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

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Short title : Perinatal consequences of *PPARG* variants

Abstract

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

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

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

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

Significance Statement

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

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

INTRODUCTION

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

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102 Besides its well-known role in adipogenesis, PPAR γ 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 γ -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 γ is
108 activated during the differentiation of villous cytotrophoblasts into syncytiotrophoblasts (5,
109 6), which ensure placental endocrine functions. PPAR γ 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.

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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

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

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

RESULTS

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

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

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

other families all harbored different *PPARG* variants. Three variants are located in exons encoding the DNA binding domain and 11 variants in exons encoding the ligand binding domain of *PPAR* γ . The *PPARG* variants p.Arg165Thr, p.Gly211Glu, p.Arg240Trp, p.Arg262Gly, p.Val318Met, p.Leu339*, p.Glu352Gln, p.Arg425Cys, p.Gln443*, and p.Pro495Leu were considered as pathogenic based on ACMG criteria, ClinVar database, or cosegregation and/or functional studies (2, 14, 15, 16, 17, 18, 19). The *PPARG* variants p.Tyr173Cys, p.Cys180Tyr, p.Pro234Thr and p.Ile434Thr are considered as deleterious, probably or possibly damaging by the SIFT and/or Polyphen-2 prediction softwares. Patients were not found to carry any additional pathogenic or likely pathogenic variant in the complete coding sequence and intronic junctions of *PPARG*, nor in 22 other genes known to be involved in lipodystrophic and/or insulin resistance syndromes (i.e. *AGPAT2*, *AKT2*, *BSCL2*, *CAV1*, *CIDEA*, *DYRK1B*, *INSR*, *LIPE*, *LMF1*, *LMNA*, *LMNB2*, *NSMCE2*, *PCYT1A*, *PIK3R1*, *PLD3*, *PLIN1*, *POC1A*, *POLD1*, *PSMB8*, *PTRF*, *TBC1D4*, *ZMPSTE4*).

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

Lipodystrophy and metabolic phenotype of patients carrying heterozygous *PPARG* variants

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

lipodystrophy. All other patients with a heterozygous *PPARG* variant present with a clinical lipodystrophy, associating in most of them limb lipoatrophy, muscular hypertrophy, android fat distribution and acanthosis nigricans.

Most patients (73.9%) have an increased BMI (median value: 25.8 kg/m², Q25: 22.25) : eleven patients are overweight (BMI 25 to 30), and three are obese (BMI ≥30). Serum leptin levels are low-to-normal with regards to BMI (median 8.4 ng/ml). Diabetes is reported in all patients except a 16-year-old man (Patient 3) and a 55-year-old woman (Patient 12), both diagnosed with hypertriglyceridemia, hepatic steatosis and insulin resistance. Most patients with diabetes are treated with insulin (56.5%), with non-optimal glucose control (median HbA1c 8.1%). Diabetes developed early in life (median age at diagnosis 24 years), and lipodystrophy later on (median age at diagnosis 37 years old), without any statistical difference between females and males regarding prevalence and age at diagnosis of diabetes and lipodystrophy. Hypertension is frequent (58.3% of the patients), diagnosed early in the course of the disease (at a median age of 28 years old). Most patients (78.2%) present with hypertriglyceridemia (median triglycerides 5.6 mmol/L). Six of them, all women (25% of the whole cohort and 37.3% of the female patients) have experienced at least one episode of acute pancreatitis. Hepatic cytolysis is observed in 70.8% of the patients, all of them being diagnosed with hepatic steatosis by echography.

Reproductive phenotype of women with FPLD3

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

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

Perinatal characteristics of patients with FPLD3

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

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

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

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

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

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

DISCUSSION

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

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

Our data suggest that early diabetes is a major characteristic of FPLD3, and is frequently reported before the diagnosis of clinical lipodystrophy. In addition, and in contrast to what is observed in most forms of lipodystrophic syndromes (23), the majority of the patients with *PPARG*-related lipodystrophy presented with a BMI greater than 25 kg/m². This could result from increased lean rather than fat mass, since muscular hypertrophy is a prominent feature of the disease, and serum leptin values are lower than expected with regards to BMI. However, a recent study reported that patients with *PPARG*-related lipodystrophy have a greater amount of adipose tissue than patients with *LMNA*-related lipodystrophy (24). The metabolic phenotype of FPLD3 could be related not only to the consequences of lipodystrophy and adipocyte dysfunction, but also, at least in part, to deleterious roles of *PPARG* pathogenic variants on other insulin-sensitizing pathways. In addition to its major role on adipogenesis, *PPAR*γ is involved in the regulation of multiple pathways modulating energy homeostasis and inflammation (25). High blood pressure, which can also develop early in patients with FPLD3, could be related to the dysregulation of *PPAR*γ-mediated vascular functions, including angiogenesis, vascular tone and cellular renin-angiotensin system (18, 26, 27). Patients with FPLD3 are also frequently affected with hepatic steatosis, which is a typical feature of lipodystrophic syndromes, and with hypertriglyceridemia, which can be severe, leading to the risk of acute pancreatitis, especially in women.

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

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

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

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

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

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

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

Declaration of interest: All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author Contribution

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

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Data sharing/ availability statement

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

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