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Major hyperinsulinemia, acanthosisnigricans, impaired glucose tolerance and ovarian hyperandrogenismcharacterizeType A insulin resistance (IR) syndromedue to dominant-negative heterozygous mutations in the insulin receptor gene (*INSR*) [1].However, two unrelated families have been described with symptomatic hypoglycemia due toheterozygous*INSR*p.Arg1201substitutions in the tyrosine kinase domain[2,3]. In these patients, major hyperinsulinemiatogether withdecreased insulin clearance was suggested torescue genetically-altered insulin signalling *in vivo*in liver and/or muscle.

We broaden the genetic spectrum of this rare phenotype of Type A insulin resistance by reporting the observations of two patients with *INSR*p.Met1180Val or p.Arg1201Gln heterozygous mutations revealed by repeated symptomatic hypoglycemia.

Two unrelated women aged16and 43(Patients 1 and 2, respectively) were referred for recurrent episodes of sudden hunger, blunted vision and dizziness in late postprandial states, which were alleviatedby food ingestion. Their medical history was unremarkable and their body mass index was normal(24.3 and 19.6 kg/m^2), without lipodystrophy. Patient 1 also displayed primary amenorrhea,hirsutism (Ferriman-Gallweyscore : 21), and acanthosisnigricans. Polycystic ovary syndrome was diagnosed, with typical hormone and echographic findings.Clinical examination of Patient 2 was normal.

In both patients, routine laboratory tests werenormal, withlow-normal fasting plasma glucose (3 to 4.8 mmol/l), as was hormonal evaluation (including cortisol, IGF-1, thyroid function), except for markedly increased fasting insulin(four to ten-foldhigher than normal values).Insulin and C-peptide levels decreased during a 48- to 72h-fast whereas glycemia remained higher than 2.1mmol/l, and endoscopic ultrasound or CT-scan did not reveal any pancreatic lesion. No sulfonylurea drug was detected in urine. In both patients, a 75g-oral glucose tolerance test (OGTT) showed a marked increase in insulin concentrations and high insulin-to-C-peptide ratios(Table).The search for serum anti-insulin and anti-insulin receptor antibodies was negative. Genetic analyses revealed *INSR*heterozygousmutations in the two patients. Patient 1 harbored the novel *INSR*p.Met1180Valsubstitution, which was not

reported in the 1000 Genome Project and theExACdatabases and was predicted to be damaging by PolyPhen-2, SIFT, and Mutation Taster. Interestingly, at the same codon, the p.Met1180Ileheterozygous substitution was previously associated with a classical Type A insulin resistance syndrome [4]. The previously described *INSR*p.Arg1201Gln mutation [2] was detected in Patient 2.

The 48-year-old mother of Patient 1reportedhypoglycemia and irregular menses, displaying low fasting glucose with high insulin and insulin-to-C-peptide ratio (2.4 mmol/l, 355 pmol/l and 0.39, respectively). She carried the *INSR* p.Met1180Val mutation. *INSR* sequencing was normal in the two asymptomatic children of Patient 2. Symptoms of hypoglycaemia decreased under metformin in affected patients.

In adults, hyperinsulinemic hypoglycemia is mainly due to inappropriate secretion of insulin by insulinomas and rarely related to antiinsulin auto-antibodies with acute dissociation of insulin from immune complexes[5]. Rare paradoxical hypoglycemia can also occurin severe insulin resistance states. Antiinsulin receptor auto-antibodies, responsible for Type B insulin resistance, may induce hypoglycemia due to partial agonist effects[5,6]. In severe congenital insulin resistance syndromes with biallelic*INSR* mutations, major hyperinsulinism with prolonged insulin half-life andvariable tissue-specific residual function of insulin receptors can lead to bothhypoglycemia and hyperglycemia[1].Our observations further demonstrate that hyperinsulinemichypoglycemia in adults can reveal different heterozygous mutations in the insulin receptor tyrosine kinase domain, whether associated or not with acanthosisnigricans, impaired glucose tolerance and/or ovarian hyperandrogenism.

Table. Plasma glucose, insulin and C-peptide concentrations during oral 75g-oral glucose tolerance test in patients 1 and 2.

	0 min	30 min	60 min	120 min	180 min
Glucose (mmol/l)					
Patient 1 (*INSR*p.Met1180Val)	3.4	6.2	5.0	5.3	5.8
Patient 2 (*INSR*p.Arg1201Gln)	4.8	12.7	9.0	4.6	3.2
Insulin (pmol/l) (reference value at fast <80)					
Patient1	604	2243	2584	3195	3910
Patient 2	335	2072	3555	3058	1337
C-peptide (pmol/l) (reference value at fast <760)					
Patient1	860	5300	4533	4667	6500
Patient 2	570	2330	3200	2620	1270
Insulin-to-C-peptide ratio (reference value at fast <0.10)					
Patient 1	0.70	0.42	0.57	0.68	0.60
Patient2	0.59	0.89	1.11	1.17	1.05

Mutation nomenclature isbased on the recommended guidelines from the HumanGenome Variation Society and the nucleotide accession number NM_000208.3 (proteinreferencesequence P06213), corresponding to the encodedinsulinreceptorpreproprotein. This explains the discrepancybetween the current and previous nomenclatures ofthe described*INSR*substitutions p.Arg1201/p.Arg1174[2,3], and p.Met1180/p.Met1153 [4].

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Disclosure of interest

The authors have no conflict of interest to disclose.

Author contributions

V.P., C.F, D.M and C.V. wrote the manuscript. V.P., C.F., C.C., P.T. and D.M. produced clinical data. O.L. conducted the genetic analyses. All the authors contributed to the discussion and reviewed the manuscript.