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## **Hypoglycemia revealing heterozygous insulin receptor mutations**

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Major hyperinsulinemia, acanthosis nigricans, impaired glucose tolerance and ovarian hyperandrogenism characterize Type A insulin resistance (IR) syndrome due to dominant-negative heterozygous mutations in the insulin receptor gene (*INSR*) [1]. However, two unrelated families have been described with symptomatic hypoglycemia due to heterozygous *INSR*p.Arg1201 substitutions in the tyrosine kinase domain [2,3]. In these patients, major hyperinsulinemia together with decreased insulin clearance was suggested to rescue 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 aged 16 and 43 (Patients 1 and 2, respectively) were referred for recurrent episodes of sudden hunger, blunted vision and dizziness in late postprandial states, which were alleviated by food ingestion. Their medical history was unremarkable and their body mass index was normal (24.3 and 19.6 kg/m<sup>2</sup>), without lipodystrophy. Patient 1 also displayed primary amenorrhea, hirsutism (Ferriman-Gallwey score: 21), and acanthosis nigricans. Polycystic ovary syndrome was diagnosed, with typical hormone and echographic findings. Clinical examination of Patient 2 was normal.

In both patients, routine laboratory tests were normal, with low-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-fold higher than normal values). Insulin and C-peptide levels decreased during a 48- to 72h-fast whereas glycemia remained higher than 2.1 mmol/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* heterozygous mutations in the two patients. Patient 1 harbored the novel *INSR*p.Met1180Val substitution, which was not

reported in the 1000 Genome Project and the ExAC databases and was predicted to be damaging by PolyPhen-2, SIFT, and Mutation Taster. Interestingly, at the same codon, the p.Met1180Ile heterozygous 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 1 reported hypoglycemia 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 occur in 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 and variable tissue-specific residual function of insulin receptors can lead to both hypoglycemia and hyperglycemia [1]. Our observations further demonstrate that hyperinsulinemic hypoglycemia in adults can reveal different heterozygous mutations in the insulin receptor tyrosine kinase domain, whether associated or not with acanthosis nigricans, 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
<b>Glucose (mmol/l)</b>					
Patient 1 ( <i>INSR</i> p.Met1180Val)	3.4	6.2	5.0	5.3	5.8
Patient 2 ( <i>INSR</i> p.Arg1201Gln)	4.8	12.7	9.0	4.6	3.2
<b>Insulin (pmol/l)</b> (reference value at fast <80)					
Patient1	604	2243	2584	3195	3910
Patient 2	335	2072	3555	3058	1337
<b>C-peptide (pmol/l)</b> (reference value at fast <760)					
Patient1	860	5300	4533	4667	6500
Patient 2	570	2330	3200	2620	1270
<b>Insulin-to-C-peptide ratio</b> (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 is based on the recommended guidelines from the Human Genome Variation Society and the nucleotide accession number NM\_000208.3 (protein reference sequence P06213), corresponding to the encoded insulin receptor preproprotein. This explains the discrepancy between the current and previous nomenclatures of the 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.