HbA1c, presence of diabetes and/or hypertension, liver steatosis assessed by echography,  
149 history of acute pancreatitis and use of insulin therapy were recorded, as well as, in women,  
150 age at menarche, presence of polycystic ovary syndrome (PCOS) as defined by the Rotterdam

151 criteria (13), antecedent of treatment for impaired fertility, number and outcomes of  
152 pregnancies. Patients' perinatal data were collected, including prenatal metabolic environment  
153 (maternal hypertriglyceridemia before pregnancy, diagnosis of hypertension or diabetes  
154 during pregnancy, or pre-eclampsia), exposure to maternal smoking during pregnancy,  
155 diagnosis of oligo/polyhydramnios, and neonatal data (gestational age at birth, birth weight  
156 and height, neonatal hypoglycemia).

157

158 Data are expressed as mean/SD and/or median/25<sup>th</sup> quartile (Q25). Differences between  
159 groups were analyzed with non parametric Mann-Whitney-Wilcoxon test or Fisher exact tests.  
160 Statistical analyses were performed with using GraphPad Prism version 8 (GraphPad  
161 softwear, San Diego, CA, USA). Values of  $p < 0.05$  were considered significant.

162

## 163 **RESULTS**

### 164 **Patients, molecular diagnosis and parental inheritance of *PPARG* variants**

165 *PPARG* variants associated with a typical familial partial lipodystrophy (FPLD) phenotype  
166 were observed in 19 independent families (31 patients), referred to our Reference Center. Five  
167 patients were excluded from the analysis: three patients died before the inclusion, a patient  
168 did not wish to participate and a patient was lost to follow-up. We therefore studied 26  
169 patients (18 women and 8 men) from 15 families. Their mean age was 40.1 years old (SD  
170 19.1, range 0-83) at investigation and 33.3 years old (SD 19.2, range 0-83) at molecular  
171 diagnosis (Table 1).

172

173 All patients carry a heterozygous *PPARG* variant except Patient 17, issued from an endogamy  
174 marriage, who is homozygous for the *PPARG* (p.Tyr173Cys) variant. Patients from two  
175 unrelated families were diagnosed with the same *PPARG* (p.Arg425Cys) variant, whereas



176 other families all harbored different *PPARG* variants. Three variants are located in exons  
177 encoding the DNA binding domain and 11 variants in exons encoding the ligand binding  
178 domain of PPAR $\gamma$ . The *PPARG* variants p.Arg165Thr, p.Gly211Glu, p.Arg240Trp,  
179 p.Arg262Gly, p.Val318Met, p.Leu339\*, p.Glu352Gln, p.Arg425Cys, p.Gln443\*, and  
180 p.Pro495Leu were considered as pathogenic based on ACMG criteria, ClinVar database, or  
181 cosegregation and/or functional studies (2, 14, 15, 16, 17, 18, 19). The *PPARG* variants  
182 p.Tyr173Cys, p.Cys180Tyr, p.Pro234Thr and p.Ile434Thr are considered as deleterious,  
183 probably or possibly damaging by the SIFT and/or Polyphen-2 prediction softwares. Patients  
184 were not found to carry any additional pathogenic or likely pathogenic variant in the complete  
185 coding sequence and intronic junctions of *PPARG*, nor in 22 other genes known to be  
186 involved in lipodystrophic and/or insulin resistance syndromes (i.e. *AGPAT2*, *AKT2*, *BSCL2*,  
187 *CAVI*, *CIDEC*, *DYRK1B*, *INSR*, *LIPE*, *LMF1*, *LMNA*, *LMNB2*, *NSMCE2*, *PCYT1A*, *PIK3R1*,  
188 *PLD3*, *PLIN1*, *POC1A*, *POLD1*, *PSMB8*, *PTRF*, *TBC1D4*, *ZMPSTE4*).

189

190 The parental origin of the *PPARG* variant was confirmed by molecular analyses in ten among  
191 25 heterozygous patients : 6 of them carried a maternally-inherited, and 4 a paternally-  
192 inherited *PPARG* variant (Table 1).

193

#### 194 **Lipodystrophy and metabolic phenotype of patients carrying heterozygous *PPARG*** 195 **variants**

196 Table 2 presents the main metabolic features of the patients carrying heterozygous *PPARG*  
197 variants, with the exception of Patient 15, a premature newborn who died 24 hours after birth  
198 (12). Their median age at investigation was 45 years. Patient 8, a 83 years old man, was  
199 diagnosed after familial screening. He presented with high blood pressure, diabetes and  
200 hypertriglyceridemia diagnosed in the elderly, but did not present with obvious clinical

201 lipodystrophy. All other patients with a heterozygous *PPARG* variant present with a clinical  
202 lipodystrophy, associating in most of them limb lipoatrophy, muscular hypertrophy, android  
203 fat distribution and acanthosis nigricans.  
204 Most patients (73.9%) have an increased BMI (median value: 25.8 kg/m<sup>2</sup>, Q25: 22.25) :  
205 eleven patients are overweight (BMI 25 to 30), and three are obese (BMI ≥30). Serum leptin  
206 levels are low-to-normal with regards to BMI (median 8.4 ng/ml). Diabetes is reported in all  
207 patients except a 16-year-old man (Patient 3) and a 55-year-old woman (Patient 12), both  
208 diagnosed with hypertriglyceridemia, hepatic steatosis and insulin resistance. Most patients  
209 with diabetes are treated with insulin (56.5%), with non-optimal glucose control (median  
210 HbA1c 8.1%). Diabetes developed early in life (median age at diagnosis 24 years), and  
211 lipodystrophy later on (median age at diagnosis 37 years old), without any statistical  
212 difference between females and males regarding prevalence and age at diagnosis of diabetes  
213 and lipodystrophy. Hypertension is frequent (58.3% of the patients), diagnosed early in the  
214 course of the disease (at a median age of 28 years old). Most patients (78.2%) present with  
215 hypertriglyceridemia (median triglycerides 5.6 mmol/L). Six of them, all women (25% of the  
216 whole cohort and 37.3% of the female patients) have experienced at least one episode of acute  
217 pancreatitis. Hepatic cytolysis is observed in 70.8% of the patients, all of them being  
218 diagnosed with hepatic steatosis by echography.

219

### 220 **Reproductive phenotype of women with FPLD3**

221 Seventeen adult women with FPLD3, due to heterozygous *PPARG* variants, were studied,  
222 with a median age at investigation of 48 years old (Table 2). Their median age at first  
223 menstruation was 12 years. After clinical, biological and ultrasound examination, PCOS was  
224 diagnosed in 12 among 16 patients (75%) using the Rotterdam criteria (20). Eleven among 12  
225 women trying to conceive obtained pregnancy, two of them through medically-assisted

226 procreation (ovarian stimulation in Patient 7, *in vitro* fertilization in Patient 6). Six  
227 pregnancies among 25 did not lead to a live birth : one was interrupted by abortion, four by  
228 early miscarriages (two in the context of diabetes), and one by fetal death (occurring in a  
229 patient with diabetes). Among the 11 women who had at least one pregnancy, all had  
230 metabolic alterations, *i.e.* either diabetes (n=5), hypertension (n=4), and/or  
231 hypertriglyceridemia (n=10) diagnosed before pregnancy, and/or developed gestational  
232 diabetes (n=3). Preeclampsia was diagnosed in three patients.

233

### 234 **Perinatal characteristics of patients with FPLD3**

235 Perinatal data were available in 17 patients with heterozygous *PPARG* variants (Table 3 and  
236 Supplemental Table). A majority of them (9 among 17, 52.9%) was born premature (< 37  
237 weeks of amenorrhea). The median gestational age at birth was 36 weeks of amenorrhea  
238 (range 31-41). The median birth weight of patients was 2200g (range 1200-4000g). Six  
239 patients (42.9%) were small for gestational age and five patients (35.7%) were large for  
240 gestational age. Two newborns experienced neonatal hypoglycemia: Patient 2 was born from  
241 a mother with diabetes during pregnancy, and Patient 4 was born premature and small for  
242 gestational age without dysmetabolic maternal context. Amniotic fluid disorders were  
243 reported in three cases. Oligohydramnios was diagnosed during the fetal life of Patient 3,  
244 Patient 6 and Patient 15 (in the context of maternal diabetes for Patient 6 and 15).  
245 Polyhydramnios was diagnosed during the prenatal life of Patient 15, who was born  
246 premature and died in the neonatal period (12). Patient 25 was born in a context of maternal  
247 diabetes, hypertension, and preeclampsia (Table 3 and Supplemental Table).

248

249 Both the maternal dysmetabolic environment, or the placental expression of a *PPARG* variant  
250 carried by the fetus, could contribute to perinatal deleterious outcomes. Therefore, we

251 compared the perinatal characteristics of patients with heterozygous *PPARG* variants  
252 according to the presence or absence of fetal exposure to a maternal dysmetabolic  
253 environment. Data from 17 patients were available (Table 4). Patients whose mothers were  
254 diagnosed with diabetes, and/or high blood pressure during pregnancy and/or  
255 hypertriglyceridemia before pregnancy were considered as exposed to a dysmetabolic  
256 environment during fetal life (n=8). All heterozygous patients carrying a maternally-inherited  
257 variant (n=6), but none of those carrying a paternally-inherited variant (n=4), reach the  
258 criteria to be classified in this group (Table 4 and Supplemental Table).

259  
260 The maternal age at delivery (median 25 years) was similar in patients exposed or not to a  
261 dysmetabolic intrauterine environment (Table 4). Importantly, the median gestational age at  
262 birth was low, and the prevalence of prematurity was high, both in patients exposed to  
263 maternal metabolic alterations (37 weeks of amenorrhea, and 37.5% of prevalence,  
264 respectively), and in patients not exposed (36 weeks of amenorrhea, and 66.7% of  
265 prevalence), without any statistical difference between the two groups. Newborns were  
266 frequently large for gestational age in the group exposed to maternal dysmetabolic  
267 environment, as expected (71.4% of them, *versus* 0% in the non-exposed group, p=0.02). In  
268 contrast, the great majority of patients with *PPARG* variants who developed in a favorable  
269 metabolic intrauterine environment was born small for gestational age (n=6, 85.7%, versus  
270 0% in the dysmetabolic group, p=0.005). To note, patients born small for gestational age were  
271 preserved from maternal smoking during their fetal life, which is a known cause of low birth  
272 weight.

273

274 **Perinatal and metabolic features of the patient carrying the homozygous *PPARG***  
275 **(p.Tyr173Cys) variant**

276 Patient 17, born from parents originating from the same island of the New Caledonia  
277 archipelago, carried a homozygous *PPARG* variant. She was born preterm and small for  
278 gestational age (610g, 28 weeks of amenorrhea), after cesarean delivery for fetal distress in  
279 the context of retro-placental hematoma. Diabetes, severe acanthosis nigricans and  
280 hypertriglyceridemia were diagnosed before pregnancy in her mother. Her father was known  
281 to suffer from severe hypertension with renal insufficiency without other information. Patient  
282 17 presented at birth with generalized lipoatrophy, muscular hypertrophy,  
283 hepatosplenomegaly, signs of virilization, and major hypertriglyceridemia (Suppl Figure).  
284 Hyperinsulinemia and hypoleptinemia were reported at the age of 2, and diabetes was  
285 diagnosed at the age of 6 years and 10 months. She showed severe developmental delay  
286 secondary to perinatal brain damage, with growth retardation and signs of bone dysplasia.  
287 Molecular investigations were performed for congenital generalized lipoatrophy at the age of  
288 3. The *PPARG* (p.Tyr173Cys) variant was present in the heterozygous state in her parents.

289

## 290 **DISCUSSION**

291 Our project aimed to characterize the multi-tissular phenotype associated with *PPARG*-related  
292 lipodystrophy in the largest series reported to date, involving 26 patients originating from 15  
293 unrelated families. Given the importance of PPAR $\gamma$  not only in the regulation of adipogenesis  
294 and metabolism (1, 21), but also in placental formation and functions (4, 22), we studied  
295 metabolic features, reproductive functions in women, and perinatal characteristics of the  
296 patients. We enlarge the knowledge of the FPLD3 phenotype by showing that the disease is  
297 associated with severe and early metabolic complications, including PCOS in women, and  
298 could involve growth retardation and increased risk of prematurity during the prenatal life.  
299 Based on our results, we recommend that the multidisciplinary care of patients with FPLD3

300 should also include prenatal monitoring of offspring in affected families, in either case of  
301 maternal or paternal potential transmission of the disease.

302

303 Our data suggest that early diabetes is a major characteristic of FPLD3, and is frequently  
304 reported before the diagnosis of clinical lipodystrophy. In addition, and in contrast to what is  
305 observed in most forms of lipodystrophic syndromes (23), the majority of the patients with  
306 *PPARG*-related lipodystrophy presented with a BMI greater than 25 kg/m<sup>2</sup>. This could result  
307 from increased lean rather than fat mass, since muscular hypertrophy is a prominent feature of  
308 the disease, and serum leptin values are lower than expected with regards to BMI. However, a  
309 recent study reported that patients with *PPARG*-related lipodystrophy have a greater amount  
310 of adipose tissue than patients with *LMNA*-related lipodystrophy (24). The metabolic  
311 phenotype of FPLD3 could be related not only to the consequences of lipodystrophy and  
312 adipocyte dysfunction, but also, at least in part, to deleterious roles of *PPARG* pathogenic  
313 variants on other insulin-sensitizing pathways. In addition to its major role on adipogenesis,  
314 *PPAR* $\gamma$  is involved in the regulation of multiple pathways modulating energy homeostasis and  
315 inflammation (25). High blood pressure, which can also develop early in patients with  
316 FPLD3, could be related to the dysregulation of *PPAR* $\gamma$ -mediated vascular functions,  
317 including angiogenesis, vascular tone and cellular renin-angiotensin system (18, 26, 27).  
318 Patients with FPLD3 are also frequently affected with hepatic steatosis, which is a typical  
319 feature of lipodystrophic syndromes, and with hypertriglyceridemia, which can be severe,  
320 leading to the risk of acute pancreatitis, especially in women.

321

322 Adipose tissue homeostasis and insulin response are important determinant of reproductive  
323 function in women. However, a few studies have described the reproductive phenotype in  
324 women with lipodystrophy syndromes (21, 28, 29, 30, 31, 32). In our cohort, 75% of women

325 with *PPARG* heterozygous variants present with PCOS and 81.2% with hirsutism.  
326 Nevertheless, our data suggest that fertility is preserved in most cases, the requirement to  
327 medically-assisted procreation being comparable to the general population in women with  
328 FPLD3 from our study. When pregnant, all women with FPLD3 present with diabetes,  
329 hypertension, and/or hypertriglyceridemia. Almost 50% of women with FPLD3 had diabetes  
330 before pregnancy and more than 25% developed a gestationnel diabetes. This is in  
331 accordance with previous results based on a model of pregnancy in *PPAR* $\gamma$ 2 knockout mice,  
332 showing that *PPARG*-dependent healthy adipose tissue expansion and function are mandatory  
333 for physiological metabolic adaptations during pregnancy (33).

334

335 *In vitro* and *in vivo* studies showed an essential role of *PPARG* in placental development in  
336 mice (22, 34, 35). Strikingly, *PPARG* inactivation in mice results in defects in trophoblast  
337 differentiation and uterine vascular remodeling leading to embryonic lethality (36, 37), which  
338 is prevented by trophoblastic re-expression of *PPARG* (22). *PPARG* was shown to control  
339 major processes allowing the vascular exchange interface between maternal and fetal blood in  
340 humans (8, 34, 35). Some *PPARG* variants have been associated with an increased genetic  
341 susceptibility of abruptio placentae (38) and preterm birth (39) in the general population. In  
342 addition, gene expression of *PPARG* in placentas from women who gave birth to babies born  
343 small for gestational age was reported to be two-fold lower as compared to controls, and to be  
344 associated to fetal and placental weights (10). Nevertheless, the pathophysiological role of  
345 *PPARG* during human pregnancy is largely unknown. As the placenta is a post-zygotic organ,  
346 it shares with the fetus the same genetic heritage. In an attempt to study the placental  
347 consequences of the lipodystrophy-related *PPARG* variants, we collected the perinatal data of  
348 18 patients recruited in our national reference center for lipodystrophic diseases. Our results  
349 took into account the prenatal metabolic environment, which depends on the maternal *PPARG*

350 genetic status, and impacts the perinatal outcomes. All patients known to carry a maternally-  
351 inherited variant, but none of the patients carrying a paternally-inherited variant, were  
352 exposed to an intrauterine dysmetabolic environment. However, the prevalence of prematurity  
353 was high in patients carrying a heterozygous *PPARG* variant (52.9%), and did not differ  
354 according to the prenatal metabolic environment. In addition, while maternal metabolic  
355 alterations were, as expected, major risk factors for increased birth weight with regards to  
356 gestational age, 85.7% of patients without dysmetabolic prenatal exposure were small for  
357 gestationnel age. Taken together, our results suggest that growth restriction and prematurity  
358 could be linked to defective placental development and functions induced by lipodystrophy-  
359 related *PPARG* variants. They are in line with our previous *in vitro* study, which showed that  
360 the lipodystrophy-associated *PPARG* (p.Glu352Gln) variant, expressed in human trophoblast  
361 cells, inhibits the differentiation of villous cytotrophoblasts into syncytiotrophoblasts (19). In  
362 addition, *PPAR* $\gamma$  was shown to promote uteroplacental perfusion by increasing nitric oxide  
363 and decreasing downregulating endothelin-1 production (8). Defects in foetal vascularization  
364 impairing availability of nutrients could thus play a role in FPLD3-associated growth  
365 restriction and prematurity. Whatever the mechanism involved, our results underline the  
366 importance of a close metabolic and obstetrical follow-up of pregnant women either  
367 diagnosed with FPLD3, or susceptible to bear a child with a paternally-transmitted *PPARG*  
368 variant.

369

370 Our cohort includes the first reported patient carrying an homozygous lipodystrophy-  
371 associated *PPARG* variant. She presented with congenital generalized lipodystrophy, as  
372 reported in the only case previously described with biallelic *PPARG* pathogenic variants (40).  
373 The *PPARG* variant identified in the patient from our study affects the DNA binding domain  
374 of the protein (p.Tyr173Cys), which was also the case for the two variants previously reported



375 in the compound heterozygous state [*PPARG* (p.Glu138Valfs\*168) and (p.Arg164Trp)].  
376 Metabolic complications appeared early in life with hypertriglyceridemia and  
377 hepatosplenomegaly at birth, and diabetes diagnosed at the age of 6 years. Biallelic  
378 lipodystrophy-associated *PPARG* variants probably induce important prenatal adverse effects,  
379 since the patient described here was born preterm and small for gestational age (610g, 28  
380 weeks of amenorrhea), and the previous case also suffered from intrauterine growth  
381 restriction (birthweight of 940g at 32 weeks) (40).

382

383 We present here the largest cohort of patient carrying a *PPARG* variant with study of  
384 lipodystrophy, metabolic, reproductive and perinatal aspects. Our results highlight specific  
385 features of the disease, with early onset of diabetes, before the clinical recognition of  
386 lipodystrophy, which could contribute to disease underdiagnosis, especially since patients are  
387 frequently overweighted. Precocious high blood pressure, muscular hypertrophy,  
388 hypertriglyceridemia and familial history are important signs to help diagnosis. For the first  
389 time, we show that lipodystrophy-related *PPARG* variants are likely to impact fetal  
390 development and parturition, with risk of impaired fetal growth and prematurity. This justifies  
391 a close metabolic and obstetrical follow-up of women with FPLD3, and the monitoring of  
392 fetal growth of the descendants of all subjects, male or female, bearing *PPARG* pathogenic  
393 variants. This study also justifies further investigations regarding the pathophysiological role  
394 and potential therapeutic modulation of PPAR $\gamma$  in human pregnancy.

395

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398

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404

#### 405 ***Author Contribution***

406 CG, CVi and CVa designed and conducted the research, analysed the data and wrote the  
407 manuscript. All authors made substantial contributions to conception, design, acquisition of  
408 data, data analyses and data interpretation. OL, IL and CVi generated and/or analyzed the  
409 genetic data. IM, FA, XD, CD,BF, SG, BG, SH, YH, EN, CPi, CPo, JPT referred some  
410 patients and contribute to the phenotypic description. All authors revised the manuscript  
411 critically for important intellectual content and gave their approval of the final version to be  
412 published.. CVa and CVi are the guarantor of this work and takes responsibility for the  
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414

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421

#### 422 ***Data sharing/ availability statement***

423 The datasets presented in this article are not readily available because of the sensitive nature  
424 of the data and possible high risks associated with patient confidentiality. Requests to access  
425 the datasets should be directed to [camille.vatier@aphp.fr](mailto:camille.vatier@aphp.fr).

426

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