

## Update of variants identified in the pancreatic beta-cell $K_{ATP}$ channel genes *KCNJ11* and *ABCC8* in individuals with congenital hyperinsulinism and diabetes

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## **Abstract**

The most common genetic cause of neonatal diabetes and hyperinsulinism are pathogenic variants in *ABCC8* and *KCNJ11*. These genes encode the subunits of the beta-cell ATP sensitive potassium channel, a key component of the glucose-stimulated insulin secretion pathway. Mutations in the two genes cause dysregulated insulin secretion; inactivating mutations cause an over-secretion of insulin leading to congenital hyperinsulinism, whilst activating mutations cause the opposing phenotype, diabetes. This review focuses on variants identified in *ABCC8* and *KCNJ11*, the phenotypic spectrum and the treatment implications for individuals with pathogenic variants.

**Key words:** Neonatal Diabetes, Congenital Hyperinsulinism, *ABCC8*, *KCNJ11*, K-ATP channel

ATP-sensitive potassium ( $K_{ATP}$ ) channels were found to couple glucose metabolism to membrane electrical activity and insulin release over 30 years ago (Ashcroft, et al., 1984; Cook and Hales, 1984; Rorsman and Trube, 1985). This landmark discovery was fundamental to furthering understanding of the insulin secretion pathway whereby glucose metabolism results in a change in ratio of ADP and ATP. Binding of ATP to the channel induces channel closure, depolarisation of the membrane and activation of voltage-dependent calcium channels leading to calcium influx and insulin granule exocytosis (Figure 1a).

Given the role of the  $K_{ATP}$  channel in insulin secretion, it is not unexpected that variants in *KCNJ11*, encoding the four pore-forming inwardly rectifying Kir6.2 subunits, and *ABCC8*, encoding the four sulphonylurea receptor 1 (SUR1) subunits of the channel, can cause hypo- or hyperglycaemia (Babenko, et al., 2006; Gloyn, et al., 2004b; Thomas, et al., 1996; Thomas, et al., 1995). Identifying these mutations is important for informing prognosis, medical management and recurrence risk.

Over recent years, the number of variants identified in these two genes has expanded tremendously. In 2006, 124 disease-causing mutations were reported which increased to 265 pathogenic variants 3 years later (Flanagan, et al., 2009; Gloyn, et al., 2006b). By combining published reports together with data from 5 international molecular genetic screening laboratories in the UK, Denmark, France and the United States of America we now report 953 pathogenic *ABCC8* and *KCNJ11* variants (Supp Tables S1-S6) and discuss the role of these genes in congenital hyperinsulinism (CHI) and monogenic diabetes.

### **Congenital Hyperinsulinism**

CHI is characterised by the inappropriate secretion of insulin despite low blood glucose which can result in irreversible brain damage if not promptly treated

(Helleskov, et al., 2017). The condition has a variable phenotype usually presenting during the neonatal period or infancy with seizures and/or coma and a large birth weight due to high levels of insulin acting as a growth factor *in utero*.

Although most cases of CHI are sporadic rare familial forms have been well documented. Sporadic CHI has an estimated incidence of between 1 in 27,000 and 1 in 50,000 live births (Glaser, et al., 2000; Otonkoski, et al., 1999). However, in some isolated populations, or in countries with high rates of consanguineous unions, the incidence is higher (i.e. 1 in 2,675 to 1 in 3,200) (Mathew, et al., 1988; Otonkoski, et al., 1999).

#### ***CHI due to $K_{ATP}$ channel mutations***

Loss-of-function *ABCC8* mutations were first described in 1995 (Thomas, et al., 1995). These mutations either prevent trafficking of the channel to the membrane surface or are associated with channels that reach the surface but are not fully responsive to MgADP activation (figure 1) (Ashcroft, 2005; Nichols, et al., 1996; Taschenberger, et al., 2002). The majority of *ABCC8* loss-of-function mutations are recessively acting with a small number of dominant missense mutations reported which produce channels that traffic to the membrane but have impaired mgADP activation.

Fewer loss of function mutations have been reported in *KCNJ11* in keeping with the gene being much smaller (1173 vs 4749 bases, respectively) (Thomas, et al., 1996). Similarly to *ABCC8*, both dominant and recessively acting *KCNJ11* mutations have been described (Pinney, et al., 2013). Together mutations in these two genes account for 36%-70% of CHI cases (Kapoor, et al., 2013; Snider, et al., 2013).

Mouse models for  $K_{ATP}$  channel CHI exist, however, their inability to fully recapitulate the human phenotype means that they have limited value for studying specific disease mechanisms. For example, mice generated with a deletion of *ABCC8* or *KCNJ11*, or the homozygous recessive *KCNJ11* mutation p.(Tyr12Ter), do not have the sustained neonatal hypoglycaemia observed in humans with homozygous null mutations. Instead the blood glucose levels normalise in the mouse within a few days of birth with glucose intolerance developing in later life (Hugill, et al., 2010; Miki, et al., 1998; Seghers, et al., 2000). The differences in the phenotype between mice and humans are not fully understood but highlight the need to develop human-specific models for studying disease mechanisms.

### ***Clinical Management of $K_{ATP}$ Channel CHI***

In 2015, the Pediatric Endocrine Society published recommendations for the evaluation and management of persistent hypoglycaemia in neonates, infants and children (Thornton, et al., 2015). The main treatment for CHI is the  $K_{ATP}$  channel-opener diazoxide, however patients with *ABCC8/KCNJ11* mutations which prevent trafficking to the membrane do not respond to the drug as diazoxide targets the SUR1 subunit of the  $K_{ATP}$  channel. For approximately 50% of patients with mutations that do not prevent the channel from reaching the membrane, diazoxide is an effective treatment (Boodhansingh, et al., 2019). For patients with diazoxide-unresponsive CHI, second line treatment with somatostatin analogues may be helpful to control hypoglycaemia although adverse effects to somatostatin analogues, and likewise diazoxide, have been reported (Demirbilek, et al., 2014; Herrera, et al., 2018).

The mode of inheritance of the  $K_{ATP}$  channel mutation determines the pancreatic histological subtype (de Lonlay, et al., 1997; de Lonlay, et al., 2002; Jack, et al., 2000; Rahier, et al., 1984). Inheritance of two recessively-acting or one dominant

*ABCC8/KCNJ11* mutation results in diffuse disease affecting the entire pancreas. Focal disease is caused by somatic loss of the maternal chromosome 11p15.5 region by uniparental disomy which unmasks a paternally-inherited  $K_{ATP}$  channel mutation at 11p15.1. These focal lesions often appear histologically as small regions of islet adenomatosis which develop as a result of the imbalanced expression of maternally imprinted tumour suppressor genes H19 and  $p57^{Kip2}$ , and the increased expression of the paternally derived insulin-like growth factor II gene (Craigie, et al., 2018; Damaj, et al., 2008; de Lonlay, et al., 1997). Rarely, giant focal lesions have been described where virtually the whole of the pancreas is affected (Ismail, et al., 2012). Atypical mosaic disease has also been reported in a small number of cases (Han, et al., 2017; Houghton, et al., 2019; Hussain, et al., 2008; Sempoux, et al., 2011).

The identification of a single recessively-acting  $K_{ATP}$  channel mutation in an individual with CHI predicts focal disease with 84-97% sensitivity with a positive predictive value up to 94% (Mohnike, et al., 2014; Snider, et al., 2013).  $^{18}F$ -DOPA PET/CT scanning can identify and localize a focal lesion prior to surgery (Otonkoski, et al., 2006). Intraoperative ultrasound may further aid the surgeon to perform tissue-sparing pancreatic resection in focal CHI which is potentially curative (Bendix, et al., 2018).

## **DIABETES MELLITUS**

Diabetes is the opposing disorder to CHI and results from hyper- rather than hypoglycaemia. Current estimates suggest that approximately 0.4% of all diabetes (and up to 3.5% of those diagnosed under 30 years of age) has a monogenic cause (Shepherd, et al., 2016; Shields, et al., 2017). Individuals diagnosed with monogenic diabetes outside of infancy are generally classified as having Maturity Onset Diabetes of the Young (MODY), whilst Neonatal Diabetes (NDM) describes congenital diabetes. In individuals with NDM, impaired insulin secretion results in a

low birth weight and hyperglycaemia diagnosed before the age of 6 months (Hattersley and Ashcroft, 2005). The minimal incidence of NDM has been calculated to be between 1 in 89,000 and 1 in 160,949 live births (Grulich-Henn, et al., 2010; Wiedemann, et al., 2010).

### **Later-onset diabetes due to $K_{ATP}$ channel mutations**

Dominantly acting mutations in the  $K_{ATP}$  channel genes have been rarely described in individuals with later-onset diabetes in the absence of documented hyper- or hypoglycaemia in the neonatal period (Tarasov, et al., 2008)(Bowman, et al., 2012; Hartemann-Heurtier, et al., 2009; Huopio, et al., 2003; Koufakis, et al., 2019). The mechanism(s) leading to this variable penetrance are not fully understood and may differ according to whether the mutation is causing a gain or loss of channel function. Interestingly, in one study the generation of a mouse model harbouring a homozygous dominantly-acting loss-of-function *ABCC8* mutation p.(Glu1507Lys) recapitulated the biphasic phenotype with the mice having increased insulin secretion in early life and reduced insulin secretion later on. This was shown to be resulting from a reduction in insulin content rather than a reduction of islet number and/or size. Heterozygosity for the mutation did however not result in a phenotype in the mouse, further highlighting differences between the mouse models and human disease (Shimomura, et al., 2013).

### **Neonatal diabetes due to $K_{ATP}$ channel mutations**

Strong support for the role of gain-of-function  $K_{ATP}$  channel mutations in the aetiology of diabetes came from the observation that mice over-expressing a mutant  $K_{ATP}$  channel with reduced ATP sensitivity developed diabetes within 2 days (Koster, et al., 2000). In 2004, the first heterozygous activating *KCNJ11* mutations causing NDM were described in humans with activating *ABCC8* mutations reported two years later (Babenko, et al., 2006; Gloyn, et al., 2004b; Proks, et al., 2006). Together mutations

in these two genes have now been shown to account for approximately 40% of NDM cases (De Franco, et al., 2015; Stoy, et al., 2008).

Both dominant and recessive activating mutations are frequently identified in *ABCC8*. Conversely for *KCNJ11*, all but one of the mutations reported so far, p.(Gly324Arg), have been dominantly acting. The majority (~60%) of dominant mutations arise “*de novo*” so there is often no family history of diabetes although germline mosaicism has been observed in some families (Edghill, et al., 2007; Gloyn, et al., 2004a).

There is added complexity associated with *ABCC8* mutations, as compound heterozygosity for both an activating and an inactivating mutation can cause diabetes (Ellard, et al., 2007). Furthermore, a recessively-inherited *ABCC8* nonsense variant has been reported in two cases with NDM which leads to the deletion of the in-frame exon 17 likely resulting in enhanced sensitivity of the channel to intracellular MgADP/ATP (Flanagan, et al., 2017).

The specific  $K_{ATP}$  channel mutation identified determines whether the diabetes will cause permanent or transient NDM (Gloyn, et al., 2005; Patch, et al., 2007). Variable penetrance within families with mutations leading to transient diabetes is observed with some individuals being diagnosed with diabetes at birth yet others developing diabetes for the first time in adulthood (see previous section on adult-onset diabetes) (Flanagan, et al., 2006).

### ***Spectrum of central nervous system (CNS) features in $K_{ATP}$ channel NDM***

CNS features are frequently reported in individuals with  $K_{ATP}$  channel NDM due to the Kir6.2 and SUR1 proteins being expressed in the brain (Karschin, et al., 1997; Liss, et al., 1999; Sakura, et al., 1995; Schmahmann and Sherman, 1998). The most severe neurological phenotype is termed Developmental delay, Epilepsy and



Neonatal Diabetes (DEND) syndrome which includes muscle weakness and hypotonia (Hattersley and Ashcroft, 2005). Intermediate DEND (iDEND) syndrome is diagnosed when epilepsy is absent or presents after the age of 12 months (Gloyn, et al., 2006a). Clinical studies have reported CNS features in ≈20-30% of individuals with  $K_{ATP}$  channel permanent NDM (De Franco, et al., 2015; Massa, et al., 2005; Sagen, et al., 2004).

Since these initial reports, studies in larger cohorts of individuals affected with  $K_{ATP}$  channel NDM have characterised the neurological features in more detail. Additional features reported include autism and attention deficit hyperactivity disorder (ADHD), anxiety and sleep disorders, dyspraxia and learning difficulties resulting in impaired attention, memory, visuospatial abilities and executive function (Beltrand, et al., 2015; Bowman, et al., 2016; Bowman, et al., 2018a; Bowman, et al., 2017; Busiah, et al., 2013; Landmeier, et al., 2017). Importantly, it is now recognised that some degree of impairment can be detected on neuropsychological testing in the majority of patients with  $K_{ATP}$  channel mutations even if there is no obvious CNS involvement (Busiah, et al., 2013; Carmody, et al., 2016).

### ***Clinical management of neonatal diabetes and CNS features due to $K_{ATP}$ channel mutations***

The identification of a  $K_{ATP}$  channel mutation can impact on the medical management of patients with NDM as ~90% can transfer from insulin injections to high-dose sulphonylurea tablets (Pearson, et al., 2006; Zung, et al., 2004). Sulphonylureas bind to the SUR1 subunit of the  $K_{ATP}$  channel and close it independently of ATP, resulting in excellent long-term glycaemic control and improved quality of life for affected patients and their families (Babenko, et al., 2006; Bowman, et al., 2018b; Rafiq, et al., 2008). Patients who are unable to transfer to sulphonylureas tend to have a longer duration of diabetes prior to attempting transfer or functionally severe

mutations (Babiker, et al., 2016; Thurber, et al., 2015). Few side effects and no episodes of severe hypoglycaemia involving seizures or loss of consciousness have been reported in individuals with sulphonylurea-treated neonatal diabetes (Bowman, et al., 2018b; Codner, et al., 2005; Kumaraguru, et al., 2009; Lanning, et al., 2018).

Sulphonylureas can improve the neurological features in people with  $K_{ATP}$  channel NDM, particularly in the first year of treatment (Beltrand, et al., 2015; Fendler, et al., 2013; Stoy, et al., 2008). However, these features do not fully resolve on sulphonylureas and persist long-term into adulthood (Bowman, et al., 2018a; Bowman, et al., 2018b). Higher doses of sulphonylureas are recommended for patients with severe neurological features in an attempt to mitigate this (<https://www.diabetesgenes.org/>). In addition, starting sulphonylurea therapy as early as possible after a genetic diagnosis is crucial as the largest improvements appear to occur in younger patients (Beltrand, et al., 2015; Shah, et al., 2012).

### **GENETIC VARIATION IN *ABCC8* AND *KCNJ11***

*KCNJ11* (MIM# 600937) is located 4.5Kb from *ABCC8* on chromosome 11p15.1 and has a single exon encoding for the 390-amino acid Kir6.2 protein (GenBank NM\_000525.3). *ABCC8* consists of 39 exons which encode for the 1,582 amino acids of SUR1 (NM\_001287174.1) (MIM# 600509). This gene has an alternatively spliced recognition site at the 5' end of exon 17 which results in two different transcripts differing in length by a single amino acid (GenBank AH003589.2). This alternative splicing has led to discrepancies in the literature for nomenclature of variants present in 17-39 which differ by a single amino acid depending on the isoform used (1581 amino acids, NM\_000249.3 and 1582 amino acids, NM\_001287174.1). For the purpose of this review we have described *ABCC8* variants according to the longer isoform (NM\_001287174.1).

### ***Disease-causing variants***

A total of 748 *ABCC8* and 205 *KCNJ11* pathogenic or likely pathogenic variants have been identified in individuals with CHI or NDM (Table 1 and Supp Tables S1 and S4 - please note that these tables are meant to direct to the appropriate references and laboratories. The tables do not provide in-depth clinical information and variants which had been previously reported as pathogenic with a GnomAD frequency compatible with the disease frequency (as calculated by <http://cardiodb.org/allelefrequencyapp/> using a biallelic mode of inheritance, a prevalence of 1/50,000, an allelic heterogeneity of 0.1, genetic heterogeneity of 0.5, and penetrance of 0.5) were not re-assessed).

Founder mutations have been identified in many populations with the best recognised example being the *ABCC8* p.(Phe1388del) and c.3992-9G>A mutations present in >90% of cases from the Ashkenazi Jewish population (Nestorowicz, et al., 1996; Otonkoski, et al., 1999). In the Irish population, a deep intronic *ABCC8* founder mutation at position c.1333-1013G>A has been described which generates a cryptic splice site and causes pseudoexon activation (Flanagan, et al., 2013). Founder mutations have also been reported in Hispanic (Aguilar-Bryan and Bryan, 1999), Bedouin (Tornovsky, et al., 2004), Spanish (Fernandez-Marmiesse, et al., 2006) Finnish (Otonkoski, et al., 1999) and Turkish populations (Flanagan, et al., 2013).

### ***Common variation in ABCC8 and KCNJ11***

368 benign/likely benign variants and variants of uncertain significance have been observed in both genes (Supp Tables S2, S3, S5 and S6). Two common variants in linkage disequilibrium, p.(Glu23Lys) in *KCNJ11* and p.(Ser1370Ala) in *ABCC8*, predispose to type 2 diabetes (Florez, et al., 2004). Whilst their effect size is small (odds ratio ~1.2), given that 58% of the population carry at least one lysine allele at

residue 23 in *KCNJ11*, this equates to a sizeable population risk (Gloyn, et al., 2003; Nielsen, et al., 2003).

### ***Variant Interpretation***

Given the highly polymorphic nature of *ABCC8* and *KCNJ11*, the occurrence of both activating and inactivating mutations, the multiple modes of inheritance of disease and the variable penetrance associated with dominantly acting mutations, interpreting variants identified in these genes can be extremely challenging. Whilst the identification of a null *ABCC8* or *KCNJ11* variant(s) in an individual with CHI provides strong evidence for pathogenicity, finding a missense variant is insufficient to assign disease causality and as such additional support is required to achieve a 'pathogenic' classification according to the guidelines set out by the American College of Medical Genetics (Richards, et al., 2015).

Large variant databases such as GnomAD and LOVD are powerful tools which aid in variant interpretation and allow for re-classification of variants (Fokkema, et al., 2011; Lek, et al., 2016). As such, some variants previously reported as pathogenic in the literature have now been found to be too common to be causative of disease and have now be reassigned as a variant of uncertain significance or a benign variant (Supp tables S2, S3, S5 and S6).

### **FUTURE PROSPECTS**

Whilst sulphonylureas provide a safe and effective treatment for the majority of individuals with  $K_{ATP}$  channel NDM, for patients with CHI pharmacological management of the condition is not always successful. Current efforts are therefore focussing on the development of new pharmacological treatments for this condition (Banerjee, et al., 2017; De Leon, et al., 2008; Ng, et al., 2018; Patel, et al., 2018; Powell, et al., 2011; Senniappan, et al., 2014).

Progress is also being made in terms of genetic screening, with a recent report describing the use of non-invasive prenatal testing of a paternally-inherited *KCNJ11* activating mutation in cell-free fetal DNA (De Franco, et al., 2017). Implementation of non-invasive prenatal testing for maternally-inherited mutations will be extremely important as a previous study suggested that sulphonylurea can cross the placenta and influence fetal growth with implications for treatment of monogenic diabetes pregnancies (Myngheer, et al., 2014; Shepherd, et al., 2017).

## **SUMMARY**

The discovery of both inactivating and activating  $K_{ATP}$  channel mutations has firmly established the critical role of the channel in insulin secretion. The highly polymorphic nature of the two genes along with the occurrence of both gain-of-function and loss-of-function mutations as well as multiple different modes of inheritance can make variant interpretation extremely challenging. Rapid testing is absolutely crucial for all patients with CHI or NDM because finding a mutation has a huge impact on the clinical management of these conditions.

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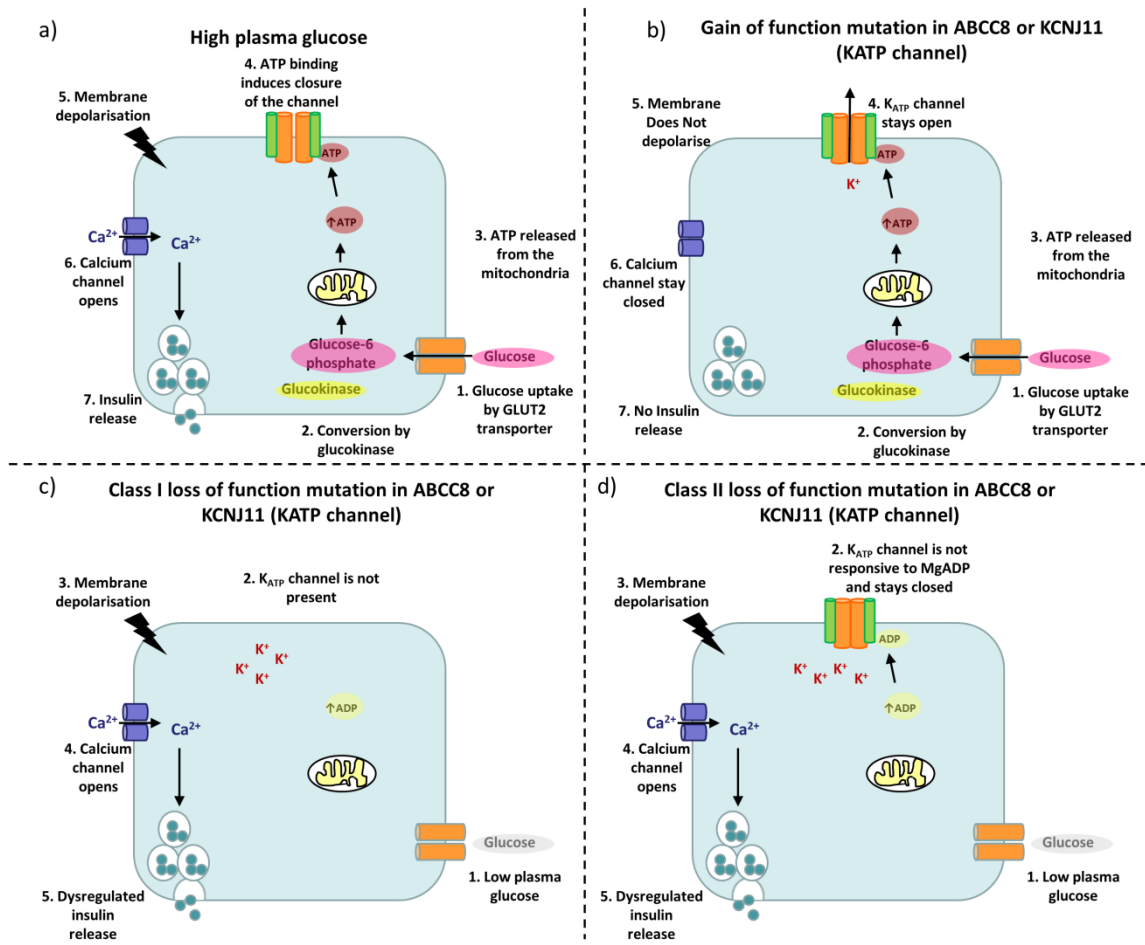
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#### **DATA AVAILABILITY STATEMENT**

All the novel variants reported in this manuscript have been uploaded to LOVD (<https://www.lovd.nl/>).

**Figure 1: Schematic representation of insulin secretion in the pancreatic beta-cell a) In a normal cell in a high plasma glucose environment b) In a cell with an activating  $K_{ATP}$  channel mutation c) In a cell with an inactivating mutation resulting in absence/reduction in protein at the membrane surface d) In a cell with a inactivating mutation that impairs the stimulatory effect of MgADP A)**

Glucose is metabolised following entry into the beta-cell via a GLUT transporter. This results in change in the ATP:ADP ratio leading to channel closure and membrane depolarisation and activation of voltage-dependent calcium channels. Calcium enters the cell which triggers insulin release. B) An activating mutation in a  $K_{ATP}$  channel gene results in the membrane being maintained in a hyperpolarised state. Calcium channels remain closed and insulin is not secreted. C) Loss of function mutations can result in an absence/reduction in protein at the membrane surface. This keeps the membrane in a depolarised state regardless of the metabolic state ultimately leading to unregulated insulin secretion D) Loss of function missense mutations can produce channels that traffic to the membrane but have impaired mgADP activation.



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