Somatic paternal UPD on chromosome 11p15 in focal form of congenital hyperinsulinism (CHI) causes monoallelic expression of mutant ABCC8 and KCNJ11

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Background
Congenital hyperinsulinism (CHI) is a disorder characterized by dysregulation of insulin secretion that leads to severe hypoglycemia in neonates and infants. There are two major forms of CHI. The diffuse form affects all β-cells in the pancreas and is caused by autosomal recessive or dominant inherited mutations. The focal form of CHI is caused by an autosomal recessive mutation in the genes ABCC8 and KCNJ11 inherited from the father and a second somatic event in the affected islet of Langerhans.

Objective
Several possible mechanisms exist which may cause the second genetic event in focal CHI: maternal deletion, paternal duplication or paternal UPD 11p15. We report molecular genetic examination of focal pancreatic lesions of patients receiving therapeutic surgery to discover the genetic mechanisms in focal form of CHI.

Mechanisms of CHI
Most commonly, mutations occur in ABCC8 (45%) and KCNJ11 (58%). Both genes are located on chromosome 11p15. The BWS imprinting region is located in proximity to these genes on 11p15.5.

Material and Methods
Patients with proven ABCC8 or KCNJ11 mutations and treated by surgical therapy were selected from the German Registry for Congenital Hyperinsulinism. Genomic DNA and RNA were extracted from pancreatic tissue. Loss of heterozygosity (LOH) and gene expression levels were analysed by PCR, RT-PCR and Sanger sequencing in 11 patients with focal form of CHI. Deletions, duplications and uniparental isodisomy (UPD) were tested by methylation-specific MLPA (MS-MLPA).

Results

Conclusions
Molecular genetic analysis of ABCC8 and KCNJ11 in pancreatic lesions revealed expression of the paternally transmitted mutant allele and loss of the maternal allele. This supports somatic mosaicism specific in pancreatic endocrine cells. Both, ABCC8 and KCNJ11, are located in proximity to the Beckwith-Wiedemann imprinting region on chromosome 11p15 that is also known for UPD. Paternal UPD is responsible for LOH and leads to a growth advantage of β-cells in focal lesions. This growth advantage results from increased expression of genes, which promote proliferation (IGF2) and decreased expression of genes which inhibit proliferation (CDKN1C, H19).

References

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