

Clinical characteristics of congenital hyperinsulinism caused by dominant *KCNJ11/ABCC8* mutations.

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OBJECTIVES

Congenital hyperinsulinism (HI) is the most common cause of hypoglycemia in children and infants. It is characterized by a dysregulation of insulin secretion from pancreatic β -cells and mostly associated with recessive inactivating mutations in the β -cell ATP-sensitive potassium (K_{ATP}) channel genes - *KCNJ11* and *ABCC8*. Dominantly inherited mutations in these genes are usually associated with mild forms of diazoxide responsive HI. Recently monoallelic K_{ATP} genes mutations were reported to be a rare cause of severe diazoxide unresponsive diffuse forms of HI.

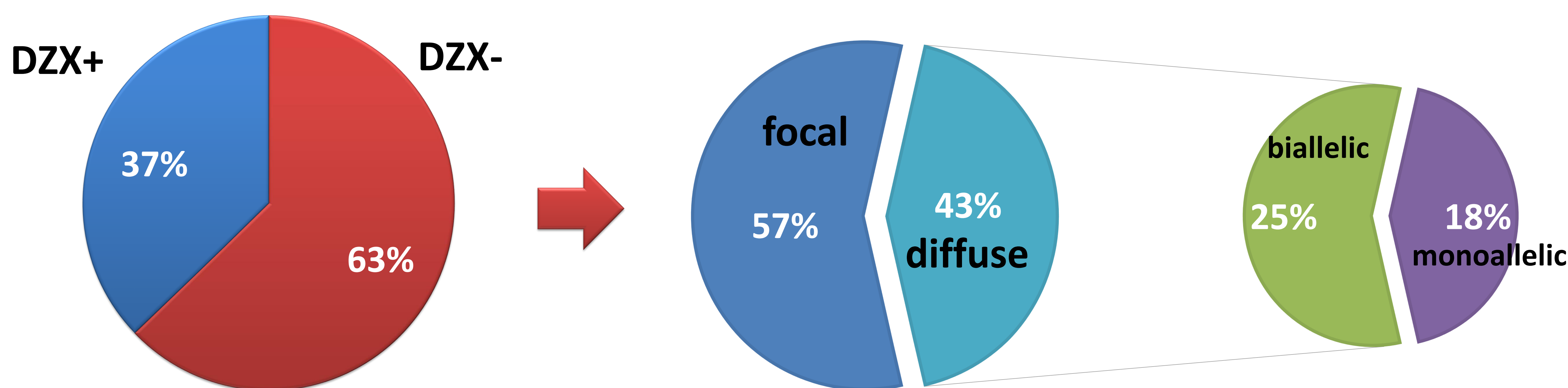
We report clinical and genetic characteristics of the group of patients with diazoxide unresponsive diffuse form of HI caused by a single heterozygous mutation in K_{ATP} genes.

RESULTS

A total of 187 patients with CHI were identified in Russia since 2009. 78 of them (41,7%) were found to have monoallelic or biallelic mutations in *ABCC8/KCNJ11* genes in 60 and 18 cases respectively.

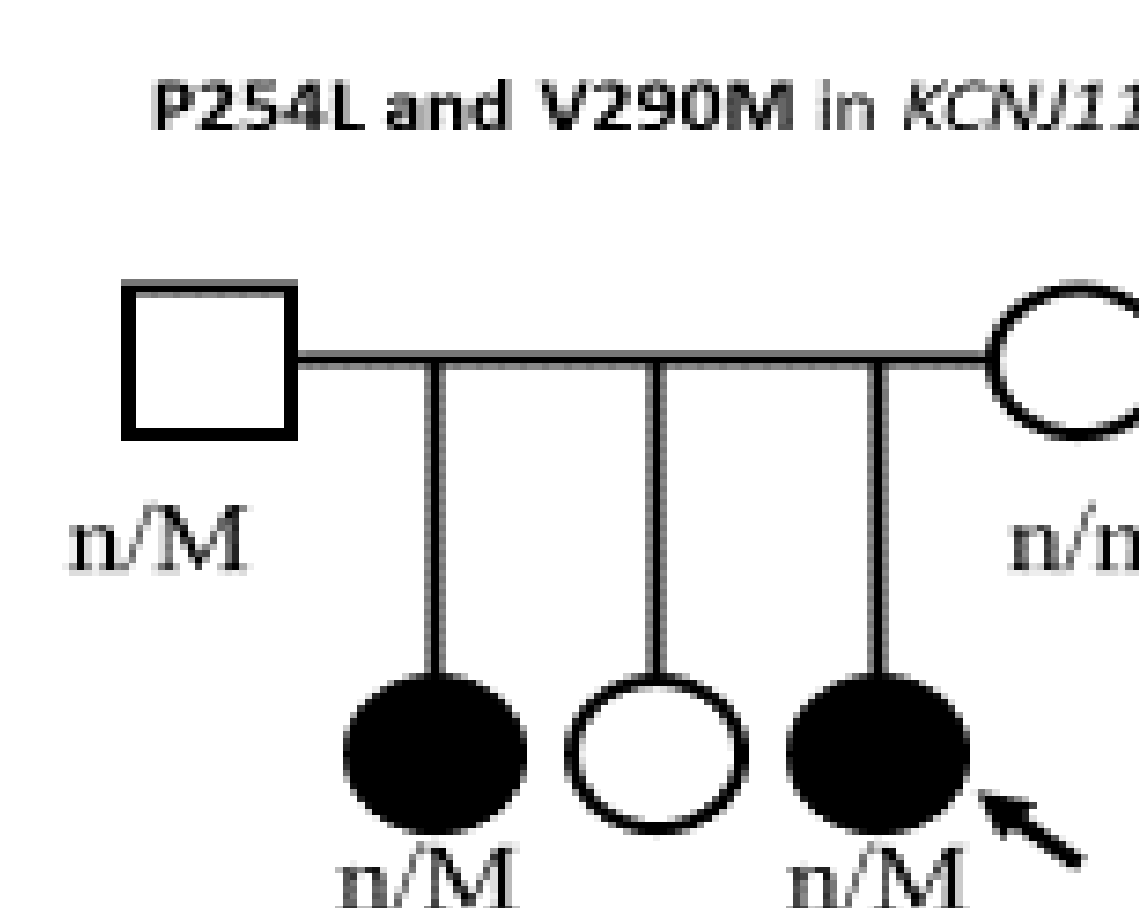
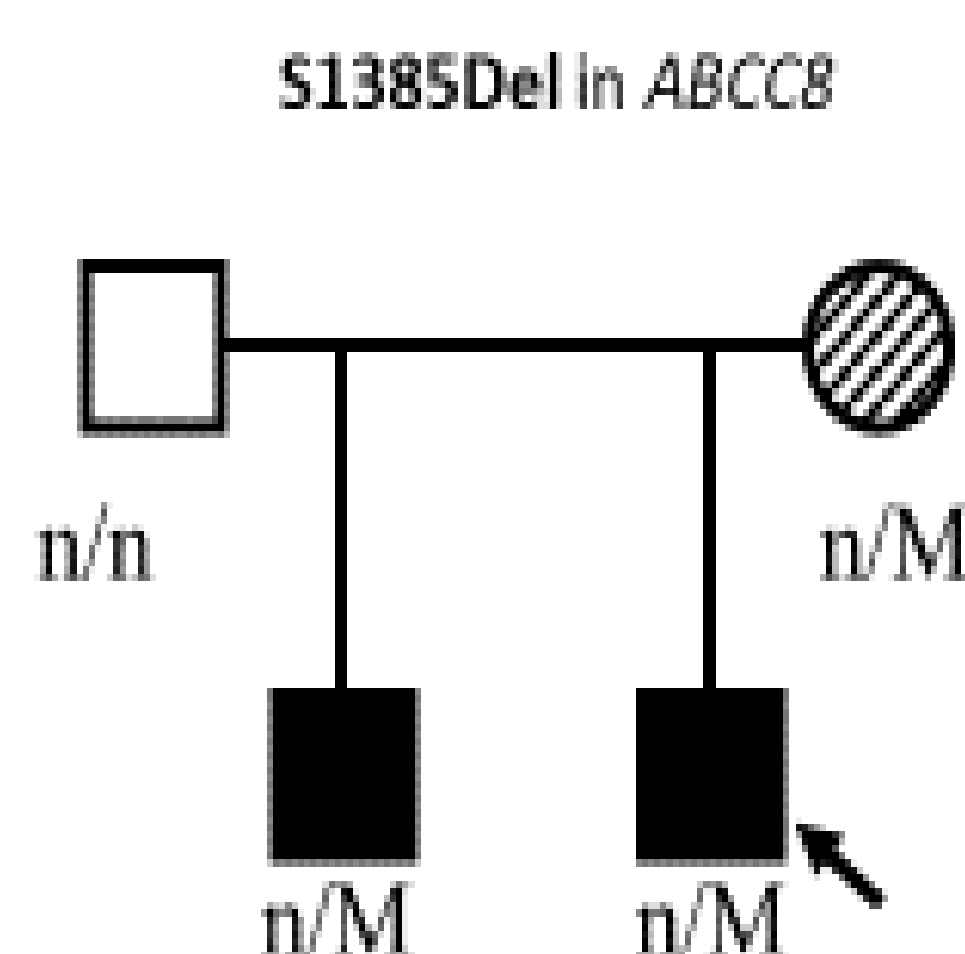
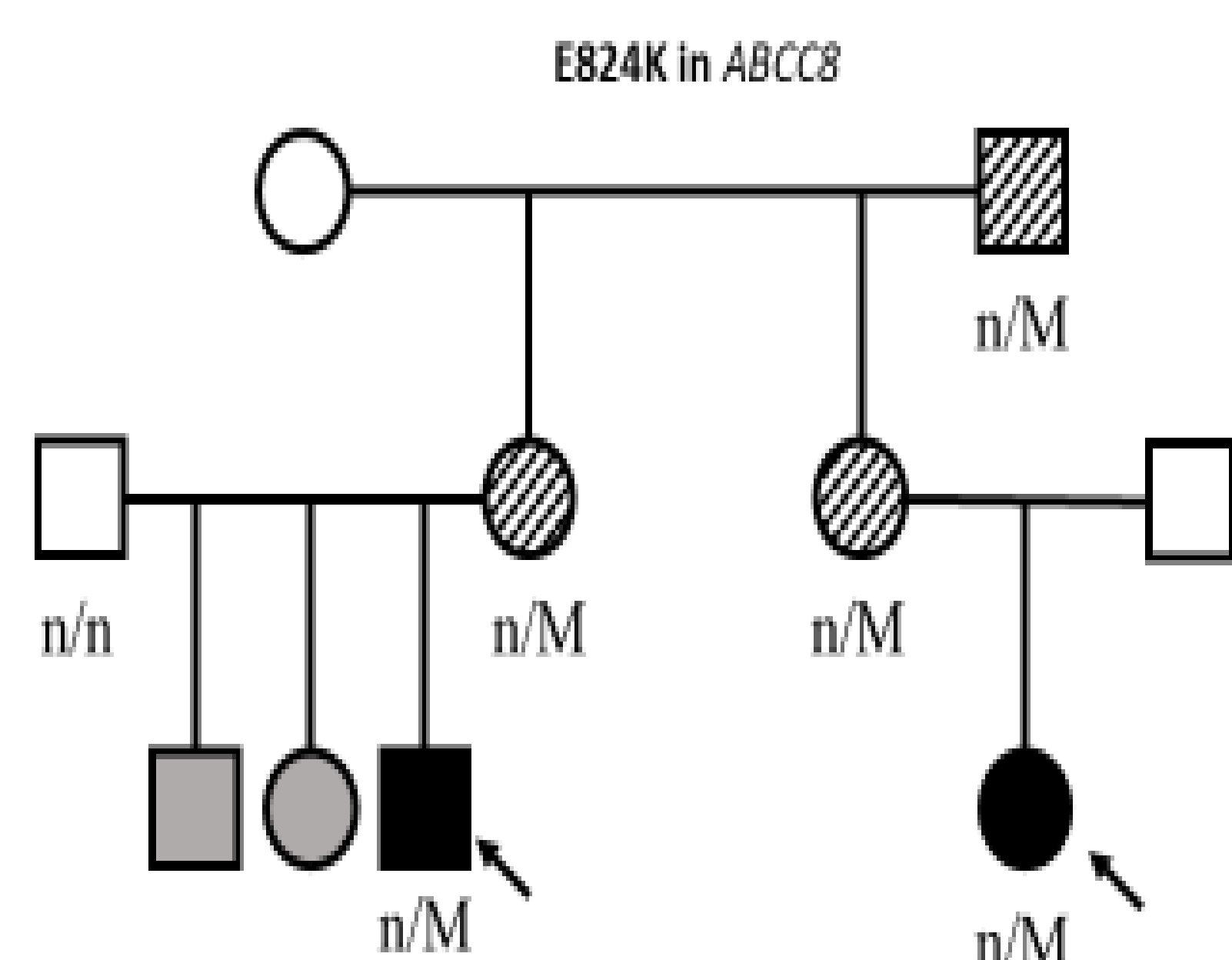
Focal form of the disease was diagnosed in 28 children (35,9%), all of them were found to carry heterozygous paternal mutation. 9 children (4 females) with diazoxide unresponsive diffuse HI from 6 different families were found to have a single *KCNJ11* or *ABCC8* gene mutation. In 3 families mutation was on maternal site, in 1 case - on paternal site and 2 children had denovo mutations.

HI patients with mutations in *ABCC8/KCNJ11* genes



Biochemical and clinical investigations of parents were possible in 3 families and included fasting test, standard OGTT and Hb1AC measurements. No one had hypoglycemia. In 2 families mothers who carried mutations were found to have either glucose intolerance or gestational diabetes. All the mutation carriers, including probands and those who were asymptomatic, were born LGA.

| gene | mutation | n | inheritance |
|---------------|-------------------------------|---|-------------|
| <i>KCNJ11</i> | c.G868A:p.V290M | 2 | paternal |
| | c.C761T:p.P254L | | |
| | c.G617A:p.R206H | 1 | maternal |
| <i>ABCC8</i> | c.G2143A:p.V715M | 1 | denovo |
| | c.G2470A:p.E824K | 2 | maternal |
| | c.C4154G:p.S1385C | 1 | Denovo |
| | c.4153_4155del:p.1385_1385del | 2 | maternal |



CONCLUSIONS

In our cohort dominant K_{ATP} genes mutations account for 18,3% of the children with diffuse diazoxide unresponsive CHI. The variability of clinical presentation in mutation carriers among the family is unclear. Additional studies of possible modifying genes are needed for better understating the behavior of dominantly acting mutations.