

# Развитие метаболического синдрома в молодом возрасте как проявление семейной парциальной липодистрофии 3 типа (дефект гена *PPARG*): первое описание клинического случая в России

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Распространенность метаболического синдрома (МС) во всем мире крайне высока (около 20–25%), разработаны диагностические критерии этого состояния, показана его связь с увеличением риска сердечно-сосудистых осложнений в 2 раза и смертности от них в 3 раза по сравнению с общей популяцией. Однако до сих пор нет единого представления о причинах развития МС; ключевая роль отводится сочетанию наследственной предрасположенности к инсулинорезистентности (ИР) и факторам внешней среды. Особого внимания требует развитие МС в молодом возрасте, что может быть проявлением наследственной липодистрофии. Впервые в России описана семья (3 клинических случая) с семейной парциальной липодистрофией (СПЛД) 3-го типа, обусловленной гетерозиготной мутацией p.R212Q в гене *PPARG* (MIM#601487). Изучение редких форм наследственной ИР, в частности, СПЛД, способствует лучшему пониманию такой распространенной клинической проблемы как МС.

**Ключевые слова:** метаболический синдром; семейная парциальная липодистрофия 3-го типа; *PPARG*, инсулинорезистентность; нарушение толерантности к глюкозе; *acanthosis nigricans*; синдром поликистозных яичников

## Development of metabolic syndrome at a young age as a manifestation of familial partial lipodystrophy type 3 (*PPARG* mutation): the first description of its clinical case in Russia.

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Metabolic syndrome (MS) is extremely common (20%–25% of the world's population), and its diagnostic criteria are defined and well known. It has been shown that patients who have MS are twice as likely to die from a cardiovascular complication and three times as likely to suffer from it compared with patients without MS. However, the underlying cause of MS remains to be clearly elucidated, although inherited factors, such as insulin resistance (IR), and external factors are considered to play a key role in this process. Special attention should be paid to MS in young patients, who may present the first manifestation of inherited lipodystrophy. The study describes the first known family in Russia (three clinical cases) with familial partial lipodystrophy (FPLD) type 3 caused by heterozygous p.R212Q *PPARG* mutation (MIM#601487). The study reports rare forms of inherited IR, such as FPLD, and contributes to a better understanding of common disorders such as MS.

**Key words:** metabolic syndrome; familial partial lipodystrophy type 3; *PPARG*; insulin resistance; impaired glucose tolerance; *acanthosis nigricans*; polycystic ovary syndrome

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The prevalence of metabolic syndrome (MS) is extremely high worldwide (approximately 20%–25%), which is significant given that it is associated with double the risk of cardiovascular complications and triple the risk of death compared with the general population [1]. According to a resolution of the International Diabetes Federation passed in 2006 [1], the following criteria must be met to make a diagnosis of MS:

- Central obesity (waist circumference for Europeans:  $\geq 80$  cm for women and  $\geq 94$  cm for men);
- Hypertriglyceridaemia  $\geq 150$  mg/dl ( $\geq 1.7$  mmol/l) before the start of specific treatment or when there is a history of hypolipidaemic therapy;
- Reduction in the concentration of high-density lipoprotein (HDL) cholesterol to  $<40$  mg/dl (1.03 mmol/l) for men and  $<50$  mg/dl (1.29 mmol/l) for women before the start of specific treatment or when there is a history of hypolipidaemic therapy;
- Elevated systolic arterial blood pressure  $\geq 130$  mmHg or diastolic arterial blood pressure  $\geq 85$  mmHg before the start of specific treatment or when there is a history of antihypertensive therapy;
- Elevated fasting plasma glucose level  $\geq 100$  mg/dl (5.6 mmol/l) before the start of specific treatment or when there is previously diagnosed type 2 diabetes mellitus.

Despite these advances, there is no agreement on the causes of MS. Nevertheless, a key role is believed to be played by a combination of environmental factors and a hereditary predisposition to insulin resistance (IR). Special attention should also be paid to the onset of MS at a young age, which may be a manifestation of familial lipodystrophy.

Hereditary lipodystrophies are a group of rare diseases characterized by complete or partial loss of subcutaneous fat and by its incorrect distribution in the body. Generalized and partial lipodystrophies are identified depending on the degree of subcutaneous fat loss. Familial partial lipodystrophies (FPLD) are characterized by diabetes mellitus with expressed IR, acanthosis nigricans, dyslipidaemia, liver steatosis, arterial hypertension and polycystic ovary syndrome. Among patients with FPLD, type 2 is most common, including laminopathies caused by a mutation of *LMNA* [2]. However, since their first description in 1999, researchers have described eight families with type 3 FPLD that are caused by heterozygote mutations in *PPARG*. Type 3 FPLD is characterized by an easier clinical course and less pathological redistribution of subcutaneous fat, with preserved manifestations of MS [3]. Thus, type 3 FPLD requires special attention by clinicians to ensure timely diagnosis in the cases of combined expressed metabolic impairments at a young age. This will ensure effective treatment of the patients and timely genetic consulting for their families [4].

## Clinical case description

Patient A was first examined in the endocrinology clinic of the First Sechenov Medical University in 2012. At that time, she was aged 25 years and presented with polycystic ovary syndrome with IR, menstrual irregularity (oligomenorrhea) and failure to get pregnant after 2 years of unprotected sex.

The patient's examination revealed the following:

- Hirsutism (the hair growth rate 18);
- Non-uniform distribution of subcutaneous fat, with lipohypertrophy in the face, neck and posterior triangle of the neck as well as excessive abdominal fat (waist circumference = 86 cm; hip circumference = 96 cm), sufficient fat in the arms and lipodystrophy in the area of shanks, hips, buttocks and belly (Fig. 1);
- Moderate acanthosis nigricans in the armpits (Fig. 2).

## Clinical and Family History

The patient had a history of urolithiasis since a young age (microlites in the right kidney), but her early development was otherwise normal. Although she started to have menses at the age of 13, her periods were irregular and painful, lasting 5–6 days



Fig. 1. Physical appearance of patient A. The red arrow indicates the lipohypertrophic areas and the black arrow indicates the lipodystrophic areas.



Fig. 2. Acanthosis nigricans in the armpits of patient A.

with a periodicity of 30–90 days. At the age of 23, she took an oral contraceptive (combined ethinyl estradiol and drospirenone) for 6 months because of anovulatory oligomenorrhea, after which she developed multiple xanthomas on her buttocks, back and shoulders. At this point, dyslipidaemia and hepatosplenomegaly were first discovered. At the age of 25 years, the patient was hospitalized with regular pain in the right hypochondrium and diagnosed with non-alcoholic steatohepatitis, chronic cholecystitis and a gallbladder polyp. She was treated with a course of hepatoprotective and cholagogue therapy with ursodeoxycholic acid and her clinical condition improved. Tests performed at that admission revealed hyperinsulinaemia (insulin 20  $\mu\text{U}/\text{ml}$ ) and IR [fasting glucose level, 4.9 mmol/l and homeostatic model assessment for IR or homeostatic model assessment (HOMA)-IR, 4.4], dyslipidaemia (triglycerides, 10.5 mmol/l; total cholesterol, 7.0 mmol/l and very low-density lipoprotein cholesterol, VLDL, 2.07 mmol/l) and hyperuricaemia (uric acid 450.9  $\mu\text{mol}/\text{l}$ ).

Since 2013 (age 26 years), the patient developed hypertension with a blood pressure of 180/100 mmHg and a heart rate of 100–110 beats/min. Echocardiography showed a dilated left ventricle with a false chord, and although the valves were intact, there was mild subvalvular regurgitation. Abdominal ultrasound showed moderate hepatomegaly, with the left lobe measuring 86 mm and the right lobe measuring 168 mm, and diffuse transformations of the fatty hepatosis type; there was also splenomegaly to 162  $\times$  56 mm. The pelvic ultrasound revealed multi-follicular ovaries, measuring 39  $\times$  31  $\times$  24 mm, with signs of chronic anovulation. The two-dimensional (2D) magnetic resonance imaging (MRI) spectroscopy of the liver (conducted in the Russian Cardiology Research and Production Complex, under the Russian Ministry of Health) revealed 38% and 56% shares of the fatty tissue in segments 6 and 7 of the left liver lobe, respectively (normal value,  $\leq 6.5\%$ ), confirming the diagnosis of fatty hepatosis (Fig. 3).

An oral glucose tolerance test was first performed

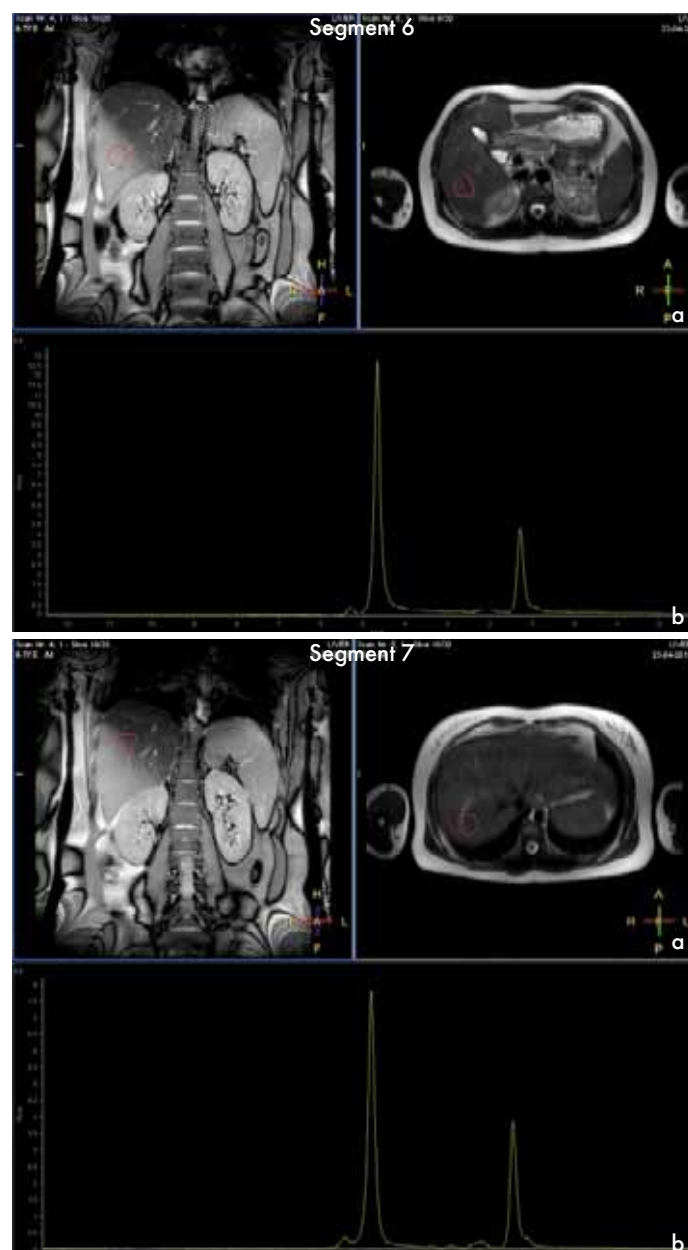


Fig. 3. Time-resolved {3.2 [EN] Please check the spelt out abbreviation} spectroscopy of liver segments 6 and 7 in patient A.

a) Positioning of the volume to perform spectroscopy in the frontal and axial scans; b) MR-spectrum, high peaks of water (4.7 parts per million) and fat (1.3 parts per million) are observed.

in 2015, which revealed a fasting glucose level of 4.6 mmol/l and an impaired glucose tolerance of 11.0 mmol/l after 2 h. Hypercorticism was excluded by testing daily excretion of free cortisol in the urine. A hyperinsulinaemic-euglycaemic clamp test was conducted in the Endocrinology Research Center in 2015 and showed an M-index of 3.56 mg/kg/min, which corresponds to moderately expressed IR (normal value is  $>6$ , low is 4–6 and expressed is  $<2$ ). Hormonal testing revealed the following: leptin, 5.3 ng/ml (1.1–27.6); TTH, {3.1 [EN] Please expand the abbreviation} 1.4  $\mu\text{units}/\text{ml}$  (0.4–4.0); progesterone, 1.0 nmol/l (10.6–89.1); testosterone, 2.9 nmol

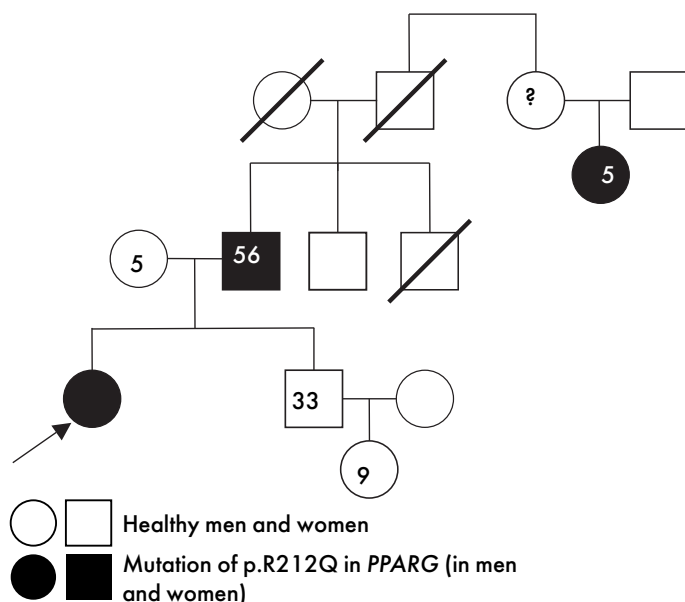


Fig. 4. The genealogic tree of the family of patient A.

(0.5–2.6); androstenedione, 22.1 nmol/l (1.0–11.5); dehydroepiandrosterone, 15.1  $\mu$ mol/l (1.0–11.7); estradiol, 175 nmol/l (77–277); prolactin, 196  $\mu$ units/ml (40–670) and intact parathormone, 1.7 pmol/l (1.3–6.8).

The genealogy of the family of patient A is summarized in Fig. 4. The father of patient A was 56 years old and had been diagnosed with the following: diabetes mellitus at the age of 54 years, for which he was on insulin therapy with satisfactory control, arterial hypertension, coronary disease (exertional angina), rheumatoid arthritis since the age of 30, gout and haemorrhoids. The father's cousin, a 54-year-old woman, had dyslipidaemia (with predominant increase in triglycerides at 26 mmol/l), coronary disease (angina of effort, functional class 3, with a history of acute myocardial infarctions in 2009 and 2012), aortal atherosclerosis (aortal stenosis of atherosclerotic origin but not hemodynamically significant), hypertrophy of the left ventricle of the heart, pancreonecrosis (2007), diabetes mellitus (fasting glucose level, 7.3 mmol/l) since 2014 and hyperuricaemia.

The patient was suspected of having FPLD given the characteristic history, family history and examination findings. Particular relevance was given to the redistribution of subcutaneous fat in a partial lipodystrophy pattern, presence of acanthosis nigricans and history of polycystic ovary syndrome, hyperandrogenism, IR, impaired glucose tolerance, hypertension and dyslipidaemia with predominant hypertriglyceridaemia from a young age.

### Genetic Tests

Genomic DNA was isolated from peripheral leukocytes using standard techniques. For the proband, the genetic analysis was conducted with the method of massively parallel sequencing (Ion Torrent plat-

form), using the Custom Ion Ampliseq panel with primers for multiplex amplification of *ZMPSTE24*, *LMNA*, *BSCL2*, *PLIN1*, *PTRF*, *LMNB2*, *POLD1*, *AKT2*, *CIDEA*, *PIK3CA*, *PPARG*, *PSMB8*, *CAVI*, *PPP1R3A*, and *AGPAT2*. Bioinformatic processing of the sequencing data was performed with the ANNOVAR software package (<http://annovar.openbioinformatics.org/>). Molecular genetic analysis of the *PPARG* fragment with the proband's relatives was conducted with the Sanger sequencing method using the ABI Genetic Analyzer 3130 (Applied Biosystems, USA). As the reference sequence of the coding area for *PPARG*, we used Genbank (<http://www.ncbi.nlm.nih.gov/sites/entrez>) reference NM\_015869.4. Mutations were indicated in accordance with previously published recommendations [5]. All family members who underwent genetic testing gave their written informed consent.

A heterozygous adenine–guanine transition in position 635 of *PPARG* was revealed in the proband (c.635G>A), which caused a substitution of arginine for glutamine in position 212 (p.R212Q). Similar mutations were present in the patient's father and his cousin, whereas a wild-type sequence of this fragment was present in two healthy relatives of the patient (her mother and brother). Because substitution of p.R212Q has not yet been described, we performed analysis with ANNOVAR, which revealed that the mutation of p.R212Q was pathogenic. Arginine in position 212 was shown to be in the conservative DNA binding domain of the receptor; moreover, this amino acid residue was shown to be highly conservative and possible in all vertebrate.

### Medical Treatment and Dynamic Observation

In the treatment of patients with familial lipodystrophies, strict anti-atherogenic diets, such as the Mediterranean diet, play a significant role. Therefore, a low-calorie diet was recommended, with tight restriction of animal fats and simple carbohydrates but with ample dietary fibre. The patient was also recommended to perform regular aerobic and anaerobic exercise [6]. Despite progress in understanding the aetiology and pathogenesis of FPLD, only symptomatic therapy is possible because etiotropic treatment is currently impossible. In 2013, the US Food and Drug Administration approved the use of metreleptin for the pathogenetic treatment of generalized lipodystrophies; however, the safety and efficacy of leptin in treating FPLD is still open to dispute, with the results of clinical trials still awaited. We know that the main causes of death in patients with lipodystrophies are diabetes mellitus, recurrent acute pancreatitis due to expressed hypertriglyceridemia, liver cirrhosis caused by long-standing liver steatosis and the effects of vascular atherosclerosis; consequently, treatment needs to be directed at prevention and treatment of these metabolic complications [7].

Since May 2012, patient A has been treated with metformin at a daily dose of 1000 mg. This has effectively reduced her HOMA-IR index to 3.5 and led to a glycated haemoglobin level of 4.8%. To date, thiazolidinediones (PPAR $\gamma$ -receptor agonists) are the only targeted medications available to treat diabetes mellitus that results from FPLD. Should the impaired carbohydrate metabolism progress to diabetes mellitus, thiazolidinediones in combination with metformin will be the glucose-reducing drugs of choice.

At follow-up in the endocrinology clinic in 2015, which was 2 years after starting permanent treatment with fenofibrate, significantly improved lipid metabolism was seen compared with her earlier figures of 2012: total cholesterol 4.36 mmol/l, triglycerides 4.43 mmol/l, low-density lipoprotein cholesterol 2.66 mmol/l and HDL cholesterol 0.81 mmol/l. We continued the courses of liver protecting therapy and fenofibrate because moderate elevations of alanine transaminase (64 U/l) and aspartate aminotransferase (42 U/l) were noted. The hepatic transaminases were subsequently controlled, the uric acid level normalized to 307  $\mu$ mol/l and the urolithiasis went into remission. Although the patient has tried several antihypertensives, bisoprolol бисопролол (2.5 mg/d) has achieved the best control, producing a blood pressure of 120/80 mmHg and a heart rate <90 beats/min. Other antihypertension drugs produced excessive reductions in blood pressure without reducing her heart rate, even in low doses.

## Discussion

In this case, the patient was diagnosed with a variant of the Dunnigan–Köbberling (type 3 FPLD), which could be associated with a high degree of probability to the heterozygote mutation in *PPARG*. This gene encodes the peroxisome proliferator-activated receptor, type  $\gamma$  (PPAR $\gamma$ ) protein, which is required for fatty tissue to be differentiated in vivo and in vitro [8]. According to expert consensus, the total prevalence rate of the Dunnigan–Köbberling syndrome (types 2 and 3 FPLD) is 1 case per 1 million population [7]; however, the true prevalence will only be known by establishing an international register of hereditary lipodystrophies, and it is not unlikely that many cases will remain undiagnosed due to the low degree of specialist awareness.

The defect in *PPARG* accompanying MS was first described by Barroso et al. [9] in 1999 in 2 of 85 unrelated patients with severe IR. A mutation of p.V290M was found in a female patient aged 15 years with primary amenorrhea, hirsutism, acanthosis nigricans and hyperinsulinaemia. By the age of 17, the patient also developed type 2 diabetes mellitus and arterial hypertension, which was controlled by treatment with beta-blockers. Mutation of p.P467L was revealed in another female patient with IR, type 2

diabetes mellitus and hypertension from the age of 20 years. The same mutation was also revealed in her 30-year-old son, who had diabetes mellitus and hypertension from a young age. All revealed mutations were heterozygote transitions. In 2003, Savage et al. [10] conducted a detailed study of the characteristics of the first patients with *PPARG* mutations and discovered a phenotype of partial lipodystrophy that was missed during routine examination but with clinical manifestations that were characteristic of FPLD. After discovering the association of *PPARG* with lipodystrophy, this syndrome was designated a type 3 FPLD (MIM#604367).

To raise the diagnostic accuracy, particularly when examining males, it is necessary to use supplementary methods to measure the amount of fatty tissue, such as MRI or total body densitometry. In recent MRI studies, the difference in distribution of subcutaneous fat of the limbs has been quantified for patients with types 2 and 3 FPLD, with evidence that subcutaneous fat loss (lipoatrophy) was much lower in patients with type 3 FPLD [11].

In 2002, Hegele et al. [12] described a family in Canada in which all four members had FPLD. However, because they showed no mutation of *LMNA*, the authors decided to check *PPARG*. They discovered a heterozygous mutation, p.F388L, located in exon 5 that produced a change in the ligand-binding zone of the receptor. In the same year, Agarwal and Garg [13] discovered a heterozygous mutation of p.R425C in *PPARG* in a woman with FPLD. Interestingly, four healthy relatives did not have the mutation.

In 2006, Francis G.A., et al. [14] described another family with type 3 FPLD. The mother had typical loss of subcutaneous fat in her limbs, although there were no areas of lipohypertrophy; she had diabetes mellitus with expressed IR, severe hypertriglyceridaemia and recurrent pancreatitis, while her teenage daughter had normal distribution of subcutaneous fat, yet, the tests revealed hyperinsulinaemia and dyslipidaemia in her. The disease was caused by nonsense-mutation Y355X in *PPARG*, which resulted in the formation of unstable protein with negative transcription without dominant negative activity in relation to the wild-type receptor.

In 2007, Ludtke et al. [15] discovered another heterozygous mutation of *PPARG* (C190S) in three patients from a family with clinical findings of partial lipodystrophy. The mutation was located in the DNA binding domain, and the mutant protein had a much lower ability to activate a reporter gene than the wild-type PPAR- $\gamma$ , even when rosiglitazone was administered. No dominant negative activity was revealed, and no mutation was discovered in the healthy family members or in 124 members of a control group. Also in 2007, Monajemi et al. [4] reported a heterozygous mutation of *PPARG* in a 31-year-old female patient with FPLD. From her early childhood, she had de-

veloped lipodystrophy, diabetes mellitus, IR and hypertriglyceridaemia, which had resulted in secondary pancreatitis. Heterozygous transition of p.R194W in the conservative DNA binding receptor domain was discovered during examination in comparison with 100 healthy controls. The in vitro test of the mutant protein revealed that p.R194W could not bind DNA and did not have transcription activity. The authors concluded that mutation of p.R194W prevented DNA binding because of haploinsufficiency and clinically resulted in type 3 FPLD.

In 2011, Visser et al. [11] conducted an interesting study. After analyzing the databases of three clinics (5,221 individuals), 24 patients with diabetes mellitus and signs of IR were selected. Here IR was defined as the use of  $\geq 100$  Units of insulin per day and a body mass index of  $\leq 27$  kg/m<sup>2</sup>. Of those patients, five had clinical manifestations of lipodystrophy, and the diagnosis was confirmed in two who had a mutation in *LMNA* and one who had a heterozygous mutation

in *PPARG* (p.Y151C). The functional tests showed a protein with a p.Y151C mutation that violated the binding ability of DNA, and thus, reduced the transcription activity compared with that with wild-type *PPAR $\gamma$* . No dominant negative activity was revealed.

Comparing our results to those in the literature suggests that the clinical manifestations of the disease in our patient and her relatives fit the type 3 FPLD pattern. The new *PPARG* mutation was probably causative.

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