

HISTOLOGY AND HISTOPATHOLOGY

ISSN: 0213-3911
e-ISSN: 1699-5848

Submit your article to this Journal (<http://www.hh.um.es/Instructions.htm>)

Genotype-histotype-phenotype correlations in hyperinsulinemic hypoglycemia

Authors: Annette Rønholt Larsen, Klaus Brusgaard, Henrik Thybo Christesen and Sönke Detlefsen

DOI: 10.14670/HH-18-709

Article type: REVIEW

Accepted: 2024-01-12

Epub ahead of print: 2024-01-12

Genotype-histotype-phenotype correlations in hyperinsulinemic hypoglycemia

Annette Rønholt Larsen ^{a,b,c,d,f}, Klaus Brusgaard ^{b,c,d,f}, Henrik Thybo Christesen ^{a,b,c,f*}, Sönke Detlefsen ^{b,c,e,*,**}

a Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

b Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Denmark

c Odense Pancreas Center (OPAC), Odense University Hospital, Odense, Denmark

d Department of Clinical Genetics, Odense University Hospital, Odense, Denmark

e Department of Pathology, Odense University Hospital, Odense, Denmark

f Steno Diabetes Center, Odense University Hospital, Odense, Denmark

*Contributed equally

** Corresponding author: Sönke Detlefsen. Dept. of Pathology, Odense University Hospital, J. B. Winsløws Vej 15, 5000 C, Odense, Denmark.

E-mail address: Sonke.Detlefsen@rsyd.dk

Keywords: congenital hyperinsulinism, adult-onset non-insulinoma persistent hyperinsulinemic hypoglycemia syndrome, insulinoma, insulinomatosis, nesidioblastosis, mosaicism, histology, mutational profiling.

Abbreviations:

BCNC, beta cell nuclear crowding; BWS, Beckwith-Wiedemann syndrome; CHI, congenital hyperinsulinism; FAH, focal adenomatous hyperplasia; HH, hyperinsulinemic hypoglycemia; GCK, glucokinase; GDH, glutamate dehydrogenase; GSIS, glucose-stimulated insulin secretion; HK-1, hexokinase 1; IHC, immunohistochemistry; MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumor; NI-PHHS, adult-onset non-insulinoma persistent hyperinsulinemic hypoglycemia; pUPD, paternal uniparental disomy.

Abstract

Hyperinsulinemic hypoglycemia (HH) of pancreatic origin includes congenital hyperinsulinism (CHI), insulinoma, insulinomatosis, and adult-onset non-insulinoma persistent hyperinsulinemic hypoglycemia syndrome (NI-PHHS). In this review, we describe the genotype-histotype-phenotype correlations in HH and their therapeutic implications.

CHI can occur from birth or later on in life. Histologically, diffuse CHI shows diffuse beta cell hypertrophy with a few giant nuclei per islet of Langerhans, most frequently caused by loss-of-function mutations in *ABCC8* or *KCNJ11*. Focal CHI is histologically characterized by focal adenomatous hyperplasia consisting of confluent hyperplastic islets, caused by a paternal *ABCC8/KCNJ11* mutation combined with paternal uniparental disomy of 11p15. CHI in Beckwith-Wiedemann syndrome is caused by mosaic changes in the imprinting region 11p15.4-11p15.5, leading to segmental or diffuse overgrowth of endocrine tissue in the pancreas. Morphological mosaicism of pancreatic islets is characterized by occurrence of hyperplastic (type 1) islets in one or a few lobules and small (type 2) islets in the entire pancreas. Other rare genetic causes of CHI show less characteristic or unspecific histology.

HH with a predominant adult onset includes insulinomas, which are pancreatic insulin-producing endocrine neoplasms, in some cases with metastatic potential. Insulinomas occur sporadically or as part of multiple

endocrine neoplasia type 1 due to *MEN1* mutations. *MAFA* mutations may histologically lead to insulinomatosis with insulin-producing neuroendocrine microadenomas or neuroendocrine neoplasms. NI-PHHS is mainly seen in adults and shows slight histological changes in some patients, which have been defined as major and minor criteria. The genetic cause is unknown in most cases. The diagnosis of HH, as defined by genetic, histological, and phenotypic features, has important implications for patient management and outcome.

Introduction

The term hyperinsulinemic hypoglycemia (HH) covers a broad disease spectrum that can be subdivided into primary HH, consisting of congenital hyperinsulinism (CHI), insulinoma, insulinomatosis, and adult-onset non-insulinoma persistent hyperinsulinemic hypoglycemia syndrome (NI-PHHS), and secondary HH, related to maternal diabetes, perinatal stress in neonates, bariatric surgery, medication, autoimmune insulin/receptor disease, and Münchhausen by proxy (Cryer *et al.*, 2009; Thornton *et al.*, 2015).

CHI is a rare, heterogeneous disease with a prevalence of 1:28,000-1:50,000 in the general population (Yau *et al.*, 2020), with differences in genetics, clinical presentation, histology, and response to treatment. To date, CHI has been associated with mutations in at least 11 different genes: *ABCC8*, *GCK*, *GLUD1*, *HADH*, *HK1*, *HNF1A*, *HNF4A*, *INSR*, *KCNJ11*, *UCP2*, and *SLC16A1* (Rosenfeld *et al.*, 2019; Hewat *et al.*, 2022). CHI may be dominantly or recessively inherited or arise sporadically (Dunne *et al.*, 2004; De Franco *et al.*, 2020). Histologically, CHI is classified into two main well-described forms: diffuse and focal CHI. Besides, there are other rare histological forms and histological classification is not possible in approximately 5% of surgically treated patients (Sempoux *et al.*, 2003; Sempoux *et al.*, 2004; Snider *et al.*, 2013).

Mutations in *ABCC8* and *KCNJ11* on chromosome 11p15.1, encoding the Kir6.2 and SUR1 subunits of the K_{ATP} channel, are the most common cause of severe CHI and, in large series, have been identified in 36-69% of patients (Kapoor *et al.*, 2013; Snider *et al.*, 2013). Activating mutations in *GLUD1* and *GCK* are the second and

third most common mutations in CHI, which lead to increased expression of glutamate dehydrogenase (GDH) and glucokinase (GCK), respectively (Glaser *et al.*, 1998; Stanley *et al.*, 1998; Kapoor *et al.*, 2013; Snider *et al.*, 2013). CHI is a feature of several syndromes, especially Beckwith-Wiedemann syndrome (BWS) and Kabuki syndrome (Kostopoulou *et al.*, 2021; Hewat *et al.*, 2022).

CHI usually develops in the neonatal period and may cause severe and persistent hypoglycemia, or transient forms with spontaneous remission even in patients with or without perinatal stress (DeBaun *et al.*, 2000; Kapoor *et al.*, 2008; Kumaran *et al.*, 2010; Stanescu *et al.*, 2012). Rapid diagnosis and treatment are essential to prevent brain injury in both transient and persistent CHI (Avatapalle *et al.*, 2013; Rasmussen *et al.*, 2020B). Advances in the definition of the histological features, molecular genetics, imaging techniques, medical treatment, and surgery have radically changed the management and improved the outcome of patients with CHI, also based on a deeper pathophysiological understanding of the various subtypes of CHI.

Insulinoma is a rare cause of HH and is very rare in children, with the earliest onset at 3-4 years of age (Boley *et al.*, 1960; Mann *et al.*, 1969; Service *et al.*, 1991; Padidela *et al.*, 2014; Bhatti *et al.*, 2016). This neuroendocrine tumor (NET) can spread locally and metastasize. Insulinomas may present as a part of multiple endocrine neoplasia type 1 (MEN1) syndrome, due to germline pathogenic genetic variants in *MEN1*. Clinical differential diagnoses of insulinoma include insulinomatosis (Anlauf *et al.*, 2009), NI-PHHS (Service *et al.*, 1999), insulin autoimmune syndrome (Church *et al.*, 2018), and secondary causes of HH, such as bariatric surgery (Thompson *et al.*, 2000).

In this review, we focus on the histological features of the different types of HH and their associated genetic changes, clinical characteristics, and treatment with an emphasis on genotype-histotype-phenotype correlations. The following topics will be covered: K_{ATP} channel diffuse CHI and K_{ATP} channel focal CHI, GCK-CHI, GDH-CHI, BWS-CHI, mosaic CHI, insulinoma, insulinomatosis, and NI-PHHS. A comprehensive overview of the different entities is shown in Table 1.

Nesidioblastosis

Historically, the term “nesidioblastosis” was linked to HH in neonates and infants (Laidlaw, 1938; Yakovac *et al.*, 1971; Jaffe *et al.*, 1980). Nesidioblastosis is defined as single or small packets of 2-6 beta cells scattered in the walls of small ducts or between acini. This morphological change was later interpreted as a main histological feature of the two major histological forms of CHI, denoted diffuse and focal nesidioblastosis (Goossens *et al.*, 1989). However, nesidioblastosis is present in both diffuse and focal CHI as well as in normoglycemic, age-matched controls (Rahier *et al.*, 1981, 1984; Sempoux *et al.*, 1995; Suchi *et al.*, 2003). Hence, the morphological feature of nesidioblastosis is neither sensitive nor specific for infants with CHI (Rahier *et al.*, 1981, 1984; Sempoux *et al.*, 1995; Suchi *et al.*, 2003). The term nesidioblastosis should, consequently, only be used in its histological meaning and not as the name for a disease entity.

Different forms of hyperinsulinemic hypoglycemia

K_{ATP} channel diffuse CHI

Genetic and clinical findings of K_{ATP} channel diffuse CHI

K_{ATP} channel diffuse CHI is, per definition, associated with biallelic recessive (homozygous or compound heterozygous) or monoallelic dominant loss-of-function (LOF) variants in the K_{ATP} channel genes *ABCC8* and *KCNJ11* (Kapoor *et al.*, 2013; Snider *et al.*, 2013; De Franco *et al.*, 2020). The homozygous, recessive K_{ATP} channel mutations are associated with unresponsiveness to diazoxide, which targets SUR1 (Gribble *et al.*, 1997; Shyng *et al.*, 1997; Flanagan *et al.*, 2011a; Rasmussen, *et al.*, 2020a). In a large series of patients with diazoxide-unresponsive CHI, 41% had germline mutations in *ABCC8* or *KCNJ11* (Snider *et al.*, 2013). Patients with compound heterozygous pathogenic variants may sometimes be responsive to diazoxide (Dekel *et al.*, 2002). Patients with biallelic K_{ATP} channel mutations typically have early, neonatal onset of severe CHI with a high risk of neurodevelopmental impairment if not promptly diagnosed and managed (Helleskov *et al.*, 2017; Lord, 2019; Banerjee *et al.*, 2022). Dominant LOF variants usually result in a milder form of diffuse CHI (Huopio *et al.*, 2000; Thornton *et al.*, 2003; Pinney *et al.*, 2008; Kapoor *et al.*, 2011; Oçal *et al.*, 2011). However, the

phenotypes overlap, and variable penetrance and responsiveness to diazoxide have been reported for specific variants of *ABCC8* and *KCNJ11*, even in transient diffuse CHI (Otonkoski *et al.*, 1999; Thornton *et al.*, 2003; Pinney *et al.*, 2008; Kumaran *et al.*, 2010; Flanagan, *et al.*, 2011b; Kapoor *et al.*, 2011; Macmullen *et al.*, 2011; Oçal *et al.*, 2011; Nessa *et al.*, 2015). The K_{ATP} channel LOF mutations disrupt the glucose-stimulated insulin secretion (GSIS) pathway with resultant unregulated hypersecretion of insulin from the beta cells.

Histological findings in K_{ATP} channel diffuse CHI

In K_{ATP} channel diffuse CHI, the pancreas does not present gross abnormalities. The number and size of islets are typically normal (Fig. 1A-B). Microscopically, the key finding is beta cell hypertrophy and nuclear enlargement of one or a few single cells per islet of Langerhans (Fig. 1C-D) (Rahier *et al.*, 1984, 1998; Witte *et al.*, 1984; Goossens *et al.*, 1989; Sempoux *et al.*, 1995; Solcia *et al.*, 1997; Sempoux *et al.*, 1998a; Klöppel *et al.*, 1999). Hence, K_{ATP} channel diffuse CHI is characterized by giant cell nuclei or nucleomegaly (Rahier *et al.*, 1984, 1998; Witte *et al.*, 1984; Goossens *et al.*, 1989; Sempoux *et al.*, 1995; Solcia *et al.*, 1997; Sempoux *et al.*, 1998b; Klöppel *et al.*, 1999; Han *et al.*, 2016). Nucleomegaly is usually present in 60–70% of islets of Langerhans or more (Rahier *et al.*, 1998; Han *et al.*, 2016).

Morphometric and immunohistochemical studies of K_{ATP} channel diffuse CHI

Morphometric studies show large beta cells with abundant cytoplasm and abnormally large nuclei of up to 19 μm in diameter, compared with nuclei with a mean diameter of 5-6 μm in normal beta cells. The islets of Langerhans show no endocrine cell proliferation and normal proportions and spatial organization of endocrine cell types (Witte *et al.*, 1984; Goossens *et al.*, 1989; Sempoux *et al.*, 1995; Klöppel *et al.*, 1999). The hypertrophied beta cells with giant nuclei have large Golgi areas indicating hyper-functional activity, supported by high expression of proinsulin. Insulin labeling is, however, very low due to the great uncontrolled hypersecretion of insulin (Klöppel *et al.*, 1999; Rahier *et al.*, 2011).

Treatment of K_{ATP} channel diffuse CHI

After emergency treatment to correct hypoglycemia, diazoxide is the first-line treatment for diffuse CHI with an effect in 50-60% of patients (Salomon-Estebanez *et al.*, 2016; van der Steen *et al.*, 2018; Brar *et al.*, 2020; Lord and De León, 2020). In diazoxide-unresponsive patients, somatostatin agonists may be effective (Arnoux *et al.*, 2010; Arnoux *et al.*, 2011; Le Quan Sang *et al.*, 2012; Demirbilek *et al.*, 2014; Welters *et al.*, 2015; Salomon-Estebanez *et al.*, 2016; Lord and De León, 2020). Long-acting somatostatin analogs, such as octreotide long-acting release or lanreotide, are increasingly used for the treatment of diffuse CHI (van der Steen *et al.*, 2018; Dastamani *et al.*, 2019).

In case of surgery, leading centers recommend biopsies from the head, body, and tail of the pancreas for intraoperative frozen section analysis to confirm diffuse type CHI before proceeding to subtotal pancreatectomy (Adzick *et al.*, 2019). Subtotal pancreatic resection has been performed and is still being widely used in some centers, but often leads to diabetes and sometimes to exocrine pancreatic insufficiency (malabsorption) at long-term follow-up (Lovvorn *et al.*, 1999; Meissner *et al.*, 2003; Beltrand *et al.*, 2012; Arya *et al.*, 2014; Lord *et al.*, 2015; Rasmussen *et al.*, 2020a). This has prompted experimental therapies with other drugs such as sirolimus and nifedipine, which, however, are largely ineffective (Durmaz *et al.*, 2014; Senniappan *et al.*, 2014; Banerjee *et al.*, 2017; Sikimic *et al.*, 2020). More recently, trials with novel drugs such as glucagon analogs, insulin receptor antibodies, and GLP-1 receptor agonists have been conducted (Calabria *et al.*, 2012; Lord and De León, 2020; Sikimic *et al.*, 2020), providing hope for future management.

K_{ATP} channel focal CHI

Genetic and clinical findings in K_{ATP} channel focal CHI

K_{ATP} channel focal CHI is associated with a genetic two-hit etiology with a paternal, recessively inherited heterozygous disease-causing mutation in *ABCC8* or *KCNJ11*, combined with somatic loss of the maternal allele in the 11p15.5 region (de Lonlay *et al.*, 1997; Ryan *et al.*, 1998; Verkarre *et al.*, 1998; de Lonlay-Debeney *et al.*, 1999; Glaser *et al.*, 1999; Fournet *et al.*, 2001; Snider *et al.*, 2013). Somatic mitotic recombination of

11p15.5 results in duplication of the paternal allele leading to homozygosity of the mutated *ABCC8/KCNJ11* locus and paternal uniparental disomy (pUPD) for all genes telomeric to *ABCC8/KCNJ11* (Damaj *et al.*, 2008). In the imprinting region 11p15.5, only the maternal allele expresses the tumor suppressor *CDKN1C* encoding the protein p57 and the long non-coding RNA *H19*, whereas the paternal allele expresses *IGF2* encoding insulin-like growth factor 2 (IGF2), which has proliferative and anti-apoptotic effects (Petrik *et al.*, 1998, 1999). The imbalance of expressed growth/tumor suppressor genes leads to focal CHI (de Lonlay *et al.*, 1997; Ryan *et al.*, 1998; Verkarre *et al.*, 1998; Fournet *et al.*, 2001; Damaj *et al.*, 2008). Detailed studies have shown varying recombination breakpoints and upregulation of the growth promoter gene *ASCL2* and other pancreatic transcription factors (Giurgea *et al.*, 2006a; Wieland *et al.*, 2022). The combination of focal overgrowth and hypersecretion of insulin leads to the histological features of K_{ATP} channel focal CHI. K_{ATP} channel focal CHI is found in approximately 50% of diazoxide-unresponsive CHI patients, however, with a variable prevalence of 17–65% in different studies (Bellanné-Chantelot *et al.*, 2010; Kapoor *et al.*, 2013; Lord *et al.*, 2013; Snider *et al.*, 2013; Adzick *et al.*, 2019). The positive predictive value of a monoallelic, paternal K_{ATP} channel mutation in a child with diazoxide-unresponsive CHI is 94% for the diagnosis of focal CHI with a sensitivity of 97%, as *de novo* K_{ATP} channel mutations on the paternal allele are also observed (Suchi *et al.*, 2006; Snider *et al.*, 2013). K_{ATP} channel focal CHI presents within the first days of life and is usually, but not always, diazoxide-unresponsive (Ismail *et al.*, 2012; Maiorana *et al.*, 2014). The risk of K_{ATP} channel focal CHI in offspring of paternal K_{ATP} channel mutation carriers has been estimated to 1:540 (Glaser *et al.*, 2011). Consequently, families with more than one child with focal CHI are very rare (Ismail *et al.*, 2011). Likewise, siblings with focal and diffuse CHI are exceedingly rare (Valayannopoulos *et al.*, 2007; Ismail *et al.*, 2011).

Terminology

In the literature of the past 60-70 years, K_{ATP} channel focal CHI has been referred to by many different names: Congenital islet cell adenoma (Buist *et al.*, 1971), islet cell adenomatosis (Schwartz and Zwiren, 1971), islet-cell adenoma (Baerentsen, 1973), focal islet cell adenomatosis (Klöppel *et al.*, 1975), congenital insulinoma

(Carney, 1976), pancreatic adenomas with nesidioblastosis (Dahms *et al.*, 1976), mixed islet-acinar adenomas, (Scully *et al.*, 1978), neonatal islet cell adenoma (Bordi *et al.*, 1982), focal nesidioblastosis (Goossens *et al.*, 1989), focal islet hyperplasia (Stanley, 1997), focal adenoma (Ryan *et al.*, 1998), focal adenomatous hyperplasia (FAH) (Rahier *et al.*, 1998), focal hyperinsulinism (de Lonlay-Debeney *et al.*, 1999), focal islet cell adenomatous hyperplasia (Fournet *et al.*, 2001), focal nodular adenomatosis (Smith *et al.*, 2001), focal adenomatous islet-cell hyperplasia (Crétolle *et al.*, 2002), focal persistent hyperinsulinemic hypoglycemia of infancy (FoPHHI) (Sempoux *et al.*, 2003), focal beta cell hyperfunction (Kaczirek and Niederle, 2004), and focal beta cell hypertrophy and hyperplasia (Ouyang *et al.*, 2011). We prefer the histological term focal adenomatous hyperplasia (of endocrine cells) for the lesion that defines K_{ATP} channel focal CHI.

Histological and immunohistochemical findings in K_{ATP} channel focal CHI

Focal CHI can arise anywhere in the pancreas, sometimes protruding from the pancreatic surface, and may even occur in ectopic pancreatic tissue (Jaffe *et al.*, 1982; Goossens *et al.*, 1989; de Lonlay-Debeney *et al.*, 1999; Klöppel *et al.*, 1999; Hussain *et al.*, 2006; Delonlay *et al.*, 2007; Christiansen *et al.*, 2018; Longnecker, 2021). The focal lesion is often macroscopically invisible and impalpable (Rahier *et al.*, 1998; Sempoux, Guiot, Lefevre, *et al.*, 1998; de Lonlay-Debeney *et al.*, 1999).

Microscopically, focal CHI is characterized by a FAH consisting of endocrine cells (Fig. 2A). The lesion is sometimes circular or ellipsoid, measuring from 2.5 to 13 mm, and consists of confluent hyperplastic islets (Fig. 2B-D) (Klöppel *et al.*, 1975; Dahms *et al.*, 1976; Jaffe *et al.*, 1980; Bordi *et al.*, 1982; Goudswaard *et al.*, 1986; Goossens *et al.*, 1989; Solcia *et al.*, 1997; Rahier *et al.*, 1998; Sempoux *et al.*, 1998b; de Lonlay-Debeney *et al.*, 1999; Klöppel *et al.*, 1999; Mohnike *et al.*, 2014; Bendix *et al.*, 2018; Bjarnesen *et al.*, 2021). At their periphery, a thin rim of acinar cells and/or ducts, or strands of connective tissue, are present (Fig. 2D) (Klöppel *et al.*, 1975; Dahms *et al.*, 1976; Shermeta *et al.*, 1980; Bordi *et al.*, 1982; Witte *et al.*, 1984; Goossens *et al.*,

1989; Solcia *et al.*, 1997; Rahier *et al.*, 1998; de Lonlay-Debeney *et al.*, 1999; Klöppel *et al.*, 1999; Sempoux *et al.*, 2003).

The limits of the focal lesions are sometimes ill-defined (Klöppel *et al.*, 1975; Dahms *et al.*, 1980; Klöppel and Heitz, 1984; Witte *et al.*, 1984; Goossens *et al.*, 1989; Solcia *et al.*, 1997; Sempoux *et al.*, 2003), however, a lobular structure of the area in the pancreas harboring them is maintained (Rahier *et al.*, 1998; de Lonlay-Debeney *et al.*, 1999; Sempoux *et al.*, 2003).

Cragie *et al.* observed differences at the periphery of the lesions in a study of 25 surgical specimens (Cragie *et al.*, 2018). In 28% of the cases, the focal lesion projected into adjoining normal pancreatic tissue without clear delineation from normal tissue. In these cases, severe hypoglycemia was detected within a few days following birth. In the remaining patients, the FAH was encapsulated within a defined matrix capsule. These findings remain to be confirmed by others. Occasionally, multiple adjacent lobules are involved (DeLonlay *et al.*, 2007). Like normal islets of Langerhans, beta cells comprise the main endocrine cell type in focal CHI, but at their periphery, also alpha, delta, and gamma cells are found (Dahms *et al.*, 1980; Goossens *et al.*, 1989; Rahier *et al.*, 1998; Klöppel *et al.*, 1999; Sempoux *et al.*, 2003).

Morphometric and immunohistochemical studies of K_{ATP} channel focal CHI

Early investigations by morphometry and immunohistochemistry (IHC) revealed the presence of alpha, beta, delta, and gamma cells within the lesion (Jaffe *et al.*, 1980; Bordi *et al.*, 1982; Klöppel and Heitz, 1984; Witte *et al.*, 1984; Goossens *et al.*, 1991; Solcia *et al.*, 1997; Sempoux *et al.*, 2003). About 80-90% of cells, including hypertrophied cells, are beta cells (Fig. 2B) (Klöppel *et al.*, 1975; Jaffe *et al.*, 1982; Witte *et al.*, 1984; Goossens *et al.*, 1989; Solcia *et al.*, 1997). In normal infants, the beta cell population accounts for ~50%, alpha cells for ~20%, and delta cells for ~30% (Fig. 2C) (Rahier *et al.*, 1981; Stefan *et al.*, 1983).

Nucleomegaly was quantified in the FAH with high-content analysis of the volume of the nuclei using transmission electron microscopy data (Han *et al.*, 2016). Nucleomegaly was sometimes present, but eight

times less frequently compared with diffuse CHI (Han *et al.*, 2016), in keeping with previous findings of a lower frequency of large nuclei in focal vs. diffuse CHI (Rahier *et al.*, 1998; Sempoux *et al.*, 1998b).

Sempoux *et al.* used IHC double staining of the cellular proliferation marker Ki-67 and insulin for measuring the mean beta cell labeling index, defined as the number of Ki-67 labeled beta cell nuclei per 1000 beta cell nuclei. The mean beta cell labeling index was four times higher in the focal lesion compared with islets of Langerhans in age-matched controls (Sempoux *et al.*, 1998a). A similar beta cell proliferation rate study was performed by Kassem *et al.* with almost identical results (Kassem *et al.*, 2000). The maternally expressed protein cyclin-dependent kinase inhibitor 1C (CDKN1C), also known as p57 or Kip2, is consistently absent in the FAH, following the pUPD genetic changes in the lesion (Kassem *et al.*, 2001; Sempoux *et al.*, 2003; Suchi *et al.*, 2006; Mohnike *et al.*, 2014).

SUR1, encoded by *ABCC8*, is expressed significantly less on the beta cell surface in focal CHI compared with endocrine cells outside the lesion (Sempoux *et al.*, 2003), compatible with the variable failure of mutated K_{ATP} channels to either synthesize, mature, assemble, traffick, or reach the beta cell surface (Dunne *et al.*, 2004). IHC double staining of proinsulin and insulin revealed that the hyper-functional beta cells in focal CHI have a large Golgi proinsulin/beta cell area, with strong proinsulin labeling, but relatively few insulin granules and low insulin labeling (Sempoux *et al.*, 1995, 2003), as compared with diffuse CHI. A significant increase in apoptosis was found in FAH compared with age-matched controls (Kassem *et al.*, 2000). In keeping with these findings, rare patients with suggested K_{ATP} channel focal CHI not subjected to surgery had spontaneous clinical remission at follow-up (Yorifuji *et al.*, 2011).

Changes in islets outside the focal adenomatous hyperplasia

In many centers performing surgery on patients with CHI, biopsies from different portions of the pancreas are submitted for frozen section analysis to distinguish between focal and diffuse K_{ATP} channel CHI (Adzick *et al.*, 2004; Suchi *et al.*, 2004; Barthlen, 2011; Adzick *et al.*, 2019). For these reasons, it is relevant to be familiar with the histological appearance of the pancreas, not only inside but also outside the FAH. Beta cell nuclear

crowding (BCNC) is defined as the number of beta cell nuclei per 1,000 μm^2 of beta cell cytoplasm. A BCNC above 12 was indicative of insular beta cells outside the FAH in K_{ATP} channel focal CHI compared with islets from age-matched controls and K_{ATP} channel diffuse CHI (Sempoux *et al.*, 1998b, 2003). The mean radius of the 50 largest beta cell nuclei was below 3.70 μm outside the FAH in K_{ATP} channel focal CHI and almost always higher in K_{ATP} channel diffuse CHI (Sempoux *et al.*, 1998b).

Phenotypic diversity of K_{ATP} channel focal CHI

Rare variants of K_{ATP} channel focal CHI include multifocal CHI, which is believed to develop due to two or more separate somatic maternal deletions of the 11p15 region in the same patient (Giurgea *et al.*, 2006a; Craigie *et al.*, 2018; Ni *et al.*, 2019; Rosenfeld *et al.*, 2021). Moreover, focal-extensive lesions may reach a size greater than 3 cm (Ismail *et al.*, 2012; Kühnen *et al.*, 2014), or even occupy the entire pancreas (Fig. 3) (Giurgea *et al.*, 2006a; Suchi *et al.*, 2006; Rahier *et al.*, 2011; Ismail *et al.*, 2012; Barthlen *et al.*, 2016). The size of the FAH is believed to relate closely to the time of the second somatic hit in the embryonic development of the pancreas, where early somatic 11p15 maternal deletions will lead to larger focal lesions.

Treatment of focal CHI

Focal CHI can be cured by resection of the lesion. Preoperative ^{18}F -DOPA-PET (PET/CT) imaging (Mohnike *et al.*, 2006; Otonkoski *et al.*, 2006; Laje *et al.*, 2013b; Christiansen *et al.*, 2018) is today imperative to localize focal lesions before surgery. If a focal lesion is not macroscopically identified, intraoperative frozen section analysis may be helpful to localize focal lesions (Adzick *et al.*, 2004; Suchi *et al.*, 2004; Barthlen, 2011; Adzick *et al.*, 2019). In many centers, piecemeal resection with multiple frozen sections is used (Suchi *et al.*, 2004; Barthlen *et al.*, 2010; Barthlen, 2011; Pierro and Nah, 2011; Zobel *et al.*, 2020). At our and other centers, intraoperative ultrasound is frequently used to localize small focal lesions (Adzick *et al.*, 2004; Bendix *et al.*, 2018; Adzick *et al.*, 2019; Bjarnesen *et al.*, 2021). Rare patients with focal CHI have been managed conservatively with later spontaneous clinical remission, as suggested by ^{18}F -DOPA PET/CT (Mazor-

Aronovitch *et al.*, 2007; Yorifuji *et al.*, 2011). Despite curing HH in focal CHI, neurodevelopmental impairment is still frequently observed, mostly due to late diagnosis and insufficient early treatment.

GCK-CHI

Genetic and clinical findings in GCK-CHI

Glucokinase is an enzyme encoded by the *GCK* gene that acts as a glucose sensor in the GSIS pathway and facilitates the phosphorylation of glucose to glucose-6-phosphate (Campbell and Newgard, 2021). Gain-of-function (GOF) mutations in *GCK* lead to a lowered glucose threshold for GSIS with resultant HH (Glaser *et al.*, 1998; Christesen *et al.*, 2002). GCK-CHI may be inherited in a dominant pattern (Glaser *et al.*, 1998; Christesen *et al.*, 2002; Gloyn *et al.*, 2003; Dullaart *et al.*, 2004; Barbetti *et al.*, 2009; Kassem *et al.*, 2010; Martínez *et al.*, 2017; Ping *et al.*, 2019) or occur *de novo* (Cuesta-Muñoz *et al.*, 2004; Meissner *et al.*, 2009; Sayed *et al.*, 2009; Martínez *et al.*, 2017; Ping *et al.*, 2019). To date, at least 17 GOF position variants of *GCK* causing GCK-CHI have been described (Langer *et al.*, 2021). The prevalence of GCK-CHI is estimated at 2% of all patients with CHI (Christesen *et al.*, 2008b; Snider *et al.*, 2013). The clinical picture of GCK-CHI ranges from neonatal onset severe HH necessitating subtotal pancreatectomy to apparently asymptomatic childhood with adult-onset hypoglycemic attacks (Glaser *et al.*, 1998; Christesen *et al.*, 2002; Gloyn *et al.*, 2003; Cuesta-Muñoz *et al.*, 2004; Dullaart *et al.*, 2004; Wabitsch *et al.*, 2007; Christesen *et al.*, 2008a; Barbetti *et al.*, 2009; Sayed *et al.*, 2009; Kassem *et al.*, 2010; Beer *et al.*, 2011; Challis *et al.*, 2014; Ajala *et al.*, 2016; Martínez *et al.*, 2017; Jannin *et al.*, 2018; Ping *et al.*, 2019).

Histological findings in GCK-CHI

The histology of GCK-CHI has rarely been described because of the rareness of surgically-treated patients. Reported morphologic changes range from normal pancreas to increased islet size or slightly increased nuclei size of single beta cells (Gloyn *et al.*, 2003; Cuesta-Muñoz *et al.*, 2004; Wabitsch *et al.*, 2007; Kassem *et al.*, 2010). However, even when abnormally large nuclei are present, they tend not to reach the size seen in K_{ATP}

channel diffuse CHI, and their frequency is lower (Cuesta-Muñoz *et al.*, 2004). In one case, only increased beta cell nuclei size was reported (Sayed *et al.*, 2009).

Morphometric and immunohistochemical studies of GCK-CHI

Abnormally large islets were observed in an operated infant with the *GCK* mutation p.Val91Leu (Kassem *et al.*, 2010). The mean area per islet in the head and tail of the pancreas in the infant with GCK-CHI was around 7,000 μm^2 , compared with five age-matched controls with around 1,000 - 2,000 μm^2 and diffuse CHI around 750 - 850 μm^2 . There may be some uncertainty about the islet sizes measured in this patient, which of course depend on the methods used and the significance that can be achieved due to the limited number of individuals with GCK-CHI in which similar morphometry has been performed; it seems that the islets from patients with diffuse CHI and age-matched controls used by Kassem *et al.* were possibly smaller compared with previous studies (Liu and Potter, 1962). However, ten percent of the islets of Langerhans in Kassem *et al.*'s case were larger than 13,000 μm^2 , and these large islets contained some beta cells with a large nucleus (Kassem *et al.*, 2010). Abnormally large islets were also reported in a patient with a heterozygous *de novo* *GCK* mutation p.Tyr214Cys (Cuesta-Muñoz *et al.*, 2004). Normal processing of proinsulin (with an absence of cytoplasmic labeling), increased proinsulin labeling in the Golgi area, and low insulin labeling indicate hypersecretion of insulin, similar to diffuse and focal CHI (Sempoux *et al.*, 1995; Klöppel *et al.*, 1999; Sempoux *et al.*, 2003; Cuesta-Muñoz *et al.*, 2004; Rahier *et al.*, 2011). Furthermore, the BCNC was intermediate between age-matched controls, diffuse CHI, and the FAH in K_{ATP} channel focal CHI (Cuesta-Muñoz *et al.*, 2004). The variations in the histological picture of GCK-CHI seem to reflect variations in glucokinase activity, leading to various degrees of islet size.

Treatment of GCK-CHI

Patients with GCK-CHI do not fully respond to diazoxide, as this drug is not able to correct the lowered threshold for GSIS. Reported GCK-CHI patients had, however, some benefit from diazoxide at low dosages

(Meissner *et al.*, 2009; Lord and De León, 2013), yet, this has not been described in detail in the published literature, and there seems to be no effect of this treatment in severe GCK-CHI (Cuesta-Muñoz *et al.*, 2004). Octreotide has been helpful in some cases of GCK-CHI (Wabitsch *et al.*, 2007).

GDH-CHI

Genetic and clinical findings in GDH-CHI

GLUD1 encodes the mitochondrial matrix enzyme GDH, which occurs in the mitochondria of prokaryotes and eukaryotes and is expressed in beta cells (Stanley *et al.*, 1998). GDH-CHI is also known as hyperinsulinism/hyperammonemia syndrome (Stanley *et al.*, 1998). The majority of GDH-CHI cases are due to *de novo* mutations but familial inherited transmitted mutations are also reported (Stanley *et al.*, 1998; De Lonlay *et al.*, 2001; MacMullen *et al.*, 2001; Santer *et al.*, 2001; Stanley, 2004, 2011). GDH is allosterically activated by leucine or ADP and inhibited by guanosine-5'-triphosphate (GTP) and ATP. In GDH-CHI, a GOF mutation in *GLUD1* desensitizes GDH to allosteric inhibition by GTP, while allosteric activation by leucine is uninhibited (Stanley *et al.*, 1998).

GDH-CHI typically results in milder HH compared with K_{ATP} channel CHI and is usually not detected until patients are at least a few months old (De Lonlay *et al.*, 2001; Stanley, 2004; Kapoor *et al.*, 2009), although cases may already present at day 1 (Yorifuji *et al.*, 1999; Stanley *et al.*, 2000; MacMullen *et al.*, 2001).

GDH-CHI is characterized by normal birth weight and protein-meal-induced postprandial hypoglycemia with persistent asymptomatic hyperammonemia (Stanley *et al.*, 2000; Hsu *et al.*, 2001; Stanley, 2004; Kapoor *et al.*, 2009; Palladino and Stanley, 2010). However, some patients show completely normal ammonia levels, probably due to mosaicism of the genetic changes (Kapoor *et al.*, 2009). Barrosse-Antle *et al.* reported a severe case with homozygous activating *GLUD1* mutations in exon 6 and 7, presenting with hypoglycemia, hyperammonemia, and seizures immediately after birth (Barrosse-Antle *et al.*, 2017).

Histological findings in GDH-CHI

Rahier et al. analyzed two surgical GDH-CHI cases (Rahier *et al.*, 2011). The specimens were macroscopically unremarkable. Microscopically, a few beta cell nuclei showed a moderate increase in size but the cytoplasm remained unchanged. With IHC, insulin staining was not lowered as in diffuse CHI and proinsulin expression was high. SUR1 expression was normal, compatible with a normally functioning K_{ATP} channel. In a specimen from another surgically treated GDH-CHI patient, hypertrophic islet cells were arranged in ribbon-like patterns (De Lonlay *et al.*, 2001). These morphological changes seem to reflect a clinically milder form of HH than K_{ATP} channel diffuse CHI (Stanley, 2004)

Treatment of GDH-CHI

Management of GDH-CHI includes diazoxide and a diet restricted in protein, especially leucine (Kapoor *et al.*, 2009; Stanley, 2011; Roy *et al.*, 2019). Surgery is very rarely performed, as GDH-CHI usually responds to diet and diazoxide (Stanley *et al.*, 2000; MacMullen *et al.*, 2001)

CHI in Beckwith-Wiedemann syndrome (BWS-CHI)

Genetic and clinical findings in BWS-CHI

BWS is the most common pediatric overgrowth syndrome with an estimated prevalence of 1:10,000–13,700 (Thorburn *et al.*, 1970; Mussa *et al.*, 2013). BWS is frequently diagnosed in the neonatal period or early childhood and is typically characterized by macroglossia, macrosomia, abdominal wall defects, asymmetric overgrowth, and increased risk of embryonal tumor development (DeBaun and Tucker, 1998; Weksberg *et al.*, 2010; Kalish *et al.*, 2016; Maas *et al.*, 2016; Brioude *et al.*, 2018).

As overgrowth affects a variable part of cells during embryogenesis, a broad BWS spectrum of clinical features with varying severity is, however, seen (Kalish *et al.*, 2016; Brioude *et al.*, 2018; Wang *et al.*, 2019).

HH is seen in 50% of patients with BWS and is usually mild and transient with resolution within a few days (Mussa, Di Candia, *et al.*, 2016). In 5% of cases, however, persistent hypoglycemia is observed (Elliott *et al.*, 1994; DeBaun *et al.*, 2000). The severity of HH in BWS is thought to be related to the variable percentage of mosaic changes within the pancreas (Kalish *et al.*, 2016).

BWS is caused by genetic and epigenetic changes in the imprinting centers IC1 and IC2 for imprinting chromosome 11p15.5-11p15.4, containing the genes *CDKN1C*, *H19*, *IGF2*, and *KCNQ1* (Kalish *et al.*, 2016; Mussa *et al.*, 2016b; Brioude *et al.*, 2018). An (epi-)genetic defect is seen in 80% of BWS patients (Choufani *et al.*, 2010; Eggermann *et al.*, 2014; Brioude *et al.*, 2018). The majority of patients with BWS are sporadic and 15% have a familial predisposition (Viljoen and Ramesar, 1992; Choufani *et al.*, 2010; Eggermann *et al.*, 2014; Brioude *et al.*, 2018). In sporadic cases, about 50% have a loss-of-methylation of IC2 in the maternal allele, 20% have pUPD of chromosome 11p15, 5% have a gain-of-methylation of IC1 in the maternal allele, and 5% have a mutation in *CDKN1C* (Choufani *et al.*, 2010; Eggermann *et al.*, 2014; Brioude *et al.*, 2018). A maternal *CDKN1C* mutation can be detected in 40% of familial cases (Choufani *et al.*, 2010; Eggermann *et al.*, 2014; Brioude *et al.*, 2018). The 11p15.5-11p15.4 changes commonly lead to mosaic overgrowth. Mosaic pUPD is occasionally seen for the entire chromosome 11, which does not seem to affect the clinical features, compared to cases where only a small part of this chromosome is affected (Dutly *et al.*, 1998; Cooper *et al.*, 2007). In rare cases, the genome-wide pUPD may lead to additional syndromic manifestations, including BWS-CHI (Giurgea, Sanlaville, *et al.*, 2006; Wilson *et al.*, 2008; Gogiel *et al.*, 2013; Kalish *et al.*, 2013; Christesen *et al.*, 2020).

Persistent HH in BWS is almost exclusively due to pUPD of chromosome 11p15 (Kalish *et al.*, 2016). Moreover, paternally inherited pathogenic K_{ATP} channel mutations may occur in addition to overexpression of *IGF2* and reduced expression of *H19* and *CDKN1C* (Kalish *et al.*, 2016). Hence, mosaic pUPD can uncover a recessive pathogenic K_{ATP} channel mutation resulting in HH, as also suggested by other studies (Calton *et al.*, 2013; Kocaay *et al.*, 2016).

Histological findings in BWS-CHI

In surgical pancreas specimens from patients with BWS-CHI, a distinct histological picture is characterized by overgrowth with an increase in the volume of endocrine cells (Fig. 4) (Hussain *et al.*, 2005; Laje, Palladino, *et al.*, 2013; Christesen *et al.*, 2020). The degree of morphological mosaicism in the resected pancreatic tissue varies from a focal or segmental lesion, sometimes several, to the inclusion of the entire pancreas (Kalish *et al.*, 2016).

In contrast to K_{ATP} channel focal CHI, the endocrine cells are arranged in small clusters, often enlarged islets and groups, but usually not confluent islets (Fig. 4D-F). Between the endocrine islets and cell clusters, acinar cells and small ducts are observed (Christesen *et al.*, 2020).

Morphometric and immunohistochemical studies of BWS-CHI

In a small study, the density of nuclei in the endocrine lesion was around 4,000 nuclei per 0.4 mm^2 in a BWS-CHI patient, compared with around 2,500 nuclei per 0.4 mm^2 in five randomly selected specimens with focal CHI (Christesen *et al.*, 2020). Strong proinsulin expression was reported in BWS-CHI but insulin immunostaining was weak (Hussain *et al.*, 2005). The expression of p57 was seen in approximately 5% of the endocrine cells (Christesen *et al.*, 2020), in contrast with K_{ATP} channel focal CHI, where p57 expression is absent (Kassem *et al.*, 2001; Sempoux *et al.*, 2003). Larger studies using morphometry in BWS-CHI are, to our knowledge, currently lacking.

Treatment of BWS-CHI

For those patients with BWS-CHI who are unresponsive to medical treatment, pancreatic resection is required. Preoperative ^{18}F -DOPA-PET (PET/CT) can be useful to determine the size of the overgrowth area and to exclude focal CHI (Laje *et al.*, 2013a). Even severe and prolonged BWS-CHI can improve over time, which may call for prolonged medical treatment (Laje *et al.*, 2013a).

Morphological mosaicism of pancreatic islets

Genetic findings in morphological mosaicism of pancreatic islets

Rare non-syndromal CHI patients subjected to pancreatic surgery have shown a mosaic histological picture without overgrowth, with normal SUR1 expression in the islets, and absence of germline mutations in known CHI genes (Sempoux *et al.*, 2011). In five of these patients, hexokinase 1 (HK-1), was inappropriately expressed in hyper-functional type 1 islets. The five patients were preoperative responsive, or at least transiently sensitive, to diazoxide (Henquin *et al.*, 2013). Using Sanger sequencing, a heterozygous somatic *GCK* variant, p.Ile211Phe, was later reported in one of the patients from Sempoux's cohort (Henquin *et al.*, 2013).

Although not always fully described, somatic mosaicism on the (epi-)genetic level in leukocyte DNA or pancreatic tissue is probably closely correlated with the morphological mosaic histological picture, with or without overgrowth. The emerging genetic heterogeneity of mosaic, non-syndromal CHI will probably, in the future, lead to a more detailed phenotypic characterization, according to the affected genes and the degree of mosaicism in the pancreatic tissue.

Clinical findings in morphological mosaicism of pancreatic islets

Compared with focal and diffuse CHI, patients with non-syndromal mosaicism of pancreatic islets had a lower birth weight and later onset of HH, median (range) 165 (1-270) days (Sempoux *et al.*, 2011).

Histological findings in morphological mosaicism of pancreatic islets

In the important study of Sempoux *et al.* (Sempoux *et al.*, 2011), CHI without the histological features of focal CHI, diffuse CHI, GCK-CHI, GDH-CHI, or BWS-CHI was described in 16 patients with unknown genetics. The pancreas appeared macroscopically normal. Histologically, the coexistence of two different islet types was observed (Sempoux *et al.*, 2011). Type 1 islets were hyperplastic, being around two-fold larger than type 2 islets, and confined to one or several adjacent lobules. Type 2 islets were small, shrunken, and distributed throughout the entire pancreas (Sempoux *et al.*, 2011). This histological pattern may well be caused by as

yet unidentified somatic, mosaic gene mutations restricted to the endocrine cells in type 1 islets, as later proven for a fraction of the patients. It is possible that the three cases published by Han and coworkers also represent morphological mosaicism of islets (Han *et al.*, 2017).

Morphometric and immunohistochemical findings in morphological mosaicism of pancreatic islets

Morphometric analyses showed that type 1 islets had a mean area of around 11,400 μm^2 (Sempoux *et al.*, 2011). Type 1 islets also contained numerous beta cells with abundant cytoplasm and sometimes large nuclei, however, rarely as large as in diffuse CHI. The radius of beta cell nuclei was around 5–6 μm in type 1 compared with around 4 μm in type 2 islets. In accordance with this, the BCNC was higher in type 2 vs. type 1 islets (around 14 vs. 9). Also, insulin expression was higher in type 1 than in type 2 islets (Sempoux *et al.*, 2011). p57 expression was present in both types of islets. The area of type 2 islets is not given in the article, but it was stated that type 1 islets were 2.06 fold larger than type 2 islets. The mean area in type 1 islets was 11,400 μm^2 , roughly corresponding to a mean diameter of around 0.12 mm. This would mean that type 2 islets, in the study by Sempoux and coworkers, may have had a mean diameter of roughly 0.08 mm, corresponding to a mean area of 5.540 μm^2 (Sempoux *et al.*, 2011).

Differential diagnosis of morphological mosaicism of pancreatic islets

Localized Islet Nuclear Enlargement (LINE) has been introduced as a morphological type of CHI (Adzick *et al.*, 2019). Recently, a series of 12 cases of patients with pancreatic histology consistent with LINE were published (Boodhansingh *et al.*, 2022b). Morphologically, islet cell nucleomegaly was identified in one or two contiguous regions of the pancreas. Genetically, low-level mosaic mutations were identified in the pancreas of six cases (three in *ABCC8*, three in *GCK*), out of eight cases where this analysis was done (Boodhansingh *et al.*, 2022b). Hence, it seems that LINE, in the absence of beta cell hyperplasia, is characterized by a morphology different from the morphological mosaicism of islets described above, based on data available so far.

Other less clear mosaic genotype-histotype correlations have been described, including combinations of 11pUPD and a germline or somatic mosaic *ABCC8* variant in affected parts of the pancreas (Hussain *et al.*, 2008) and germline and somatic mosaic *GLUD1* mutations, but with reportedly diffuse histology without further details (Boodhansingh *et al.*, 2022a).

In conclusion, mosaic mutations in several known CHI genes lead to mosaic histotypes and often less severe clinical hyperinsulinism compared to non-mosaic mutations in the same genes. A more detailed description of the potential different mosaic histotypes is warranted.

Treatment of morphological mosaicism of pancreatic islets

All patients with mosaicism were (at least partially) responsive to diazoxide treatment, however, with decreasing sensitivity over time, necessitating surgery. After surgical intervention, medical treatment was usually not necessary (Sempoux *et al.*, 2011).

Other forms of hyperinsulinemic hypoglycemia

Other rare syndromic or non-syndromic genotypes with CHI lack histological descriptions, as they usually can be managed conservatively without surgery. This includes CHI in association with mutations in *ADK* (ADK deficiency); *ALG3* (Congenital Disorder of Glycosylation (CDG) type 1D); *ARID12* (Coffin-Siris syndrome); *CACNA1C* (Timothy syndrome); *CACNA1D* (PASNA syndrome); *CCND2* (Megaencephaly-polymicrogyria syndrome); *CHD7* (Charge syndrome); *CREBBP* and *EP300* (Rubinstein-Taybi syndrome); *DIS3L2* (Perlman syndrome); *EIF2S3* (MEMHO syndrome); *FAH* (Tyrosinemia type 1); *FOXA2* (Pituitary hypoplasia-CHI syndrome); *GPC3* (Simpson-Golabi-Behmel syndrome); *HADH*, *HNF1A*, *HNF4A*, and *HRAS* (Costello syndrome); *INSR* and *JAG1* (Alagille syndrome type 1); *KCNQ1*, *KDM6A*, and *KMT2D* (Kabuki syndrome); *MAGEL2* (Schaaf-Yang syndrome); *MPI* (CDG type 1B); *NFIX* (Malan syndrome); *NSD1* (SOTOS syndrome); *PGM1* (CDG type 1T); *PMM2* (CDG type 1A, polycystic kidney disease); *PHOX2B* (congenital central

hypoventilation); *SLC16A1* (*MCT*, exercise-induced hyperinsulinism); *SCL25A36* and *TRMT10A* (*MMSGM1* syndrome); *UCMA* (*Poland syndrome*); *UCP2* and *YARS1* (*YARS syndrome*) (Rosenfeld *et al.*, 2019; Kostopoulou *et al.*, 2021; Hewat *et al.*, 2022; Shahroor *et al.*, 2022). Moreover, a number of contiguous gene deletions have been related to CHI.

Of special note, dominant inactivating mutations in the transcription factors *HNF4A* and *HNF1A* result in Maturity-onset diabetes of the young (MODY) type 1 and type 3, respectively, however, in some patients also macrosomia at birth and diazoxide-responsive HH with spontaneous clinical remission (Pearson *et al.*, 2007; Flanagan *et al.*, 2010; Dusatkova *et al.*, 2011; Stanescu *et al.*, 2012; McGlacken-Byrne *et al.*, 2014; Tung *et al.*, 2018; McGlacken-Byrne *et al.*, 2022). Patients with mutations in a number of other genes may also undergo spontaneous transition to diabetes without pancreatic surgery. Inhibiting *INSR* mutations lead to insulin resistance, usually presenting with permanent neonatal diabetes, but milder cases may have late disease onset with HH as the presenting feature due to a prolonged insulin half-life in the circulating blood (Rosenfeld *et al.*, 2019; Hewat *et al.*, 2022).

Insulinoma

An insulinoma is a functioning NET with unregulated hyperproduction of insulin and resultant HH (Guettier and Gorden, 2010). The incidence of insulinoma is estimated at 1:250.000 in Mayo Clinic, USA (Service *et al.*, 1991).

Genetic findings in insulinoma

Most insulinomas arise sporadically (Shin *et al.*, 2010). In adults, 4-8% are associated with *MEN1* (Service *et al.*, 1991; Anlauf *et al.*, 2009; Placzkowski *et al.*, 2009; Crippa *et al.*, 2012; Kurakawa *et al.*, 2021; Svensson *et al.*, 2022) due to autosomal dominantly inherited mutations in the tumor suppressor gene *MEN1* (Larsson *et al.*, 1988; Byström *et al.*, 1990; Chandrasekharappa *et al.*, 1997). While insulinoma is rarely a part of *MEN1* in adults, *MEN1*-associated insulinomas are commonly seen in children with this syndrome, accounting for

38–42% of all cases (Bhatti *et al.*, 2016; Melikyan *et al.*, 2023). In children, insulinomas may often be the first presentation of MEN1 (van Beek *et al.*, 2020), in contrast to parathyroid adenomas as the most frequent first presentation of MEN1 in adults (Thakker *et al.*, 2012). The *MEN1* gene is located on chromosome 11q13, and the presumed somatic second hit in the insulinoma may be caused not only by a second *MEN1* mutation but also by deletion of the entire maternal chromosome 11 including the tumor suppressor region 11p15. as suggested by (Bhatti *et al.*, 2016). The authors found evidence of maternal loss of heterozygosity for 11p15 in both MEN1-associated and sporadic insulinomas. Moreover, aneuploidy of other chromosomes was reported (Bhatti *et al.*, 2016).

MEN1 mutations are uncommon in sporadic insulinomas (Cupisti *et al.*, 2000; Jonkers *et al.*, 2005), however, in three next-generation sequencing studies, somatic *MEN1* mutations were revealed in approximately 2.4% of insulinomas (Cao *et al.*, 2013; Wang *et al.*, 2017; Hong *et al.*, 2020). Somatic mutations in other genes have also been reported in insulinomas, including *ARHGAP35*, *ATR*, *FLNC*, *H3F3A*, *KDM6A*, *LMO2*, *MLL3*, and *YY1* (Cao *et al.*, 2013; Wang *et al.*, 2017; Hong *et al.*, 2020). In a recent whole-genome sequencing study, the most frequent somatic mutations were found in *YY1* (25%), *DOCK4* (4%), *EVA1X* (2%), and *FRG1* (2%) (Hong *et al.*, 2020). In pancreatic non-functioning NETs, on the other hand, others found frequent somatic mutations in *MEN1* (42%), followed by *DAXX* (21%), *ATRX* (13%), *PTEN* (9%), and *SETD2* (5%), however, the same mutations are rarely involved in insulinomas (Hong *et al.*, 2020). More studies on a larger number of insulinomas are needed on the genetic background for the development of insulinomas with and without hereditary or somatic *MEN1* mutations.

Clinical findings in insulinoma

Insulinomas in children are rare (Boley *et al.*, 1960; Mann *et al.*, 1969; Service *et al.*, 1991; Padidela *et al.*, 2014; Bhatti *et al.*, 2016; Melikyan *et al.*, 2023). In a 60-year-study including 224 patients, only 6% of the insulinomas occurred in adolescents or children under the age of 19 (Service *et al.*, 1991), and the youngest

children were 3-4 years old (Boley *et al.*, 1960; Mann *et al.*, 1969; Service *et al.*, 1991; Padidela *et al.*, 2014; Bhatti *et al.*, 2016). Hence, it is unlikely that an insulinoma is the cause of HH before the age of 2-3 years.

In a large series of insulinoma patients, the median age at the time of surgery was 47 (8-82) years, with females constituting 59%, almost 87% had a single insulinoma, 7.1% had multiple insulinomas, and 5.8% had aggressive insulinomas (Service *et al.*, 1991). Sporadic insulinomas are typically solitary but insulinomas associated with MEN1 are frequently multicentric (Demeure *et al.*, 1991; van Beek *et al.*, 2020). Insulinoma with and without *MEN1* mutations can be malignant but behaves mostly as non-malignant (Placzkowski *et al.*, 2009; Bartsch *et al.*, 2013; Andreassen *et al.*, 2019). The Ki67 index predicts the probability of metastasis but even insulinomas with a low Ki67 index can metastasize and occasionally benign insulinomas show a high Ki67 index (Alkatout *et al.*, 2015; Andreassen *et al.*, 2019; Sada *et al.*, 2021). Malignant insulinomas are not, or very rarely, seen in children (Service *et al.*, 1991; Jaksic *et al.*, 1992; Janem *et al.*, 2010; Bhatti *et al.*, 2016). The clinical diagnosis of insulinomas is based on Whipple's triad with signs and symptoms of hypoglycemia, low blood glucose, and resolution of symptoms after rising blood glucose (Whipple, 1938). Insulinomas can be difficult to detect as symptoms may be non-specific and present for a long period before diagnosis (Service, 1995; Boukhan *et al.*, 1998; Grant, 1998). A 48h, or 72h, fasting test is the gold diagnostic test for the detection of HH in adults (Service, 1995; Hirshberg *et al.*, 2000; de Herder *et al.*, 2006; Vezzosi *et al.*, 2007; Placzkowski *et al.*, 2009; Toaiari *et al.*, 2013). In the case of a negative fasting test, an oral glucose tolerance test may provoke rebound hypoglycemia due to insulin excess (Falconi *et al.*, 2016). The presence of an insulinoma is associated with high levels of circulating proinsulin, consistent with histopathology findings suggesting insufficient insulin processing, rather than high insulin secretion (Roth *et al.*, 1992; Azzoni *et al.*, 1998; Wiesli *et al.*, 2004; Guettier *et al.*, 2013). A higher proinsulin/insulin ratio is often seen in malignant insulinomas compared with benign insulinomas (Yu *et al.*, 2017). Imaging to detect and localize the insulinoma may be difficult despite the many available imaging technique modalities, including ultrasound, CT, MRI, and various PET scan tracers, as discussed in a recent review (Prosperi *et al.*, 2022).

Histological findings in insulinoma

Insulinomas are often well-delimited endocrine tumors (Fig. 5) (Sempoux *et al.*, 2003; Padidela *et al.*, 2014; Bhatti *et al.*, 2016). The tumors are distributed equally in the different regions of the pancreas (Shin *et al.*, 2010). Insulinomas typically range from 5 to 24 mm (Klöppel and Heitz, 1988; Solcia *et al.*, 1997; Sempoux *et al.*, 2003; Bhatti *et al.*, 2016) and insulinomas exceeding 3 cm in diameter increase the risk of malignancy (Solcia *et al.*, 1997; Câmara-de-Souza *et al.*, 2018; Andreassen *et al.*, 2019; Sada *et al.*, 2021). Their cut surface is typically grey-white to red-pink-brown (Solcia *et al.*, 1997; Komminoth *et al.*, 1999; Sempoux *et al.*, 2003). The consistency is soft compared with the normal surrounding yellowish pancreatic parenchyma except in cases with fibrous stroma and/or large amounts of amyloid (Solcia *et al.*, 1997; Komminoth *et al.*, 1999; Sempoux *et al.*, 2003; Bhatti *et al.*, 2016). Different growth patterns can be observed, for example, nets or cords separated by vascularized fibrous stroma (Sempoux *et al.*, 2003; Padidela *et al.*, 2014; Bhatti *et al.*, 2016). The tumor cells are relatively uniform, cylindrical, or cuboidal-shaped with moderately abundant acidophilic cytoplasm (Sempoux *et al.*, 2003).

Insulinomas express mainly insulin (Fig. 5B) but expression of glucagon, somatostatin, and even pancreatic polypeptide is also observed in about half of cases (Liu *et al.*, 1985; Solcia *et al.*, 1997; Komminoth *et al.*, 1999; Sempoux *et al.*, 2003; Bhatti *et al.*, 2016). In addition, general neuroendocrine markers, such as chromogranin A and synaptophysin, (Fig. 5C), are strongly expressed. As with other neuroendocrine neoplasms, insulinomas are graded according to their Ki67 and mitotic index: NET grade 1 shows a Ki67-index of < 3% (and < 2 mitoses per 2 mm²), grade 2 between 3% and 20% (Fig. 5C) (and 2-20 mitoses per 2 mm²), grade 3 above 20% (and > 20 mitoses per 2 mm²). Neuroendocrine carcinomas show necrosis and an aggressive infiltration growth, in addition to a Ki67-index > 20% (often > 90%), and > 20 mitoses per 2 mm² (Lloyd, 2017). Most insulinomas are low-grade tumors (Bhatti *et al.*, 2016).

Treatment of insulinoma

Surgery is the optimal treatment for insulinomas (de Carbonnières *et al.*, 2021). Diazoxide is the primary choice for treating the symptoms of non-resectable insulinomas and is effective in 50-60% of patients (Mathur *et al.*, 2009; Öberg, 2018; Niitsu *et al.*, 2019). In diazoxide non-responders with non-resectable malignant insulinomas, somatostatin agonists can be used because of their antiproliferative effect (Matej *et al.*, 2016; Brown *et al.*, 2018).

Insulinomatosis

Insulinomatosis is a rare cause of HH in adults and is characterized by multiple small and large insulin-producing tumors (Anlauf *et al.*, 2009). Insulinomatosis is a very rare neoplastic condition; in a large series of patients with insulinomas, insulinomatosis accounted for approximately 5% (Anlauf *et al.*, 2009). To date, at least 18 cases of sporadic insulinomatosis (Anlauf *et al.*, 2009; Snaith *et al.*, 2020; Anoshkin *et al.*, 2021; Mintziras *et al.*, 2021; Tartaglia *et al.*, 2022) and three cases with familial insulinomatosis (Tragl and Mayr, 1977; Iacovazzo *et al.*, 2018; Fottner *et al.*, 2022) have been reported.

Genetic and clinical findings in insulinomatosis

Germline mutations in the *MAFA* gene have been identified in familial insulinomatosis in three unrelated families with an autosomal dominant pattern (Iacovazzo *et al.*, 2018; Fottner *et al.*, 2022). Other family members with the same *MAFA* mutation develop impaired glucose tolerance or diabetes. In addition, congenital glaucoma or cataracts may be present (Iacovazzo *et al.*, 2018; Fottner *et al.*, 2022). In one case of sporadic insulinomatosis, a germline *MAFA* in-frame deletion, p.His207del, has been reported (Mintziras *et al.*, 2021).

MAFA encodes the transcription factor MAFA, which regulates the beta cell expression of insulin and several genes involved in GSIS (Liang *et al.*, 2022). Moreover, the two reported familial missense mutations, p.Ser64Phe and p.Thr47Arg, impair MAFA phosphorylation leading to decreased proteasome-mediated

degradation and, hence, increased MAFA protein stability as a potential, at least partial, mechanism for the oncogenic capacity of these MAFA mutations (Iacovazzo *et al.*, 2018; Fottner *et al.*, 2022). The mechanisms for the development of both diabetes and insulinomatosis in MAFA patients are, however, not fully understood.

Histological findings in insulinomatosis

Insulinomatosis is histologically characterized by multiple macro-tumors (> 5 mm) and micro-adenomas (< 5 mm) that express insulin and arise synchronously and metachronously in all regions of the pancreas; metastases are rarely seen (Anlauf *et al.*, 2009).

Insulinomatosis is distinguished histologically by insulin-expressing mono-hormonal endocrine cell clusters. The tumors only stain for insulin (Anlauf *et al.*, 2009), whereas micro-adenomas in MEN1 patients often express glucagon and pancreatic polypeptide (Anlauf *et al.*, 2006). Other micro-adenomas express glucagon (glucagon-cell adenomatosis), or no hormones, as seen in von Hippel-Lindau syndrome (Périgny *et al.*, 2009; Zhou *et al.*, 2009; Miller *et al.*, 2015).

Treatment of insulinomatosis

Treatment of insulinomatosis is complicated due to the multicentric nature of the disease. In a large study, 43% of patients had persistent or recurrent disease following surgical treatment, sometimes necessitating additional surgery (Anlauf *et al.*, 2009). Medical therapy is often not successful but one patient with sporadic insulinomatosis showed complete remission after treatment with octreotide long-acting release (Tartaglia *et al.*, 2022).

Adult-onset non-insulinoma persistent hyperinsulinemic hypoglycemia syndrome

Terminology

Adult-onset NI-PHHS has been alternatively abbreviated NIPH (Vanderveen *et al.*, 2010; Anderson *et al.*, 2016), NI-PHH (Christesen, Tribble, *et al.*, 2008), NIPHS (Thompson *et al.*, 2000; Anlauf *et al.*, 2005; Won *et al.*, 2006; Sahloul *et al.*, 2007; Yamada *et al.*, 2020), or non-insulinoma pancreatogenous hypoglycemic syndrome (PHH) (Kloppel *et al.*, 2008). Adult nesidioblastosis is an alternative historical, yet incorrect, histological term in today's view.

Genetic and clinical findings in NI-PHHS

NI-PHHS is an entity that mainly affects adults, with rare cases seen in adolescence (age range from 12-82 years) (Harness *et al.*, 1981; Service *et al.*, 1999; van der Wal *et al.*, 2000; Witteles *et al.*, 2001; Kaczirek *et al.*, 2003; Anlauf *et al.*, 2005; Won *et al.*, 2006; Raffel *et al.*, 2007; Yamada *et al.*, 2020). Most patients with NI-PHHS have an unknown genetic cause. However, GCK mutations have been found in a few adults with clinical features of NI-PHHS, suggesting a genetic cause in at least some patients (Glaser *et al.*, 1998; Christesen *et al.*, 2008a). Yet, histology was not available in these studies (Glaser *et al.*, 1998; Christesen *et al.*, 2008a). Other rare adult patients presented with exercise-induced HH due to activating mutations in the *SLC16A1* promotor, none of these patients were subjected to pancreatic surgery (Otonkoski *et al.*, 2003, 2007). Insulinoma is the most important clinical differential diagnosis. NI-PHHS has, in a large series, been identified in 3-8.5% of insulinomas (Anlauf *et al.*, 2005; Raffel *et al.*, 2007; Yamada *et al.*, 2020). Another and more frequent cause of HH in adults is postprandial HH after gastric bypass surgery, a condition which should be discerned from NI-PHHS as a primary disease (Thompson *et al.*, 2000; Raffel *et al.*, 2007; Yamada *et al.*, 2020).

The clinical symptoms of NI-PHHS are usually observed during fasting, exercise, or stress, and are related to autonomic and severe neuroglycopenic hypoglycemia, leading to confusion, visual disturbances, dizziness, abnormal behavior, loss of consciousness, sweating, palpitations, and tremor (Goossens *et al.*, 1991; Service

et al., 1999; van der Wal *et al.*, 2000; Witteles *et al.*, 2001; Kaczirek *et al.*, 2003; Otonkoski *et al.*, 2007). A 72-h fast is a standard test in the diagnostic process for NI-PHHS (Service, 1995) but is unspecific in distinguishing NI-PHHS from insulinoma (Service, 1999; Kaczirek *et al.*, 2003; Starke *et al.*, 2006; Won *et al.*, 2006).

Histological findings in NI-PHHS

In surgical pancreas specimens from NI-PHHS patients, the macroscopic appearance is usually normal (Anlauf *et al.*, 2005). In around a third, the histological changes in the endocrine pancreas were minimal and difficult to distinguish from normal pancreatic tissue (Kloppel *et al.*, 2008). A feature of the islets in the remaining cases was a somewhat lobulated composition, probably resulting from irregularly sized beta cells that form small groups within the islets (Anlauf *et al.*, 2005). In a proportion of cases, however, the number and size of pancreatic islets are slightly increased (Fig. 6). Major histopathologic criteria for the histological diagnosis of NI-PHHS are 1) exclusion of an insulinoma, 2) multiple beta cells with enlarged and hyperchromatic nuclei and abundant cytoplasm, 3) islets with a normal composition of endocrine cell types, and 4) no increased proliferative activity of endocrine cells (Anlauf *et al.*, 2005). Minor histopathologic criteria are 1) irregular shape and occasional enlargement of islets (Fig. 6D), 2) increased number of islets (Fig. 6A-B), 3) lobulated islet structure, and 4) macronuclei in beta cells (Fig. 6C) (Anlauf *et al.*, 2005). Unfortunately, these criteria are relatively unspecific.

Morphometric and immunohistochemical studies of NI-PHHS

Single islets in NI-PHHS are enlarged, with a diameter of 300 μ m or more (Fig. 6D-F) (Harness *et al.*, 1981; Volk, 1985; van der Wal *et al.*, 2000; Kaczirek *et al.*, 2003; Anlauf *et al.*, 2005). As a consequence, an increased total beta cell volume can be measured (van der Wal *et al.*, 2000; Anlauf *et al.*, 2005). Beta cells show enlarged nuclei and abundant clear cytoplasm. Macronuclei were observed more often than in controls (van der Wal *et al.*, 2000; Witteles *et al.*, 2001; Anlauf *et al.*, 2005). Overexpression of islet neogenesis-associated protein was reported in a few cases (Won *et al.*, 2006). More research with the identification of (epi-)genetic,

germline, or somatic mutations, or altered regulation of insulin production or secretion, is needed to further describe the pathophysiology and related histological features of NI-PHHS. Most probably, subtypes of NI-PHHS will be identified with the need for novel nomenclature of a heterogeneous disease entity.

Diagnosis and treatment of NI-PHHS

NI-PHHS should be suspected in adolescents or adults with new-onset HH, and negative genetics and imaging for insulinoma (Witteles *et al.*, 2001; Gupta *et al.*, 2013). In the absence of secondary causes to adult-onset HH, targeted panel sequencing or whole genome sequencing should be performed to identify genetic causes. In the case of surgery, resection of 70-80% is considered the most appropriate surgery for NI-PHHS (Jabri and Bayard, 2004; Raffel *et al.*, 2007). In case of persistent hypoglycemia after surgery, diet and various medical treatments including diazoxide and somatostatin analogs can be used (Yamada *et al.*, 2020). With the improvements in the medical therapy of HH, surgery may be less often used as seen in the treatment of diffuse CHI.

Conclusion

This review provides an overview of the different histological forms of HH, their associated genetic changes, clinical characteristics, and treatment options. Histology plays, together with genetics and imaging, an important role in the diagnosis of HH, including K_{ATP} channel diffuse or focal CHI, GCK-CHI, GLUD1-CHI, BWS-CHI, mosaic CHI, insulinoma, insulinomatosis, and NI-PHHS. Improvements in the understanding of the genotype-histotype-phenotype correlations have led to considerable progress in patient management. Intra-operative frozen section microscopy can identify a focal lesion in infants with CHI and an insulinoma in adolescent and adult HH patients, assisting the surgeon in limiting the pancreatic resection. At many centers, frozen section biopsy is performed to differentiate the different histological forms of CHI, most importantly the diffuse from the focal type. Genotype-histotype-phenotype correlations are also important in genetic counseling of families with HH.

Legends

Fig. 1. K_{ATP} channel diffuse CHI. **A.** The number and size of islets of Langerhans are usually age appropriate (H&E, scale bar 500 μ m). **B.** Synaptophysin immunostaining of pancreatic islets is shown (scale bar 500 μ m). **C.** At medium-power magnification, giant nuclei in beta cells of islets of Langerhans can be observed (scale bar 250 μ m). **D.** High magnification of an islet of Langerhans with numerous giant nuclei (scale bar 500 μ m).

Fig. 2. K_{ATP} channel focal CHI. **A.** Focal adenomatous hyperplasia (FAH) measuring 12 mm at maximum diameter (H&E, scale bar 2.5 mm). **B.** Strong insulin positivity in beta cells in the FAH (insulin immunostaining, scale bar 2.5 mm). **C.** Delta cells with expression of somatostatin at the periphery of confluent islets of Langerhans in the FAH (somatostatin immunostaining, scale bar 2.5 mm). **D.** High magnification of FAH in focal CHI (H&E, scale bar 250 μ m).

Fig. 3. K_{ATP} channel focal-extensive CHI. The pancreas of a seven-month-old girl with a paternal *ABCC8* mutation was enlarged. A distal pancreatectomy was performed. The specimen measured 6.7 cm in length. Almost the entire specimen showed changes consistent with focal-extensive CHI. Representative pictures from different areas are shown. **A. – B., C. – D., E. – F., G. – H., I. – J.** H&E and synaptophysin staining different portions of the specimen, from its proximal to distal end. Confluent areas occupying various proportions in the cross-section show focal-extensive adenomatous hyperplasia (FAH). Scale bars: 2.5 mm (A), 5 mm (B-J).

Fig. 4. CHI in Beckwith-Wiedemann syndrome (BWS-CHI). **A. – C.** H&E (A), synaptophysin (B), and insulin (C) staining of a portion of the surgically resected pancreas. Overgrowth with an increase in the volume of endocrine cells in this area is shown. Scale bar: 5 mm. **D. – F.** H&E (D), synaptophysin (E), and insulin (F) staining at higher magnification. The endocrine cells are arranged in small clusters, often enlarged islets, and in groups. between the endocrine islets and cell clusters, acinar cells and small ducts are observed. Scale bars: 100 μ m (D and F), 250 μ m (E).

Fig. 5. Insulinoma that resulted in hyperinsulinemic hypoglycemia. **A.** A well-circumscribed tumor consisting of confluent trabeculae supported by a hyalinized fibrotic stroma (H&E). **B.** Strong expression of insulin in the tumor cells (insulin immunostaining). **C.** Lack of glucagon expression in the tumor cells (glucagon immunostaining). **D.** A Ki67 proliferation index in hot spots of 7%, corresponding to tumor grade 2 (dual-IHC of synaptophysin (red) and Ki67 (brown)). **E.** Higher magnification of (D). **F.** Nuclei of insulinoma cells show salt and pepper chromatin (H&E). Scale bars: A-D & F: 5.0 mm. B: 0.1 mm.

Fig. 6. Adult-onset non-insulinoma hyperinsulinemic hypoglycemia syndrome (NI-PHHS). **A.** Number and size of islets of Langerhans are slightly increased compared with normal adults (H&E, scale bar 500 μ m). **B.** Synaptophysin immunostaining emphasizes several enlarged pancreatic islets (scale bar 500 μ m). **C.** A pancreatic islet showing slight variation in the size of beta cell nuclei, which can also be seen in healthy adult pancreas (scale bar 100 μ m). **D. - F.** Enlarged islet of Langerhans with a length of around 800 μ m. **D.** H&E. **E.** Normal amount of insulin-positive beta cells (insulin immunostaining, scale bar 500 μ m). **F.** Normal amount of glucagon-positive alpha cells (glucagon immunostaining, scale bar 500 μ m).

Table 1. Summary of the main histological types of hyperinsulinemic hypoglycemia (HH) and related genotypes and phenotypes

Type of HH	Pancreatic histology	Genetics	Phenotype*
Diffuse CHI	Nucleomegaly in a few beta cells per islet of Langerhans, distributed throughout the entire pancreas.	Monoallelic or biallelic mutations in <i>ABCC8</i> or <i>KCNJ11</i> .	Macrosomia from birth. Neonatal onset, persistent HH.
Focal CHI	Focal adenomatous hyperplasia of islets of Langerhans. Size mostly between 2.5 and around 15 mm. Very rare focal extensive forms > 3 cm. Absence of p57/CDKN1C/Kip2 in the lesion.	Paternal monoallelic mutations in <i>ABCC8</i> or <i>KCNJ11</i> , and somatic loss of maternal 11p15.	Macrosomia from birth. Neonatal onset, persistent HH.
GCK-CHI	Changes range from normal pancreas to increased size of islets, or slightly increased size of nuclei of single beta cells in some islets.	Monoallelic activating mutations in <i>GCK</i> .	Neonatal onset HH.
GDH-CHI	A few beta-cell nuclei in a few islets may show a moderate increase in size.	Monoallelic activating mutations in <i>GLUD1</i> .	Neonatal or infant onset, persistent HH with mild hyperammonemia.
BWS-CHI	Overgrowth with an increase in the absolute and relative volume of endocrine cells.	Monoallelic mutation in <i>CDKN1C</i> . Somatic pUPD, biallelic expression of <i>IGF2</i> , and loss-of-expression of <i>CDKN1C</i> , <i>KCNQ1</i> , <i>H19</i> . Epigenetic loss or gain methylation.	Neonatal onset, persistent HH. Macrosomia and mosaic overgrowth defects, increased risk of cancer.
Morphological mosaicism of pancreatic islets	Hyperplastic (type 1) islets confined to one or several adjacent lobules and small, shrunk islets (type 2 islets) distributed throughout the entire pancreas. Normal expression of p57/CDKN1C/Kip2.	None, or somatic mutations in <i>GCK</i> .	Neonatal or infant onset, persistent HH.
Insulinoma	Low-grade NETs, typically WHO grade 1-2. Size typically between 6 and 25 mm. Histological expression of mainly insulin. Neuroendocrine markers, such as chromogranin A and synaptophysin, are strongly expressed.	None, or monoallelic <i>MEN1</i> mutations. Somatic mutations in <i>ARHGAP35</i> , <i>ATR</i> , <i>DOCK4</i> , <i>EVA1X</i> , <i>FLNC</i> , <i>FRG1</i> , <i>H3F3A</i> , <i>KDM6A</i> , <i>LMO2</i> , <i>MEN1</i> , <i>MLL3</i> , and <i>YY1</i> .	HH onset in late childhood, adolescence, or adulthood. Other MEN1 features are possible.
Insulinomatosis	Multiple insulin-producing neuroendocrine microadenomas (< 5 mm) and/or neuroendocrine neoplasms. Insulin-producing mono-hormonal endocrine cell clusters.	Monoallelic, or biallelic mutations in <i>MAFA</i> .	Adult onset HH. Diabetes.
NI-PHHS	Multiple beta cells with enlarged and hyperchromatic nuclei and abundant cytoplasm, islets with the normal composition of endocrine cell types. No increased proliferative activity of endocrine cells. Single enlarged islets > 300 µm.	None, or monoallelic activating <i>GCK</i> mutations.	Adult onset HH. Rare cases are seen in adolescence.

*) Only typical phenotypes of patients with pancreatic resection (severe CHI) are included. Patients with milder and transient HH phenotypes will not undergo pancreatic resection and hence often have unknown histology.

BWS (Beckwith-Wiedemann syndrome), CHI (congenital hyperinsulinism), GCK (glucokinase), GDH (glutamate dehydrogenase), HH (Hyperinsulinemic hypoglycemia), MEN1 (multiple endocrine neoplasia type 1), NETs (neuroendocrine tumors), NI-PHHS (adult-onset non-insulinoma persistent hyperinsulinemic hypoglycemia syndrome).

HISTOLOGY AND HISTOPATHOLOGY
(non-edited manuscript)

References

- Adzick N.S., Thornton P.S., Stanley C.A., Kaye R.D. and Ruchelli E. (2004). A multidisciplinary approach to the focal form of congenital hyperinsulinism leads to successful treatment by partial pancreatectomy. *J. Pediatr. Surg.* 39, 270-275.
- Adzick N.S., De Leon D.D., States L.J., Lord K., Bhatti T.R., Becker S.A. and Stanley C.A. (2019). Surgical treatment of congenital hyperinsulinism: Results from 500 pancreatectomies in neonates and children. *J. Pediatr. Surg.* 54, 27-32.
- Ajala O.N., Huffman D.M. and Ghobrial I.I. (2016). Glucokinase mutation-a rare cause of recurrent hypoglycemia in adults: A case report and literature review. *J. Community. Hosp. Intern. Med. Perspect.* 6, 32983.
- Alkatout I., Friemel J., Sitek B., Anlauf M., Eisenach P.A., Stühler K., Scarpa A., Perren A., Meyer H.E., Knoefel W.T., Klöppel G. and Sipos B. (2015). Novel prognostic markers revealed by a proteomic approach separating benign from malignant insulinomas. *Mod. Pathol.* 28, 69-79.
- Anderson B., Nostedt J., Girgis S., Dixon T., Agrawal V., Wiebe E., Senior P.A. and Shapiro A.M. (2016). Insulinoma or non-insulinoma pancreatogenous hypoglycemia? A diagnostic dilemma. *J. Surg. Case Rep.* 2016.
- Andreassen M., Ilett E., Wiese D., Slater E.P., Klose M., Hansen C.P., Gercke N., Langer S.W., Kjaer A., Maurer E., Federspiel B., Kann P.H., Bartsch D.K. and Knigge U. (2019). Surgical management, preoperative tumor localization, and histopathology of 80 patients operated on for insulinoma. *J. Clin. Endocrinol. Metab.* 104, 6129-6138.
- Anlauf M., Wieben D., Perren A., Sipos B., Komminoth P., Raffel A., Kruse M.L., Fottner C., Knoefel W.T., Monig H., Heitz P.U. and Klöppel G. (2005). Persistent hyperinsulinemic hypoglycemia in 15 adults with diffuse nesidioblastosis: Diagnostic criteria, incidence, and characterization of beta-cell changes. *Am. J. Surg. Pathol.* 29, 524-533.
- Anlauf M., Schlenger R., Perren A., Bauersfeld J., Koch C.A., Dralle H., Raffel A., Knoefel W.T., Weihe E., Ruszniewski P., Couvelard A., Komminoth P., Heitz P.U. and Klöppel G. (2006). Microadenomatosis of the endocrine pancreas in patients with and without the multiple endocrine neoplasia type 1 syndrome. *Am. J. Surg. Pathol.* 30, 560-574.
- Anlauf M., Bauersfeld J., Raffel A., Koch C.A., Henopp T., Alkatout I., Schmitt A., Weber A., Kruse M.L., Braunstein S., Kaserer K., Brauckhoff M., Dralle H., Moch H., Heitz P.U., Komminoth P., Knoefel W.T., Perren A. and Klöppel G. (2009). Insulinomatosis: A multicentric insulinoma disease that frequently causes early recurrent hyperinsulinemic hypoglycemia. *Am. J. Surg. Pathol.* 33, 339-346.
- Anoshkin K., Vasilyev I., Karandasheva K., Shugay M., Kudryavtseva V., Egorov A., Gurevich L., Mironova A., Serikov A., Kutsev S. and Strelnikov V. (2021). New regions with molecular alterations in a rare case of insulinomatosis: Case report with literature review. *Front. Endocrinol. (Lausanne)* 12, 760154.
- Arnoux J.B., Verkarre V., Saint-Martin C., Montravers F., Brassier A., Valayannopoulos V., Brunelle F., Fournet J.C., Robert J.J., Aigrain Y., Bellanné-Chantelot C. and de Lonlay P. (2011). Congenital hyperinsulinism: Current trends in diagnosis and therapy. *Orphanet. J. Rare Dis.* 6, 63.
- Arnoux J.B., de Lonlay P., Ribeiro M.J., Hussain K., Blankenstein O., Mohnike K., Valayannopoulos V., Robert J.J., Rahier J., Sempoux C., Bellanné C., Verkarre V., Aigrain Y., Jaubert F., Brunelle F. and Nihoul-Fékété C. (2010). Congenital hyperinsulinism. *Early. Hum. Dev.* 86, 287-294.
- Arya V.B., Senniappan S., Demirbilek H., Alam S., Flanagan S.E., Ellard S. and Hussain K. (2014). Pancreatic endocrine and exocrine function in children following near-total pancreatectomy for diffuse congenital hyperinsulinism. *PLoS One* 9, e98054.
- Avatapalle H.B., Banerjee I., Shah S., Pryce M., Nicholson J., Rigby L., Caine L., Didi M., Skae M., Ehtisham S., Patel L., Padidela R., Cosgrove K.E., Dunne M.J. and Clayton P.E. (2013). Abnormal neurodevelopmental outcomes are common in children with transient congenital hyperinsulinism. *Front. Endocrinol. (Lausanne)* 4, 60.

- Azzoni C., D'Adda T., Tamburrano G., Coscelli C., Madsen O.D., Scopsi L. and Bordi C. (1998). Functioning human insulinomas. An immunohistochemical analysis of intracellular insulin processing. *Virchows Arch.* 433, 495-504.
- Baerentsen H. (1973). Neonatal hypoglycaemia due to an islet-cell adenoma. *Acta. Paediatr. Scand.* 62, 207-210.
- Banerjee I., De Leon D. and Dunne M.J. (2017). Extreme caution on the use of sirolimus for the congenital hyperinsulinism in infancy patient. *Orphanet. J. Rare Dis.* 12, 70.
- Banerjee I., Raskin J., Arnoux J.B., De Leon D.D., Weinzimer S.A., Hammer M., Kendall D.M. and Thornton P.S. (2022). Congenital hyperinsulinism in infancy and childhood: Challenges, unmet needs and the perspective of patients and families. *Orphanet. J. Rare Dis.* 17, 61.
- Barbetti F., Cobo-Vuilleumier N., Dionisi-Vici C., Toni S., Ciampalini P., Massa O., Rodriguez-Bada P., Colombo C., Lenzi L., Garcia-Gimeno M.A., Bermudez-Silva F.J., Rodriguez de Fonseca F., Banin P., Aledo J.C., Baixeras E., Sanz P. and Cuesta-Muñoz A.L. (2009). Opposite clinical phenotypes of glucokinase disease: Description of a novel activating mutation and contiguous inactivating mutations in human glucokinase (GCK) gene. *Mol. Endocrinol.* 23, 1983-1989.
- Barrosse-Antle M., Su C., Chen P., Boodhansingh K.E., Smith T.J., Stanley C.A., De León D.D. and Li C. (2017). A severe case of hyperinsulinism due to hemizygous activating mutation of glutamate dehydrogenase. *Pediatr. Diabetes* 18, 911-916.
- Barthlen W. (2011). Surgery in congenital hyperinsulinism-tips and tricks not only for surgeons. A practical guide. *Semin. Pediatr. Surg.* 20, 56-59.
- Barthlen W., Mohnike W. and Mohnike K. (2010). Techniques in pediatric surgery: Congenital hyperinsulinism. *Horm. Res. Paediatr.* 74, 438-443.
- Barthlen W., Varol E., Empting S., Wieland I., Zenker M., Mohnike W., Vogelgesang S. and Mohnike K. (2016). Surgery in focal congenital hyperinsulinism (CHI) - the "hyperinsulinism germany international" experience in 30 children. *Pediatr. Endocrinol. Rev.* 14, 129-137.
- Bartsch D.K., Albers M., Knoop R., Kann P.H., Fendrich V. and Waldmann J. (2013). Enucleation and limited pancreatic resection provide long-term cure for insulinoma in multiple endocrine neoplasia type 1. *Neuroendocrinology* 98, 290-298.
- Beer N.L., van de Bunt M., Colclough K., Lukacs C., Arundel P., Chik C.L., Grimsby J., Ellard S. and Gloyn A.L. (2011). Discovery of a novel site regulating glucokinase activity following characterization of a new mutation causing hyperinsulinemic hypoglycemia in humans. *J. Biol. Chem.* 286, 19118-19126.
- Bellanné-Chantelot C., Saint-Martin C., Ribeiro M.J., Vauray C., Verkarre V., Arnoux J.B., Valayannopoulos V., Gobrecht S., Sempoux C., Rahier J., Fournet J.C., Jaubert F., Aigrain Y., Nihoul-Fékété C. and de Lonlay P. (2010). ABCC8 and KCNJ11 molecular spectrum of 109 patients with diazoxide-unresponsive congenital hyperinsulinism. *J. Med. Genet.* 47, 752-759.
- Beltrand J., Caquard M., Arnoux J.B., Laborde K., Velho G., Verkarre V., Rahier J., Brunelle F., Nihoul-Fékété C., Saudubray J.M., Robert J.J. and de Lonlay P. (2012). Glucose metabolism in 105 children and adolescents after pancreatectomy for congenital hyperinsulinism. *Diabetes Care* 35, 198-203.
- Bendix J., Laursen M.G., Mortensen M.B., Melikian M., Globa E., Detlefsen S., Rasmussen L., Petersen H., Brusgaard K. and Christesen H.T. (2018). Intraoperative ultrasound: A tool to support tissue-sparing curative pancreatic resection in focal congenital hyperinsulinism. *Front. Endocrinol. (Lausanne)* 9, 478.
- Bhatti T.R., Ganapathy K., Huppmann A.R., Conlin L., Boodhansingh K.E., MacMullen C., Becker S., Ernst L.M., Adzick N.S., Ruchelli E.D., Ganguly A. and Stanley C.A. (2016). Histologic and molecular profile of pediatric insulinomas: Evidence of a paternal parent-of-origin effect. *J. Clin. Endocrinol. Metab.* 101, 914-922.
- Bjarnesen A.P., Dahlin P., Globa E., Petersen H., Brusgaard K., Rasmussen L., Melikian M., Detlefsen S., Christesen H.T. and Mortensen M.B. (2021). Intraoperative ultrasound imaging in the surgical treatment of congenital hyperinsulinism: Prospective, blinded study. *BJS Open* 5, zraa008.

- Boley S.J., Lin J. and Schiffmann A. (1960). Functioning pancreatic adenomas in infants and children. *Surgery* 48, 592-605.
- Boodhansingh K.E., Rosenfeld E., Lord K., Adzick N.S., Bhatti T., Ganguly A., De Leon D.D. and Stanley C.A. (2022a). Mosaic GLUD1 mutations associated with hyperinsulinism hyperammonemia syndrome. *Horm. Res. Paediatr.* 95, 492-498.
- Boodhansingh K.E., Yang Z., Li C., Chen P., Lord K., Becker S.A., States L.J., Adzick N.S., Bhatti T., Shyng S.L., Ganguly A., Stanley C.A. and De Leon D.D. (2022b). Localized islet nuclear enlargement hyperinsulinism (LINE-HI) due to ABCC8 and GCK mosaic mutations. *Eur. J. Endocrinol.* 187, 301-313.
- Bordi C., Ravazzola M., Pollak A., Lubec G. and Orci L. (1982). Neonatal islet cell adenoma: A distinct type of islet cell tumor? *Diabetes Care* 5, 122-125.
- Boukhan M.P., Karam J.H., Shaver J., Siperstein A.E., Duh Q.Y. and Clark O.H. (1998). Insulinoma--experience from 1950 to 1995. *West. J. Med.* 169, 98-104.
- Brar P.C., Heksch R., Cossen K., De Leon D.D., Kamboj M.K., Marks S.D., Marshall B.A., Miller R., Page L., Stanley T., Mitchell D. and Thornton P. (2020). Management and appropriate use of diazoxide in infants and children with hyperinsulinism. *J. Clin. Endocrinol. Metab.* 105, dgaa543.
- Brioude F., Kalish J.M., Mussa A., Foster A.C., Bliet J., Ferrero G.B., Boonen S.E., Cole T., Baker R., Bertolotti M., Cocchi G., Coze C., De Pellegrin M., Hussain K., Ibrahim A., Kilby M.D., Krajewska-Walasek M., Kratz C.P., Ladusans E.J., Lapunzina P., Le Bouc Y., Maas S.M., Macdonald F., Öunap K., Peruzzi L., Rossignol S., Russo S., Shipster C., Skórka A., Tatton-Brown K., Tenorio J., Tortora C., Grønskov K., Netchine I., Hennekam R.C., Prawitt D., Tümer Z., Eggermann T., Mackay D.J.G., Riccio A. and Maher E.R. (2018). Expert consensus document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: An international consensus statement. *Nat. Rev. Endocrinol.* 14, 229-249.
- Brown E., Watkin D., Evans J., Yip V. and Cuthbertson D.J. (2018). Multidisciplinary management of refractory insulinomas. *Clin. Endocrinol. (Oxf)* 88, 615-624.
- Buist N.R., Campbell J.R. and Castro A. (1971). Congenital islet cell adenoma causing hypoglycemia in a newborn. *Pediatrics* 47, 605-610.
- Byström C., Larsson C., Blomberg C., Sandelin K., Falkmer U., Skogseid B., Oberg K., Werner S. and Nordenskjöld M. (1990). Localization of the MEN1 gene to a small region within chromosome 11q13 by deletion mapping in tumors. *Proc. Natl. Acad. Sci. USA* 87, 1968-1972.
- Calabria A.C., Li C., Gallagher P.R., Stanley C.A. and De León D.D. (2012). GLP-1 receptor antagonist exendin-(9-39) elevates fasting blood glucose levels in congenital hyperinsulinism owing to inactivating mutations in the ATP-sensitive K⁺ channel. *Diabetes* 61, 2585-2591.
- Calton E.A., Temple I.K., Mackay D.J., Lever M., Ellard S., Flanagan S.E., Davies J.H., Hussain K. and Gray J.C. (2013). Hepatoblastoma in a child with a paternally-inherited ABCC8 mutation and mosaic paternal uniparental disomy 11p causing focal congenital hyperinsulinism. *Eur. J. Med. Genet.* 56, 114-117.
- Câmara-de-Souza A.B., Toyoshima M.T.K., Giannella M.L., Freire D.S., Camacho C.P., Lourenço D.M., Jr., Rocha M.S., Bacchella T., Jureidini R., Machado M.C.C., Almeida M.Q. and Pereira M.A.A. (2018). Insulinoma: A retrospective study analyzing the differences between benign and malignant tumors. *Pancreatology* 18, 298-303.
- Campbell J.E. and Newgard C.B. (2021). Mechanisms controlling pancreatic islet cell function in insulin secretion. *Nat. Rev. Mol. Cell. Biol.* 22, 142-158.
- Cao Y., Gao Z., Li L., Jiang X., Shan A., Cai J., Peng Y., Li Y., Jiang X., Huang X., Wang J., Wei Q., Qin G., Zhao J., Jin X., Liu L., Li Y., Wang W., Wang J. and Ning G. (2013). Whole exome sequencing of insulinoma reveals recurrent T372R mutations in YY1. *Nat. Commun.* 4, 2810.
- Carney C.N. (1976). Congenital insulinoma (nesidioblastoma): Ultrastructural evidence for histogenesis from pancreatic ductal epithelium. *Arch. Pathol. Lab. Med.* 100, 352-356.
- Challis B.G., Harris J., Sleigh A., Isaac I., Orme S.M., Seevaratnam N., Dhatariya K., Simpson H.L. and Semple R.K. (2014). Familial adult onset hyperinsulinism due to an activating glucokinase mutation: Implications for pharmacological glucokinase activation. *Clin. Endocrinol. (Oxf)* 81, 855-861.

- Chandrasekharappa S.C., Guru S.C., Manickam P., Olufemi S.E., Collins F.S., Emmert-Buck M.R., Debelenko L.V., Zhuang Z., Lubensky I.A., Liotta L.A., Crabtree J.S., Wang Y., Roe B.A., Weisemann J., Boguski M.S., Agarwal S.K., Kester M.B., Kim Y.S., Heppner C., Dong Q., Spiegel A.M., Burns A.L. and Marx S.J. (1997). Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* 276, 404-407.
- Choufani S., Shuman C. and Weksberg R. (2010). Beckwith-Wiedemann syndrome. *Am. J. Med. Genet. C. Semin. Med. Genet.* 154C, 343-354.
- Christesen H.B., Jacobsen B.B., Odili S., Buettger C., Cuesta-Munoz A., Hansen T., Brusgaard K., Massa O., Magnuson M.A., Shiota C., Matschinsky F.M. and Barbetti F. (2002). The second activating glucokinase mutation (A456V): Implications for glucose homeostasis and diabetes therapy. *Diabetes* 51, 1240-1246.
- Christesen H.B., Brusgaard K., Beck Nielsen H. and Brock Jacobsen B. (2008a). Non-insulinoma persistent hyperinsulinaemic hypoglycaemia caused by an activating glucokinase mutation: Hypoglycaemia unawareness and attacks. *Clin. Endocrinol. (Oxf)* 68, 747-755.
- Christesen H.B., Tribble N.D., Molven A., Siddiqui J., Sandal T., Brusgaard K., Ellard S., Njølstad P.R., Alm J., Brock Jacobsen B., Hussain K. and Gloyn A.L. (2008b). Activating glucokinase (GCK) mutations as a cause of medically responsive congenital hyperinsulinism: Prevalence in children and characterisation of a novel GCK mutation. *Eur. J. Endocrinol.* 159, 27-34.
- Christiansen C.D., Petersen H., Nielsen A.L., Detlefsen S., Brusgaard K., Rasmussen L., Melikyan M., Ekström K., Globa E., Rasmussen A.H., Hovendal C. and Christesen H.T. (2018). 18F-DOPA PET/CT and 68Ga-DOTANOC PET/CT scans as diagnostic tools in focal congenital hyperinsulinism: A blinded evaluation. *Eur. J. Nucl. Med. Mol. Imaging.* 45, 250-261.
- Christesen H.T., Christensen L.G., Löfgren Å M., Brøndum-Nielsen K., Svensson J., Brusgaard K., Samuelsson S., Elfving M., Jonson T., Grønskov K., Rasmussen L., Backman T., Hansen L.K., Larsen A.R., Petersen H. and Detlefsen S. (2020). Tissue variations of mosaic genome-wide paternal uniparental disomy and phenotype of multi-syndromal congenital hyperinsulinism. *Eur. J. Med. Genet.* 63, 103632.
- Church D., Cardoso L., Kay R.G., Williams C.L., Freudenthal B., Clarke C., Harris J., Moorthy M., Karra E., Gribble F.M., Reimann F., Burling K., Williams A.J.K., Munir A., Jones T.H., Führer D., Moeller L.C., Cohen M., Khoo B., Halsall D. and Semple R.K. (2018). Assessment and management of anti-insulin autoantibodies in varying presentations of insulin autoimmune syndrome. *J. Clin. Endocrinol. Metab.* 103, 3845-3855.
- Cooper W.N., Curley R., Macdonald F. and Maher E.R. (2007). Mitotic recombination and uniparental disomy in beckwith-wiedemann syndrome. *Genomics* 89, 613-617.
- Craigie R.J., Salomon-Estebanez M., Yau D., Han B., Mal W., Newbould M., Cheesman E., Bitetti S., Mohamed Z., Sajjan R., Padidela R., Skae M., Flanagan S., Ellard S., Cosgrove K.E., Banerjee I. and Dunne M.J. (2018). Clinical diversity in focal congenital hyperinsulinism in infancy correlates with histological heterogeneity of islet cell lesions. *Front. Endocrinol. (Lausanne)* 9, 619.
- Crétolle C., Fékété C.N., Jan D., Nassogne M.C., Saudubray J.M., Brunelle F. and Rahier J. (2002). Partial elective pancreatectomy is curative in focal form of permanent hyperinsulinemic hypoglycaemia in infancy: A report of 45 cases from 1983 to 2000. *J. Pediatr. Surg.* 37, 155-158.
- Crippa S., Zerbi A., Boninsegna L., Capitanio V., Partelli S., Balzano G., Pederzoli P., Di Carlo V. and Falconi M. (2012). Surgical management of insulinomas: Short- and long-term outcomes after enucleations and pancreatic resections. *Arch. Surg.* 147, 261-266.
- Cryer P.E., Axelrod L., Grossman A.B., Heller S.R., Montori V.M., Seaquist E.R. and Service F.J. (2009). Evaluation and management of adult hypoglycemic disorders: An endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 94, 709-728.
- Cuesta-Muñoz A.L., Huopio H., Otonkoski T., Gomez-Zumaquero J.M., Nääntö-Salonen K., Rahier J., López-Enriquez S., García-Gimeno M.A., Sanz P., Soriguer F.C. and Laakso M. (2004). Severe persistent hyperinsulinemic hypoglycemia due to a de novo glucokinase mutation. *Diabetes* 53, 2164-2168.
- Cupisti K., Höppner W., Dotzenrath C., Simon D., Berndt I., Röher H.D. and Goretzki P.E. (2000). Lack of MEN1 gene mutations in 27 sporadic insulinomas. *Eur. J. Clin. Invest.* 30, 325-329.

- Dahms B.B., Landing B.H., Blaskovics M. and Roe T.F. (1980). Nesidioblastosis and other islet cell abnormalities in hyperinsulinemic hypoglycemia of childhood. *Hum. Pathol.* 11, 641-649.
- Dahms B.B., Lippe B.M., Dakake C., Fonkalsrud E.W. and Mirra J.M. (1976). The occurrence in a neonate of a pancreatic adenoma with nesidioblastosis in the tumor. *Am. J. Clin. Pathol.* 65, 462-466.
- Damaj L., le Lorch M., Verkarre V., Werl C., Hubert L., Nihoul-Fékété C., Aigrain Y., de Keyzer Y., Romana S.P., Bellanne-Chantelot C., de Lonlay P. and Jaubert F. (2008). Chromosome 11p15 paternal isodisomy in focal forms of neonatal hyperinsulinism. *J. Clin. Endocrinol. Metab.* 93, 4941-4947.
- Dastamani A., Güemes M., Pitfield C., Morgan K., Rajab M., Rottenburger C., Bomanji J., De Coppi P., Dattani M. and Shah P. (2019). The use of a long-acting somatostatin analogue (lanreotide) in three children with focal forms of congenital hyperinsulinaemic hypoglycaemia. *Horm. Res. Paediatr.* 91, 56-61.
- de Carbonnières A., Challine A., Cottureau A.S., Coriat R., Soyer P., Abou Ali E., Prat F., Terris B., Bertherat J., Dousset B. and Gaujoux S. (2021). Surgical management of insulinoma over three decades. *HPB (Oxford)* 23, 1799-1806.
- De Franco E., Saint-Martin C., Brusgaard K., Knight Johnson A.E., Aguilar-Bryan L., Bowman P., Arnoux J.B., Larsen A.R., Sanyoura M., Greeley S.A.W., Calzada-León R., Harman B., Houghton J.A.L., Nishimura-Meguro E., Laver T.W., Ellard S., Del Gaudio D., Christesen H.T., Bellanné-Chantelot C. and Flanagan S.E. (2020). Update of variants identified in the pancreatic β -cell k_{atp} channel genes KCNJ11 and ABCC8 in individuals with congenital hyperinsulinism and diabetes. *Hum. Mutat.* 41, 884-905.
- de Herder W.W., Niederle B., Scoazec J.Y., Pauwels S., Kloppel G., Falconi M., Kwekkeboom D.J., Oberg K., Eriksson B., Wiedenmann B., Rindi G., O'Toole D. and Ferone D. (2006). Well-differentiated pancreatic tumor/carcinoma: Insulinoma. *Neuroendocrinology* 84, 183-188.
- de Lonlay-Debeney P., Poggi-Travert F., Fournet J.C., Sempoux C., Dionisi Vici C., Brunelle F., Touati G., Rahier J., Junien C., Nihoul-Fekete C., Robert J.J. and Saudubray J.M. (1999). Clinical features of 52 neonates with hyperinsulinism. *N. Engl. J. Med.* 340, 1169-1175.
- de Lonlay P., Fournet J.C., Rahier J., Gross-Morand M.S., Poggi-Travert F., Foussier V., Bonnefont J.P., Brusset M.C., Brunelle F., Robert J.J., Nihoul-Fékété C., Saudubray J.M. and Junien C. (1997). Somatic deletion of the imprinted 11p15 region in sporadic persistent hyperinsulinemic hypoglycemia of infancy is specific of focal adenomatous hyperplasia and endorses partial pancreatectomy. *J. Clin. Invest.* 100, 802-807.
- De Lonlay P., Benelli C., Fouque F., Ganguly A., Aral B., Dionisi-Vici C., Touati G., Heinrichs C., Rabier D., Kamoun P., Robert J.J., Stanley C. and Saudubray J.M. (2001). Hyperinsulinism and hyperammonemia syndrome: Report of twelve unrelated patients. *Pediatr. Res.* 50, 353-357.
- DeBaun M.R. and Tucker M.A. (1998). Risk of cancer during the first four years of life in children from the Beckwith-Wiedemann syndrome registry. *J. Pediatr.* 132, 398-400.
- DeBaun M.R., King A.A. and White N. (2000). Hypoglycemia in beckwith-wiedemann syndrome. *Semin. Perinatol.* 24, 164-171.
- Dekel B., Lubin D., Modan-Moses D., Quint J., Glaser B. and Meyerovitch J. (2002). Compound heterozygosity for the common sulfonylurea receptor mutations can cause mild diazoxide-sensitive hyperinsulinism. *Clin. Pediatr. (Phila)* 41, 183-186.
- Delonlay P., Simon A., Galmiche-Rolland L., Giurgea I., Verkarre V., Aigrain Y., Santiago-Ribeiro M.J., Polak M., Robert J.J., Bellanne-Chantelot C., Brunelle F., Nihoul-Fekete C. and Jaubert F. (2007). Neonatal hyperinsulinism: Clinicopathologic correlation. *Hum. Pathol.* 38, 387-399.
- Demeure M.J., Klonoff D.C., Karam J.H., Duh Q.Y. and Clark O.H. (1991). Insulinomas associated with multiple endocrine neoplasia type I: The need for a different surgical approach. *Surgery* 110, 998-1004; discussion 1004-1005.
- Demirbilek H., Shah P., Arya V.B., Hinchey L., Flanagan S.E., Ellard S. and Hussain K. (2014). Long-term follow-up of children with congenital hyperinsulinism on octreotide therapy. *J. Clin. Endocrinol. Metab.* 99, 3660-3667.

- Dullaart R.P., Hoogenberg K., Rouwé C.W. and Stulp B.K. (2004). Family with autosomal dominant hyperinsulinism associated with A456V mutation in the glucokinase gene. *J. Intern. Med.* 255, 143-145.
- Dunne M.J., Cosgrove K.E., Shepherd R.M., Aynsley-Green A. and Lindley K.J. (2004). Hyperinsulinism in infancy: From basic science to clinical disease. *Physiol. Rev.* 84, 239-275.
- Durmaz E., Flanagan S.E., Parlak M., Ellard S., Akcurin S. and Bircan I. (2014). A combination of nifedipine and octreotide treatment in an hyperinsulinemic hypoglycemic infant. *J. Clin. Res. Pediatr. Endocrinol.* 6, 119-121.
- Dusatkova P., Pruhova S., Sumnik Z., Kolouskova S., Obermannova B., Cinek O. and Lebl J. (2011). HNF1A mutation presenting with fetal macrosomia and hypoglycemia in childhood prior to onset of overt diabetes. *J. Pediatr. Endocrinol. Metab.* 24, 187-189.
- Dutly F., Baumer A., Kayserili H., Yüksel-Apak M., Zerova T., Hebisch G. and Schinzel A. (1998). Seven cases of Wiedmann-Beckwith syndrome, including the first reported case of mosaic paternal isodisomy along the whole chromosome 11. *Am. J. Med. Genet.* 79, 347-353.
- Eggermann T., Algar E., Lapunzina P., Mackay D., Maher E.R., Mannens M., Netchine I., Prawitt D., Riccio A., Temple I.K. and Weksberg R. (2014). Clinical utility gene card for: Beckwith-Wiedemann syndrome. *Eur. J. Hum. Genet.* 22.
- Elliott M., Bayly R., Cole T., Temple I.K. and Maher E.R. (1994). Clinical features and natural history of Beckwith-Wiedemann syndrome: Presentation of 74 new cases. *Clin. Genet.* 46, 168-174.
- Falconi M., Eriksson B., Kaltsas G., Bartsch D.K., Capdevila J., Caplin M., Kos-Kudla B., Kwekkeboom D., Rindi G., Klöppel G., Reed N., Kianmanesh R. and Jensen R.T. (2016). ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology* 103, 153-171.
- Flanagan S.E., Kapoor R.R., Mali G., Cody D., Murphy N., Schwahn B., Siahianidou T., Banerjee I., Akcay T., Rubio-Cabezas O., Shield J.P., Hussain K. and Ellard S. (2010). Diazoxide-responsive hyperinsulinemic hypoglycemia caused by HNF4A gene mutations. *Eur. J. Endocrinol.* 162, 987-992.
- Flanagan S.E., Kapoor R.R. and Hussain K. (2011a). Genetics of congenital hyperinsulinemic hypoglycemia. *Semin. Pediatr. Surg.* 20, 13-17.
- Flanagan S.E., Kapoor R.R., Banerjee I., Hall C., Smith V.V., Hussain K. and Ellard S. (2011b). Dominantly acting ABCC8 mutations in patients with medically unresponsive hyperinsulinaemic hypoglycaemia. *Clin. Genet.* 79, 582-587.
- Fottner C., Sollfrank S., Ghiasi M., Adenauer A., Musholt T., Schad A., Miederer M., Schadmand-Fischer S., Weber M.M., Lackner K.J. and Rossmann H. (2022). Second MAFA variant causing a phosphorylation defect in the transactivation domain and familial insulinomatosis. *Cancers (Basel)* 14, 1798.
- Fournet J.C., Mayaud C., de Lonlay P., Gross-Morand M.S., Verkarre V., Castanet M., Devillers M., Rahier J., Brunelle F., Robert J.J., Nihoul-Fekete C., Saudubray J.M. and Junien C. (2001). Unbalanced expression of 11p15 imprinted genes in focal forms of congenital hyperinsulinism: Association with a reduction to homozygosity of a mutation in ABCC8 or KCNJ11. *Am. J. Pathol.* 158, 2177-2184.
- Giurgea I., Sempoux C., Bellanné-Chantelot C., Ribeiro M., Hubert L., Boddaert N., Saudubray J.M., Robert J.J., Brunelle F., Rahier J., Jaubert F., Nihoul-Fékété C. and de Lonlay P. (2006a). The Knudson's two-hit model and timing of somatic mutation may account for the phenotypic diversity of focal congenital hyperinsulinism. *J. Clin. Endocrinol. Metab.* 91, 4118-4123.
- Giurgea I., Sanlaville D., Fournet J.C., Sempoux C., Bellanné-Chantelot C., Touati G., Hubert L., Groos M.S., Brunelle F., Rahier J., Henquin J.C., Dunne M.J., Jaubert F., Robert J.J., Nihoul-Fékété C., Vekemans M., Junien C. and de Lonlay P. (2006b). Congenital hyperinsulinism and mosaic abnormalities of the ploidy. *J. Med. Genet.* 43, 248-254.
- Glaser B., Kesavan P., Heyman M., Davis E., Cuesta A., Buchs A., Stanley C.A., Thornton P.S., Permutt M.A., Matschinsky F.M. and Herold K.C. (1998). Familial hyperinsulinism caused by an activating glucokinase mutation. *N. Engl. J. Med.* 338, 226-230.

- Glaser B., Ryan F., Donath M., Landau H., Stanley C.A., Baker L., Barton D.E. and Thornton P.S. (1999). Hyperinsulinism caused by paternal-specific inheritance of a recessive mutation in the sulfonylurea-receptor gene. *Diabetes* 48, 1652-1657.
- Glaser B., Blech I., Krakinovsky Y., Ekstein J., Gillis D., Mazor-Aronovitch K., Landau H. and Abeliovich D. (2011). ABCC8 mutation allele frequency in the Ashkenazi Jewish population and risk of focal hyperinsulinemic hypoglycemia. *Genet. Med.* 13, 891-894.
- Gloyn A.L., Noordam K., Willemsen M.A., Ellard S., Lam W.W., Campbell I.W., Midgley P., Shiota C., Buettger C., Magnuson M.A., Matschinsky F.M. and Hattersley A.T. (2003). Insights into the biochemical and genetic basis of glucokinase activation from naturally occurring hypoglycemia mutations. *Diabetes* 52, 2433-2440.
- Gogiel M., Begemann M., Spengler S., Soellner L., Göretzlehner U., Eggermann T. and Strobl-Wildemann G. (2013). Genome-wide paternal uniparental disomy mosaicism in a woman with Beckwith-Wiedemann syndrome and ovarian steroid cell tumour. *Eur. J. Hum. Genet.* 21, 788-791.
- Goossens A., Gepts W., Saudubray J.M., Bonnefont J.P., Nihoul F., Heitz P.U. and Klöppel G. (1989). Diffuse and focal nesidioblastosis. A clinicopathological study of 24 patients with persistent neonatal hyperinsulinemic hypoglycemia. *Am. J. Surg. Pathol.* 13, 766-775.
- Goossens A., Heitz P. and Klöppel G. (1991). Pancreatic endocrine cells and their non-neoplastic proliferations. In: Dayal, y., editor. *Endocrine pathology of the gut and pancreas*. Vol. 1. Boca raton, fl.: Crc press; 1991, 69-104.
- Goudswaard W.B., Houthoff H.J., Koudstaal J. and Zwierstra R.P. (1986). Nesidioblastosis and endocrine hyperplasia of the pancreas: A secondary phenomenon. *Hum. Pathol.* 17, 46-54.
- Grant C.S. (1998). Insulinoma. *Surg. Oncol. Clin. N. Am.* 7, 819-844.
- Gribble F.M., Tucker S.J. and Ashcroft F.M. (1997). The essential role of the walker a motifs of SUR1 in K-ATP channel activation by Mg-ADP and diazoxide. *Embo. J.* 16, 1145-1152.
- Guettier J.M. and Gorden P. (2010). Insulin secretion and insulin-producing tumors. *Expert. Rev. Endocrinol. Metab.* 5, 217-227.
- Guettier J.M., Lungu A., Goodling A., Cochran C. and Gorden P. (2013). The role of proinsulin and insulin in the diagnosis of insulinoma: A critical evaluation of the endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 98, 4752-4758.
- Gupta R.A., Patel R.P. and Nagral S. (2013). Adult onset nesidioblastosis treated by subtotal pancreatectomy. *JOP.* 14, 286-288.
- Han B., Newbould M., Batra G., Cheesman E., Craigie R.J., Mohamed Z., Rigby L., Padidela R., Skae M., Mironov A., Starborg T., Kadler K.E., Cosgrove K.E., Banerjee I. and Dunne M.J. (2016). Enhanced islet cell nucleomegaly defines diffuse congenital hyperinsulinism in infancy but not other forms of the disease. *Am. J. Clin. Pathol.* 145, 757-768.
- Han B., Mohamed Z., Estebanez M.S., Craigie R.J., Newbould M., Cheesman E., Padidela R., Skae M., Johnson M., Flanagan S., Ellard S., Cosgrove K.E., Banerjee I. and Dunne M.J. (2017). Atypical forms of congenital hyperinsulinism in infancy are associated with mosaic patterns of immature islet cells. *J. Clin. Endocrinol. Metab.* 102, 3261-3267.
- Harness J.K., Geelhoed G.W., Thompson N.W., Nishiyama R.H., Fajans S.S., Kraft R.O., Howard D.R. and Clark K.A. (1981). Nesidioblastosis in adults. A surgical dilemma. *Arch. Surg.* 116, 575-580.
- Helleskov A., Melikyan M., Globa E., Shcherderkina I., Poertner F., Larsen A.M., Filipen K., Brusgaard K., Christiansen C.D., Hansen L.K. and Christesen H.T. (2017). Both low blood glucose and insufficient treatment confer risk of neurodevelopmental impairment in congenital hyperinsulinism: A multinational cohort study. *Front. Endocrinol. (Lausanne)* 8, 156.
- Henquin J.C., Sempoux C., Marchandise J., Godecharles S., Guiot Y., Nenquin M. and Rahier J. (2013). Congenital hyperinsulinism caused by hexokinase i expression or glucokinase-activating mutation in a subset of β -cells. *Diabetes* 62, 1689-1696.

- Hewat T.I., Johnson M.B. and Flanagan S.E. (2022). Congenital hyperinsulinism: Current laboratory-based approaches to the genetic diagnosis of a heterogeneous disease. *Front. Endocrinol. (Lausanne)* 13, 873254.
- Hirshberg B., Livi A., Bartlett D.L., Libutti S.K., Alexander H.R., Doppman J.L., Skarulis M.C. and Gorden P. (2000). Forty-eight-hour fast: The diagnostic test for insulinoma. *J. Clin. Endocrinol. Metab.* 85, 3222-3226.
- Hong X., Qiao S., Li F., Wang W., Jiang R., Wu H., Chen H., Liu L., Peng J., Wang J., Jia C., Liang X., Dai H., Jiang J., Zhang T., Liao Q., Dai M., Cong L., Han X., Guo D., Liang Z., Li D., Zheng Z., Ye C., Li S., Zhao Y., Wu K. and Wu W. (2020). Whole-genome sequencing reveals distinct genetic bases for insulinomas and non-functional pancreatic neuroendocrine tumours: Leading to a new classification system. *Gut*. 69, 877-887.
- Hsu B.Y., Kelly A., Thornton P.S., Greenberg C.R., Dilling L.A. and Stanley C.A. (2001). Protein-sensitive and fasting hypoglycemia in children with the hyperinsulinism/hyperammonemia syndrome. *J. Pediatr.* 138, 383-389.
- Huopio H., Reimann F., Ashfield R., Komulainen J., Lenko H.L., Rahier J., Vauhkonen I., Kere J., Laakso M., Ashcroft F. and Otonkoski T. (2000). Dominantly inherited hyperinsulinism caused by a mutation in the sulfonylurea receptor type 1. *J. Clin. Invest.* 106, 897-906.
- Hussain K., Cosgrove K.E., Shepherd R.M., Luharia A., Smith V.V., Kassem S., Gregory J.W., Sivaprasadarao A., Christesen H.T., Jacobsen B.B., Brusgaard K., Glaser B., Maher E.A., Lindley K.J., Hindmarsh P., Dattani M. and Dunne M.J. (2005). Hyperinsulinemic hypoglycemia in Beckwith-Wiedemann syndrome due to defects in the function of pancreatic beta-cell adenosine triphosphate-sensitive potassium channels. *J. Clin. Endocrinol. Metab.* 90, 4376-4382.
- Hussain K., Seppänen M., Nääntö-Salonen K., Adzick N.S., Stanley C.A., Thornton P. and Minn H. (2006). The diagnosis of ectopic focal hyperinsulinism of infancy with [18F]-dopa positron emission tomography. *J. Clin. Endocrinol. Metab.* 91, 2839-2842.
- Hussain K., Flanagan S.E., Smith V.V., Ashworth M., Day M., Pierro A. and Ellard S. (2008). An ABCC8 gene mutation and mosaic uniparental isodisomy resulting in atypical diffuse congenital hyperinsulinism. *Diabetes* 57, 259-263.
- Iacovazzo D., Flanagan S.E., Walker E., Quezado R., de Sousa Barros F.A., Caswell R., Johnson M.B., Wakeling M., Brändle M., Guo M., Dang M.N., Gabrovská P., Niederle B., Christ E., Jenni S., Sipos B., Nieser M., Frilling A., Dhatriya K., Chanson P., de Herder W.W., Konukiewicz B., Klöppel G., Stein R., Korbonits M. and Ellard S. (2018). *MAFA* missense mutation causes familial insulinomatosis and diabetes mellitus. *Proc. Natl. Acad. Sci. USA* 115, 1027-1032.
- Ismail D., Smith V.V., de Lonlay P., Ribeiro M.J., Rahier J., Blankenstein O., Flanagan S.E., Bellanné-Chantelot C., Verkarre V., Aigrain Y., Pierro A., Ellard S. and Hussain K. (2011). Familial focal congenital hyperinsulinism. *J. Clin. Endocrinol. Metab.* 96, 24-28.
- Ismail D., Kapoor R.R., Smith V.V., Ashworth M., Blankenstein O., Pierro A., Flanagan S.E., Ellard S. and Hussain K. (2012). The heterogeneity of focal forms of congenital hyperinsulinism. *J. Clin. Endocrinol. Metab.* 97, E94-99.
- Jabri A.L. and Bayard C. (2004). Nesidioblastosis associated with hyperinsulinemic hypoglycemia in adults: Review of the literature. *Eur. J. Intern. Med.* 15, 407-410.
- Jaffe R., Hashida Y. and Yunis E.J. (1980). Pancreatic pathology in hyperinsulinemic hypoglycemia of infancy. *Lab. Invest.* 42, 356-365.
- Jaffe R., Hashida Y. and Yunis E.J. (1982). The endocrine pancreas of the neonate and infant. *Perspect. Pediatr. Pathol.* 7, 137-165.
- Jaksic T., Yaman M., Thorner P., Wesson D.K., Filler R.M. and Shandling B. (1992). A 20-year review of pediatric pancreatic tumors. *J. Pediatr. Surg.* 27, 1315-1317.
- Janem W., Sultan I., Ajlouni F., Deebajeh R., Haddad H., Sughayer M.A. and Goussous R.Y. (2010). Malignant insulinoma in a child. *Pediatr. Blood Cancer*. 55, 1423-1426.

- Jannin A., Espiard S., Douillard C., Pasquier F., Bellanné-Chantelot C. and Vantyghem M.C. (2018). Hyperinsulinemic hypoglycemia without insulinoma: Think of activating glucokinase mutation. *Presse Med.* 47, 595-597.
- Jonkers Y.M., Claessen S.M., Perren A., Schmid S., Komminoth P., Verhofstad A.A., Hofland L.J., de Krijger R.R., Slootweg P.J., Ramaekers F.C. and Speel E.J. (2005). Chromosomal instability predicts metastatic disease in patients with insulinomas. *Endocr. Relat. Cancer.* 12, 435-447.
- Kaczirek K., Soleiman A., Schindl M., Passler C., Scheuba C., Prager G., Kaserer K. and Niederle B. (2003). Nesidioblastosis in adults: A challenging cause of organic hyperinsulinism. *Eur. J. Clin. Invest.* 33, 488-492.
- Kaczirek K. and Niederle B. (2004). Nesidioblastosis: An old term and a new understanding. *World. J. Surg.* 28, 1227-1230.
- Kalish J.M., Conlin L.K., Bhatti T.R., Dubbs H.A., Harris M.C., Izumi K., Mostoufi-Moab S., Mulchandani S., Saitta S., States L.J., Swarr D.T., Wilkens A.B., Zackai E.H., Zelle K., Bartolomei M.S., Nichols K.E., Palladino A.A., Spinner N.B. and Deardorff M.A. (2013). Clinical features of three girls with mosaic genome-wide paternal uniparental isodisomy. *Am. J. Med. Genet. A* 161a, 1929-1939.
- Kalish J.M., Boodhansingh K.E., Bhatti T.R., Ganguly A., Conlin L.K., Becker S.A., Givler S., Mighion L., Palladino A.A., Adzick N.S., De León D.D., Stanley C.A. and Deardorff M.A. (2016). Congenital hyperinsulinism in children with paternal 11p uniparental isodisomy and Beckwith-Wiedemann syndrome. *J. Med. Genet.* 53, 53-61.
- Kapoor R.R., Locke J., Colclough K., Wales J., Conn J.J., Hattersley A.T., Ellard S. and Hussain K. (2008). Persistent hyperinsulinemic hypoglycemia and maturity-onset diabetes of the young due to heterozygous HNF4A mutations. *Diabetes* 57, 1659-1663.
- Kapoor R.R., Flanagan S.E., Fulton P., Chakrapani A., Chadeaux B., Ben-Omran T., Banerjee I., Shield J.P., Ellard S. and Hussain K. (2009). Hyperinsulinism-hyperammonaemia syndrome: Novel mutations in the GLUD1 gene and genotype-phenotype correlations. *Eur. J. Endocrinol.* 161, 731-735.
- Kapoor R.R., Flanagan S.E., James C.T., McKiernan J., Thomas A.M., Harmer S.C., Shield J.P., Tinker A., Ellard S. and Hussain K. (2011). Hyperinsulinaemic hypoglycaemia and diabetes mellitus due to dominant ABCC8/KCNJ11 mutations. *Diabetologia* 54, 2575-2583.
- Kapoor R.R., Flanagan S.E., Arya V.B., Shield J.P., Ellard S. and Hussain K. (2013). Clinical and molecular characterisation of 300 patients with congenital hyperinsulinism. *Eur. J. Endocrinol.* 168, 557-564.
- Kassem S.A., Ariel I., Thornton P.S., Scheimberg I. and Glaser B. (2000). Beta-cell proliferation and apoptosis in the developing normal human pancreas and in hyperinsulinism of infancy. *Diabetes* 49, 1325-1333.
- Kassem S.A., Ariel I., Thornton P.S., Hussain K., Smith V., Lindley K.J., Aynsley-Green A. and Glaser B. (2001). P57(KIP2) expression in normal islet cells and in hyperinsulinism of infancy. *Diabetes* 50, 2763-2769.
- Kassem S., Bhandari S., Rodríguez-Bada P., Motaghedi R., Heyman M., García-Gimeno M.A., Cobo-Vuilleumier N., Sanz P., Maclaren N.K., Rahier J., Glaser B. and Cuesta-Muñoz A.L. (2010). Large islets, beta-cell proliferation, and a glucokinase mutation. *N. Engl. J. Med.* 362, 1348-1350.
- Klöppel G., Altenähr E. and Menke B. (1975). The ultrastructure of focal islet cell adenomatosis in the newborn with hypoglycemia and hyperinsulinism. *Virchows Arch. A. Pathol. Anat. Histol.* 366, 223-236.
- Klöppel G. and Heitz P.U. (1984). Nesidioblastosis: A clinical entity with heterogeneous lesions of the pancreas. In: Falkmer, S., Håkanson R. and Sundler, F., editors Amsterdam, The Netherlands: Elsevier *Evolution and Tumour Pathology of the Neuroendocrine System*, 349-370.
- Klöppel G. and Heitz P.U. (1988). Pancreatic endocrine tumors. *Pathol. Res. Pract.* 183, 155-168.
- Klöppel G., Reinecke-Lüthge A. and Koschoreck F. (1999). Focal and diffuse beta cell changes in persistent hyperinsulinemic hypoglycemia of infancy. *Endocr. Pathol.* 10, 299-304.
- Kloppel G., Anlauf M., Raffel A., Perren A. and Knoefel W.T. (2008). Adult diffuse nesidioblastosis: Genetically or environmentally induced? *Hum. Pathol.* 39, 3-8.

- Kocaay P., Şiklar Z., Ellard S., Yagmurlu A., Çamtosun E., Erden E., Berberoglu M. and Flanagan S.E. (2016). Coexistence of mosaic uniparental isodisomy and a KCNJ11 mutation presenting as diffuse congenital hyperinsulinism and hemihypertrophy. *Horm. Res. Paediatr.* 85, 421-425.
- Komminoth P., Heitz P.U. and Roth J. (1999). Human insulinomas: Clinical, cellular, and molecular aspects. *Endocr. Pathol.* 10, 269-281.
- Kostopoulou E., Dastamani A., Güemes M., Clement E., Caiulo S., Shanmugananda P., Dattani M., Gilbert C., Hurst J.A. and Shah P. (2021). Syndromic forms of hyperinsulinaemic hypoglycaemia-a 15-year follow-up study. *Clin. Endocrinol. (Oxf)* 94, 399-412.
- Kumaran A., Kapoor R.R., Flanagan S.E., Ellard S. and Hussain K. (2010). Congenital hyperinsulinism due to a compound heterozygous ABCC8 mutation with spontaneous resolution at eight weeks. *Horm. Res. Paediatr.* 73, 287-292.
- Kurakawa K.I., Okada A., Manaka K., Konishi T., Jo T., Ono S., Uda K., Michihata N., Matsui H., Fushimi K., Yamaguchi S., Yamauchi T., Nangaku M., Yasunaga H. and Kadowaki T. (2021). Clinical characteristics and incidences of benign and malignant insulinoma using a national inpatient database in Japan. *J. Clin. Endocrinol. Metab.* 106, 3477-3486.
- Kühnen P., Matthae R., Arya V., Hauptmann K., Rothe K., Wächter S., Singer M., Mohnike W., Eberhard T., Raile K., Lauffer L.M., Jakoubov R., Hussain K. and Blankenstein O. (2014). Occurrence of giant focal forms of congenital hyperinsulinism with incorrect visualization by (18) F DOPA-PET/CT scanning. *Clin. Endocrinol. (Oxf)* 81, 847-854.
- Laidlaw G.F. (1938). Nesidioblastoma, the islet tumor of the pancreas. *Am. J. Pathol.* 14, 125-134.125.
- Laje P., Palladino A.A., Bhatti T.R., States L.J., Stanley C.A. and Adzick N.S. (2013a). Pancreatic surgery in infants with Beckwith-Wiedemann syndrome and hyperinsulinism. *J. Pediatr. Surg.* 48, 2511-2516.
- Laje P., States L.J., Zhuang H., Becker S.A., Palladino A.A., Stanley C.A. and Adzick N.S. (2013b). Accuracy of PET/CT scan in the diagnosis of the focal form of congenital hyperinsulinism. *J. Pediatr. Surg.* 48, 388-393.
- Langer S., Waterstradt R., Hillebrand G., Santer R. and Baltrusch S. (2021). The novel GCK variant p.Val455Leu associated with hyperinsulinism is susceptible to allosteric activation and is conducive to weight gain and the development of diabetes. *Diabetologia* 64, 2687-2700.
- Larsson C., Skogseid B., Oberg K., Nakamura Y. and Nordenskjöld M. (1988). Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. *Nature* 332, 85-87.
- Le Quan Sang K.H., Arnoux J.B., Mamoune A., Saint-Martin C., Bellanné-Chantelot C., Valayannopoulos V., Brassier A., Kayirangwa H., Barbier V., Broissand C., Fabreguettes J.R., Charron B., Thalabard J.C. and de Lonlay P. (2012). Successful treatment of congenital hyperinsulinism with long-acting release octreotide. *Eur. J. Endocrinol.* 166, 333-339.
- Liang J., Chirikjian M., Pajvani U.B. and Bartolomé A. (2022). MafA regulation in β -cells: From transcriptional to post-translational mechanisms. *Biomolecules* 12, 535.
- Liu H.M. and Potter E.L. (1962). Development of the human pancreas. *Arch. Pathol.* 74, 439-452.
- Liu T.H., Tseng H.C., Zhu Y., Zhong S.X., Chen J. and Cui Q.C. (1985). Insulinoma. An immunocytochemical and morphologic analysis of 95 cases. *Cancer* 56, 1420-1429.
- Lloyd R.V.O., R.Y.; Klöppel.G.; Rosai, J. (2017). W. Health organization, who classification of tumours of endocrine organs. I. Agency for research on cancer. World Health Organization classification of tumours, 10th, 4th edition 209-239.
- Longnecker D.S. (2021). Anatomy and histology of the pancreas.
- Lord K. and De León D.D. (2013). Monogenic hyperinsulinemic hypoglycemia: Current insights into the pathogenesis and management. *Int. J. Pediatr. Endocrinol.* 2013, 3.
- Lord K., Dzata E., Snider K.E., Gallagher P.R. and De León D.D. (2013). Clinical presentation and management of children with diffuse and focal hyperinsulinism: A review of 223 cases. *J. Clin. Endocrinol. Metab.* 98, E1786-1789.

- Lord K., Radcliffe J., Gallagher P.R., Adzick N.S., Stanley C.A. and De León D.D. (2015). High risk of diabetes and neurobehavioral deficits in individuals with surgically treated hyperinsulinism. *J. Clin. Endocrinol. Metab.* 100, 4133-4139.
- Lord K. (2019). Neurodevelopmental outcomes. In: De León-crutchlow dd, stanley ca, editors. *Congenital hyperinsulinism a practical guide to diagnosis and management*.
- Lord K. and De León D.D. (2020). Meeting report: Updates in diagnosis and management of hyperinsulinism and neonatal hypoglycemia: Highlights from the fourth international hyperinsulinism symposium. *Pediatr. Endocrinol. Rev.* 17, 268-277.
- Lovvorn H.N., 3rd, Nance M.L., Ferry R.J., Jr., Stolte L., Baker L., O'Neill J.A., Jr., Schnaufer L., Stanley C.A. and Adzick N.S. (1999). Congenital hyperinsulinism and the surgeon: Lessons learned over 35 years. *J. Pediatr. Surg.* 34, 786-792; discussion 792-783.
- MacMullen C., Fang J., Hsu B.Y., Kelly A., de Lonlay-Debeney P., Saudubray J.M., Ganguly A., Smith T.J. and Stanley C.A. (2001). Hyperinsulinism/hyperammonemia syndrome in children with regulatory mutations in the inhibitory guanosine triphosphate-binding domain of glutamate dehydrogenase. *J. Clin. Endocrinol. Metab.* 86, 1782-1787.
- Macmullen C.M., Zhou Q., Snider K.E., Tewson P.H., Becker S.A., Aziz A.R., Ganguly A., Shyng S.L. and Stanley C.A. (2011). Diazoxide-unresponsive congenital hyperinsulinism in children with dominant mutations of the β -cell sulfonylurea receptor SUR1. *Diabetes* 60, 1797-1804.
- Maiorana A., Barbetti F., Boiani A., Rufini V., Pizzoferrero M., Francalanci P., Faletra F., Nichols C.G., Grimaldi C., de Ville de Goyet J., Rahier J., Henquin J.C. and Dionisi-Vici C. (2014). Focal congenital hyperinsulinism managed by medical treatment: A diagnostic algorithm based on molecular genetic screening. *Clin. Endocrinol. (Oxf)* 81, 679-688.
- Mann J.R., Rayner P.H. and Gourevitch A. (1969). Insulinoma in childhood. *Arch. Dis. Child.* 44, 435-442.
- Martínez R., Gutierrez-Nogués Á., Fernández-Ramos C., Velayos T., Vela A., Navas M. and Castaño L. (2017). Heterogeneity in phenotype of hyperinsulinism caused by activating glucokinase mutations: A novel mutation and its functional characterization. *Clin. Endocrinol. (Oxf)* 86, 778-783.
- Matej A., Bujwid H. and Wroński J. (2016). Glycemic control in patients with insulinoma. *Hormones (Athens)* 15, 489-499.
- Mathur A., Gorden P. and Libutti S.K. (2009). Insulinoma. *Surg. Clin. North. Am.* 89, 1105-1121.
- Mazor-Aronovitch K., Gillis D., Lobel D., Hirsch H.J., Pinhas-Hamiel O., Modan-Moses D., Glaser B. and Landau H. (2007). Long-term neurodevelopmental outcome in conservatively treated congenital hyperinsulinism. *Eur. J. Endocrinol.* 157, 491-497.
- McGlacken-Byrne S.M., Hawkes C.P., Flanagan S.E., Ellard S., McDonnell C.M. and Murphy N.P. (2014). The evolving course of HNF4A hyperinsulinaemic hypoglycaemia--a case series. *Diabet Med* 31, e1-5.
- McGlacken-Byrne S.M., Mohammad J.K., Conlon N., Gubaeva D., Siersbæk J., Schou A.J., Demirbilek H., Dastamani A., Houghton J.A.L., Brusgaard K., Melikyan M., Christesen H., Flanagan S.E., Murphy N.P. and Shah P. (2022). Clinical and genetic heterogeneity of HNF4A/HNF1A mutations in a multicentre paediatric cohort with hyperinsulinaemic hypoglycaemia. *Eur. J. Endocrinol.* 186, 417-427.
- Meissner T., Wendel U., Burgard P., Schaetzle S. and Mayatepek E. (2003). Long-term follow-up of 114 patients with congenital hyperinsulinism. *Eur. J. Endocrinol.* 149, 43-51.
- Meissner T., Marquard J., Cobo-Vuilleumier N., Maringa M., Rodríguez-Bada P., García-Gimeno M.A., Baixeras E., Weber J., Olek K., Sanz P., Mayatepek E. and Cuesta-Muñoz A.L. (2009). Diagnostic difficulties in glucokinase hyperinsulinism. *Horm. Metab. Res.* 41, 320-326.
- Melikyan M., Gubaeva D., Shadrina A., Bolmasova A., Kareva M., Tiulpakov A., Efremenkova A., Sokolov Y., Brusgaard K., Christesen H.T., Andersen K., Stepanov A., Averyanova J., Makarov S. and Gurevich L. (2023). Insulinoma in childhood: A retrospective review of 22 patients from one referral centre. *Front. Endocrinol. (Lausanne)* 14, 1127173.
- Miller H.C., Kidd M., Modlin I.M., Cohen P., Dina R., Drymoussis P., Vlavianos P., Klöppel G. and Frilling A. (2015). Glucagon receptor gene mutations with hyperglucagonemia but without the glucagonoma syndrome. *World J. Gastrointest. Surg.* 7, 60-66.

- Mintziras I., Peer K., Goerlach J., Goebel J.N., Ramaswamy A., Slater E.P., Kann P.H. and Bartsch D.K. (2021). Adult proinsulinomatosis associated with a MAFA germline mutation as a rare cause of recurrent hypoglycemia. *Pancreas* 50, 1450-1453.
- Mohnike K., Blankenstein O., Christesen H.T., De Lonlay J., Hussain K., Koopmans K.P., Minn H., Mohnike W., Mutair A., Otonkoski T., Rahier J., Ribeiro M., Schoenle E. and Fékété C.N. (2006). Proposal for a standardized protocol for 18F-DOPA-PET (PET/CT) in congenital hyperinsulinism. *Horm. Res.* 66, 40-42.
- Mohnike K., Wieland I., Barthlen W., Vogelgesang S., Empting S., Mohnike W., Meissner T. and Zenker M. (2014). Clinical and genetic evaluation of patients with KATP channel mutations from the german registry for congenital hyperinsulinism. *Horm. Res. Paediatr.* 81, 156-168.
- Mussa A., Russo S., De Crescenzo A., Chiesa N., Molinatto C., Selicorni A., Richiardi L., Larizza L., Silengo M.C., Riccio A. and Ferrero G.B. (2013). Prevalence of Beckwith-Wiedemann syndrome in north west of Italy. *Am. J. Med. Genet.* 161A, 2481-2486.
- Mussa A., Di Candia S., Russo S., Catania S., De Pellegrin M., Di Luzio L., Ferrari M., Tortora C., Meazzini M.C., Brusati R., Milani D., Zampino G., Montirosso R., Riccio A., Selicorni A., Cocchi G. and Ferrero G.B. (2016a). Recommendations of the scientific committee of the Italian Beckwith-Wiedemann syndrome association on the diagnosis, management and follow-up of the syndrome. *Eur. J. Med. Genet.* 59, 52-64.
- Mussa A., Russo S., De Crescenzo A., Freschi A., Calzari L., Maitz S., Macchiaiolo M., Molinatto C., Baldassarre G., Mariani M., Tarani L., Bedeschi M.F., Milani D., Melis D., Bartuli A., Cubellis M.V., Selicorni A., Cirillo Silengo M., Larizza L., Riccio A. and Ferrero G.B. (2016b). (Epi)genotype-phenotype correlations in Beckwith-Wiedemann syndrome. *Eur. J. Hum. Genet.* 24, 183-190.
- Maas S.M., Vansenne F., Kadouch D.J., Ibrahim A., Blik J., Hopman S., Mannens M.M., Merks J.H., Maher E.R. and Hennekam R.C. (2016). Phenotype, cancer risk, and surveillance in Beckwith-Wiedemann syndrome depending on molecular genetic subgroups. *Am. J. Med. Genet. A* 170, 2248-2260.
- Nessa A., Aziz Q.H., Thomas A.M., Harmer S.C., Tinker A. and Hussain K. (2015). Molecular mechanisms of congenital hyperinsulinism due to autosomal dominant mutations in ABCC8. *Hum. Mol. Genet.* 24, 5142-5153.
- Ni J., Ge J., Zhang M., Hussain K., Guan Y., Cheng R., Xi L., Zheng Z., Ren S. and Luo F. (2019). Genotype and phenotype analysis of a cohort of patients with congenital hyperinsulinism based on DOPA-PET CT scanning. *Eur. J. Pediatr.* 178, 1161-1169.
- Niitsu Y., Minami I., Izumiyama H., Hashimoto K., Yoshimoto T., Satou F., Tsujino M., Ota K., Kudo A., Tanabe M., Yamada T. and Ogawa Y. (2019). Clinical outcomes of 20 Japanese patients with insulinoma treated with diazoxide. *Endocr. J.* 66, 149-155.
- Öberg K. (2018). Management of functional neuroendocrine tumors of the pancreas. *Gland. Surg.* 7, 20-27.
- Oçal G., Flanagan S.E., Hacıhamdioğlu B., Berberoğlu M., Siklar Z., Ellard S., Savas Erdevi S., Okulu E., Akin I.M., Atasay B., Arsan S. and Yağmurlu A. (2011). Clinical characteristics of recessive and dominant congenital hyperinsulinism due to mutation(s) in the ABCC8/KCNJ11 genes encoding the ATP-sensitive potassium channel in the pancreatic beta cell. *J. Pediatr. Endocrinol. Metab.* 24, 1019-1023.
- Otonkoski T., Ammälä C., Huopio H., Cote G.J., Chapman J., Cosgrove K., Ashfield R., Huang E., Komulainen J., Ashcroft F.M., Dunne M.J., Kere J. and Thomas P.M. (1999). A point mutation inactivating the sulfonylurea receptor causes the severe form of persistent hyperinsulinemic hypoglycemia of infancy in Finland. *Diabetes* 48, 408-415.
- Otonkoski T., Kaminen N., Ustinov J., Lapatto R., Meissner T., Mayatepek E., Kere J. and Sipilä I. (2003). Physical exercise-induced hyperinsulinemic hypoglycemia is an autosomal-dominant trait characterized by abnormal pyruvate-induced insulin release. *Diabetes* 52, 199-204.
- Otonkoski T., Nääntö-Salonen K., Seppänen M., Veijola R., Huopio H., Hussain K., Tapanainen P., Eskola O., Parkkola R., Ekström K., Guiot Y., Rahier J., Laakso M., Rintala R., Nuutila P. and Minn H. (2006). Noninvasive diagnosis of focal hyperinsulinism of infancy with [18F]-DOPA positron emission tomography. *Diabetes* 55, 13-18.

- Otonkoski T., Jiao H., Kaminen-Ahola N., Tapia-Paez I., Ullah M.S., Parton L.E., Schuit F., Quintens R., Sipilä I., Mayatepek E., Meissner T., Halestrap A.P., Rutter G.A. and Kere J. (2007). Physical exercise-induced hypoglycemia caused by failed silencing of monocarboxylate transporter 1 in pancreatic beta cells. *Am. J. Hum. Genet.* 81, 467-474.
- Ouyang D., Dhall D. and Yu R. (2011). Pathologic pancreatic endocrine cell hyperplasia. *World J. Gastroenterol.* 17, 137-143.
- Padidela R., Fiest M., Arya V., Smith V.V., Ashworth M., Rampling D., Newbould M., Batra G., James J., Wright N.B., Dunne M.J., Clayton P.E., Banerjee I. and Hussain K. (2014). Insulinoma in childhood: Clinical, radiological, molecular and histological aspects of nine patients. *Eur. J. Endocrinol.* 170, 741-747.
- Palladino A.A. and Stanley C.A. (2010). The hyperinsulinism/hyperammonemia syndrome. *Rev. Endocr. Metab. Disord.* 11, 171-178.
- Pearson E.R., Boj S.F., Steele A.M., Barrett T., Stals K., Shield J.P., Ellard S., Ferrer J. and Hattersley A.T. (2007). Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. *PLoS Med.* 4, e118.
- Périgny M., Hammel P., Corcos O., Larochelle O., Giraud S., Richard S., Sauvanet A., Belghiti J., Ruzsniowski P., Bedossa P. and Couvelard A. (2009). Pancreatic endocrine microadenomatosis in patients with von hippel-lindau disease: Characterization by VHL/HIF pathway proteins expression. *Am. J. Surg. Pathol.* 33, 739-748.
- Petrik J., Arany E., McDonald T.J. and Hill D.J. (1998). Apoptosis in the pancreatic islet cells of the neonatal rat is associated with a reduced expression of insulin-like growth factor II that may act as a survival factor. *Endocrinology* 139, 2994-3004.
- Petrik J., Pell J.M., Arany E., McDonald T.J., Dean W.L., Reik W. and Hill D.J. (1999). Overexpression of insulin-like growth factor-ii in transgenic mice is associated with pancreatic islet cell hyperplasia. *Endocrinology* 140, 2353-2363.
- Pierro A. and Nah S.A. (2011). Surgical management of congenital hyperinsulinism of infancy. *Semin. Pediatr. Surg.* 20, 50-53.
- Ping F., Wang Z. and Xiao X. (2019). Clinical and enzymatic phenotypes in congenital hyperinsulinemic hypoglycemia due to glucokinase-activating mutations: A report of two cases and a brief overview of the literature. *J. Diabetes. Investig.* 10, 1454-1462.
- Pinney S.E., MacMullen C., Becker S., Lin Y.W., Hanna C., Thornton P., Ganguly A., Shyng S.L. and Stanley C.A. (2008). Clinical characteristics and biochemical mechanisms of congenital hyperinsulinism associated with dominant KATP channel mutations. *J. Clin. Invest.* 118, 2877-2886.
- Pinney S.E., Ganapathy K., Bradfield J., Stokes D., Sasson A., Mackiewicz K., Boodhansingh K., Hughes N., Becker S., Givler S., Macmullen C., Monos D., Ganguly A., Hakonarson H. and Stanley C.A. (2013). Dominant form of congenital hyperinsulinism maps to HK1 region on 10q. *Horm. Res. Paediatr.* 80, 18-27.
- Placzkowski K.A., Vella A., Thompson G.B., Grant C.S., Reading C.C., Charboneau J.W., Andrews J.C., Lloyd R.V. and Service F.J. (2009). Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987-2007. *J. Clin. Endocrinol. Metab.* 94, 1069-1073.
- Prosperi D., Gentiloni Silveri G., Panzuto F., Faggiano A., Russo V.M., Caruso D., Polici M., Lauri C., Filice A., Laghi A. and Signore A. (2022). Nuclear medicine and radiological imaging of pancreatic neuroendocrine neoplasms: A multidisciplinary update. *J. Clin. Med.* 11.
- Raffel A., Krausch M.M., Anlauf M., Wieben D., Braunstein S., Klöppel G., Röher H.D. and Knoefel W.T. (2007). Diffuse nesidioblastosis as a cause of hyperinsulinemic hypoglycemia in adults: A diagnostic and therapeutic challenge. *Surgery* 141, 179-184; discussion 185-176.
- Rahier J., Wallon J. and Henquin J.C. (1981). Cell populations in the endocrine pancreas of human neonates and infants. *Diabetologia* 20, 540-546.
- Rahier J., Guiot Y. and Sempoux C. (2011). Morphologic analysis of focal and diffuse forms of congenital hyperinsulinism. *Semin. Pediatr. Surg.* 20, 3-12.

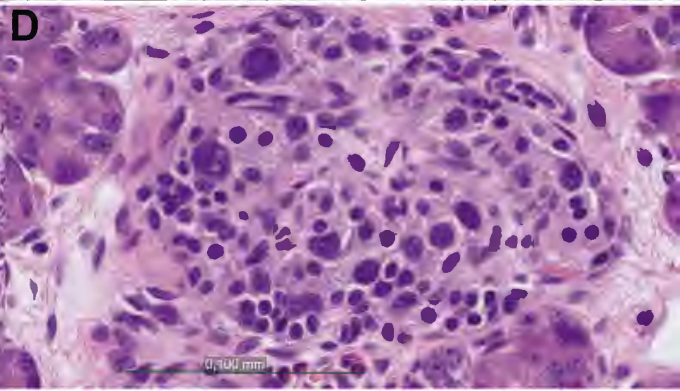
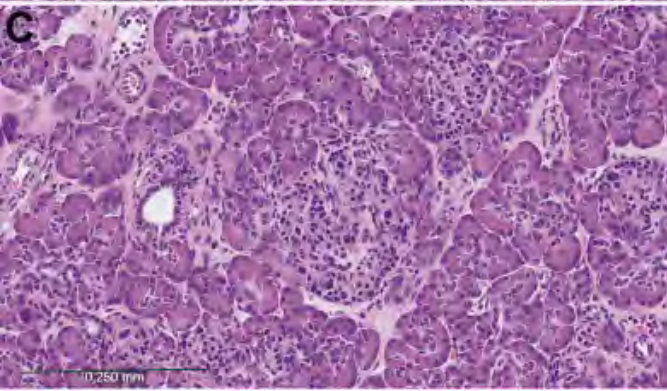
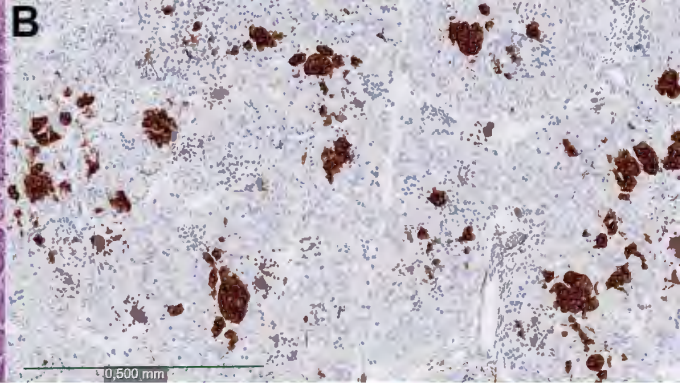
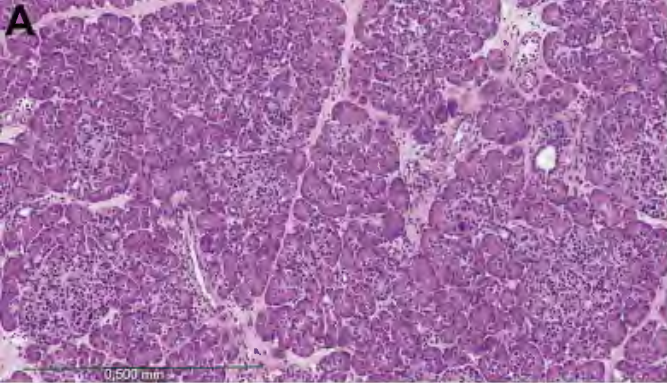
- Rahier J., Fält K., Müntefering H., Becker K., Gepts W. and Falkmer S. (1984). The basic structural lesion of persistent neonatal hypoglycaemia with hyperinsulinism: Deficiency of pancreatic D cells or hyperactivity of B cells? *Diabetologia* 26, 282-289.
- Rahier J., Sempoux C., Fournet J.C., Poggi F., Brunelle F., Nihoul-Fekete C., Saudubray J.M. and Jaubert F. (1998). Partial or near-total pancreatectomy for persistent neonatal hyperinsulinaemic hypoglycaemia: The pathologist's role. *Histopathology* 32, 15-19.
- Rasmussen A.G., Melikian M., Globa E., Detlefsen S., Rasmussen L., Petersen H., Brusgaard K., Rasmussen A.H., Mortensen M.B. and Christesen H.T. (2020a). The difficult management of persistent, non-focal congenital hyperinsulinism: A retrospective review from a single, tertiary center. *Pediatr. Diabetes* 21, 441-455.
- Rasmussen A.H., Wehberg S., Pørtner F., Larsen A.M., Filipssen K. and Christesen H.T. (2020b). Correction to: Neurodevelopmental outcomes after moderate to severe neonatal hypoglycemia. *Eur. J. Pediatr.* 179, 1993.
- Rosenfeld E., Ganguly A. and De Leon D.D. (2019). Congenital hyperinsulinism disorders: Genetic and clinical characteristics. *Am. J. Med. Genet. C. Semin. Med. Genet.* 181, 682-692.
- Rosenfeld E., Mitteer L., Boodhansingh K., Becker S.A., McKnight H., Boyajian L., Ackermann A.M., Kalish J.M., Bhatti T.R., States L.J., Adzick N.S., Lord K. and De León D.D. (2021). Case report: Two distinct focal congenital hyperinsulinism lesions resulting from separate genetic events. *Front. Pediatr.* 9, 699129.
- Roth J., Klöppel G., Madsen O.D., Storch M.J. and Heitz P.U. (1992). Distribution patterns of proinsulin and insulin in human insulinomas: An immunohistochemical analysis in 76 tumors. *Virchows Arch. B Cell Pathol. Incl. Mol. Pathol.* 63, 51-61.
- Roy K., Satapathy A.K., Houhton J.A.L., Flanagan S.E., Radha V., Mohan V., Sharma R. and Jain V. (2019). Congenital hyperinsulinemic hypoglycemia and hyperammonemia due to pathogenic variants in *GLUD1*. *Indian J. Pediatr.* 86, 1051-1053.
- Ryan F., Devaney D., Joyce C., Nestorowicz A., Permutt M.A., Glaser B., Barton D.E. and Thornton P.S. (1998). Hyperinsulinism: Molecular aetiology of focal disease. *Arch. Dis. Child.* 79, 445-447.
- Sada A., Yamashita T.S., Glasgow A.E., Habermann E.B., Thompson G.B., Lyden M.L., Dy B.M., Halfdanarson T.R., Vella A. and McKenzie T.J. (2021). Comparison of benign and malignant insulinoma. *Am. J. Surg.* 221, 437-447.
- Sahloul R., Yaqub N., Driscoll H.K., Leidy J.W., Jr., Parkash J., Matthews K.A. and Chertow B.S. (2007). Noninsulinoma pancreatogenous hypoglycemia syndrome: Quantitative and immunohistochemical analyses of islet cells for insulin, glucagon, somatostatin, and pancreatic and duodenal homeobox protein. *Endocr. Pract.* 13, 187-193.
- Salomon-Estebanez M., Flanagan S.E., Ellard S., Rigby L., Bowden L., Mohamed Z., Nicholson J., Skae M., Hall C., Craigie R., Padidela R., Murphy N., Randell T., Cosgrove K.E., Dunne M.J. and Banerjee I. (2016). Conservatively treated congenital hyperinsulinism (CHI) due to K-ATP channel gene mutations: Reducing severity over time. *Orphanet J. Rare. Dis.* 11, 163.
- Santer R., Kinner M., Passarge M., Superti-Furga A., Mayatepek E., Meissner T., Schneppenheim R. and Schaub J. (2001). Novel missense mutations outside the allosteric domain of glutamate dehydrogenase are prevalent in european patients with the congenital hyperinsulinism-hyperammonemia syndrome. *Hum. Genet.* 108, 66-71.
- Sayed S., Langdon D.R., Odili S., Chen P., Buettger C., Schiffman A.B., Suchi M., Taub R., Grimsby J., Matschinsky F.M. and Stanley C.A. (2009). Extremes of clinical and enzymatic phenotypes in children with hyperinsulinism caused by glucokinase activating mutations. *Diabetes* 58, 1419-1427.
- Schwartz J.F. and Zwiren G.T. (1971). Islet cell adenomatosis and adenoma in an infant. *J. Pediatr.* 79, 232-238.
- Scully R.E., Galdabini J.J. and McNeely B.U. (1978). Case records of the massachusetts general hospital. Weekly clinicopathological exercises. Case 30-1978. *N. Engl. J. Med.* 299, 241-248.
- Sempoux C., Guiot Y., Jaubert F. and Rahier J. (2004). Focal and diffuse forms of congenital hyperinsulinism: The keys for differential diagnosis. *Endocr. Pathol.* 15, 241-246.

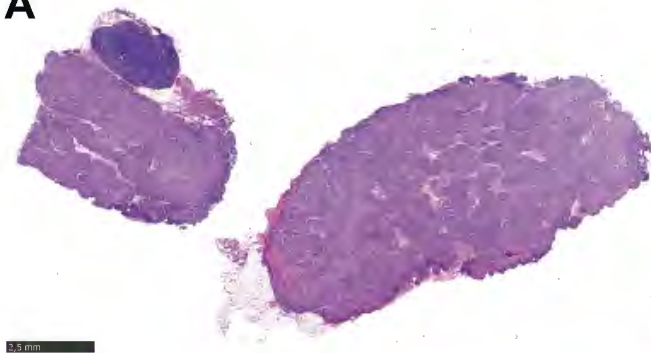
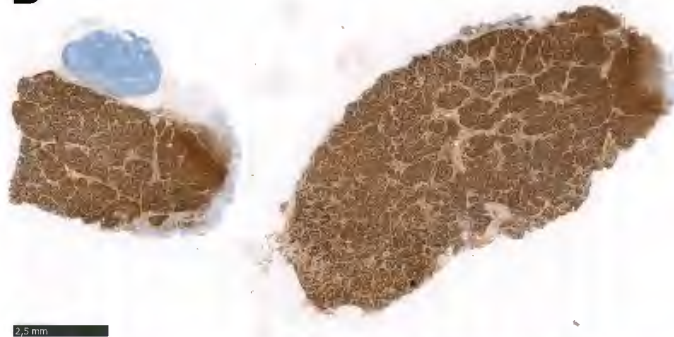
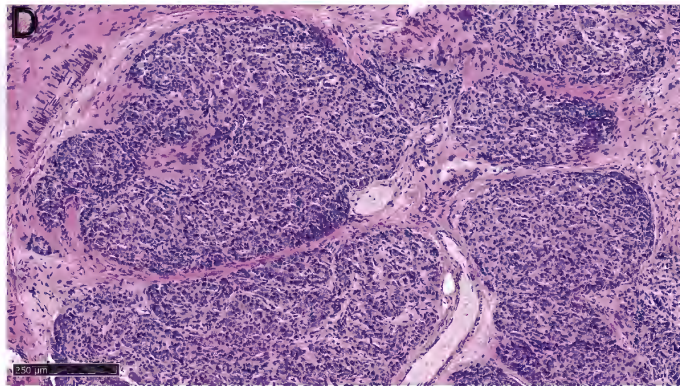
- Sempoux C., Poggi F., Brunelle F., Saudubray J.M., Fekete C. and Rahier J. (1995). Nesidioblastosis and persistent neonatal hyperinsulinism. *Diabetes Metab.* 21, 402-407.
- Sempoux C., Guiot Y., Dubois D., Nollevaux M.C., Saudubray J.M., Nihoul-Fekete C. and Rahier J. (1998a). Pancreatic B-cell proliferation in persistent hyperinsulinemic hypoglycemia of infancy: An immunohistochemical study of 18 cases. *Mod. Pathol.* 11, 444-449.
- Sempoux C., Guiot Y., Lefevre A., Nihoul-Fékété C., Jaubert F., Saudubray J.M. and Rahier J. (1998b). Neonatal hyperinsulinemic hypoglycemia: Heterogeneity of the syndrome and keys for differential diagnosis. *J. Clin. Endocrinol. Metab.* 83, 1455-1461.
- Sempoux C., Guiot Y., Dahan K., Moulin P., Stevens M., Lambot V., de Lonlay P., Fournet J.C., Junien C., Jaubert F., Nihoul-Fekete C., Saudubray J.M. and Rahier J. (2003). The focal form of persistent hyperinsulinemic hypoglycemia of infancy: Morphological and molecular studies show structural and functional differences with insulinoma. *Diabetes* 52, 784-794.
- Sempoux C., Capito C., Bellanne-Chantelot C., Verkarre V., de Lonlay P., Aigrain Y., Fekete C., Guiot Y. and Rahier J. (2011). Morphological mosaicism of the pancreatic islets: A novel anatomopathological form of persistent hyperinsulinemic hypoglycemia of infancy. *J. Clin. Endocrinol. Metab.* 96, 3785-3793.
- Senniappan S., Alexandrescu S., Tatevian N., Shah P., Arya V., Flanagan S., Ellard S., Rampling D., Ashworth M., Brown R.E. and Hussain K. (2014). Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia. *N. Engl. J. Med.* 370, 1131-1137.
- Service F.J., McMahon M.M., O'Brien P.C. and Ballard D.J. (1991). Functioning insulinoma--incidence, recurrence, and long-term survival of patients: A 60-year study. *Mayo Clin. Proc.* 66, 711-719.
- Service F.J. (1995). Hypoglycemic disorders. *N. Engl. J. Med.* 332, 1144-1152.
- Service F.J. (1999). Diagnostic approach to adults with hypoglycemic disorders. *Endocrinol. Metab. Clin. North Am.* 28, 519-532.
- Service F.J., Natt N., Thompson G.B., Grant C.S., van Heerden J.A., Andrews J.C., Lorenz E., Terzic A. and Lloyd R.V. (1999). Noninsulinoma pancreatogenous hypoglycemia: A novel syndrome of hyperinsulinemic hypoglycemia in adults independent of mutations in Kir6.2 and SUR1 genes. *J. Clin. Endocrinol. Metab.* 84, 1582-1589.
- Shahroor M.A., Lasorsa F.M., Porcelli V., Dweikat I., Di Noia M.A., Gur M., Agostino G., Shaag A., Rinaldi T., Gasparre G., Guerra F., Castegna A., Todisco S., Abu-Libdeh B., Elpeleg O. and Palmieri L. (2022). PNC2 (SLC25A36) deficiency associated with the hyperinsulinism/hyperammonemia syndrome. *J. Clin. Endocrinol. Metab.* 107, 1346-1356.
- Shermeta D.W., Mendelsohn G. and Haller J.A. Jr. (1980). Hyperinsulinemic hypoglycemia of the neonate associated with persistent fetal histology and function of the pancreas. *Ann. Surg.* 191, 182-186.
- Shin J.J., Gorden P. and Libutti S.K. (2010). Insulinoma: Pathophysiology, localization and management. *Future Oncol.* 6, 229-237.
- Shyng S., Ferrigni T. and Nichols C.G. (1997). Regulation of KATP channel activity by diazoxide and MgADP. Distinct functions of the two nucleotide binding folds of the sulfonylurea receptor. *J. Gen. Physiol.* 110, 643-654.
- Sikimic J., Hoffmeister T., Gresch A., Kaiser J., Barthlen W., Wolke C., Wieland I., Lendeckel U., Krippeit-Drews P., Düfer M. and Drews G. (2020). Possible new strategies for the treatment of congenital hyperinsulinism. *Front. Endocrinol. (Lausanne)* 11, 545638.
- Smith V.V., Malone M. and Risdon R.A. (2001). Focal or diffuse lesions in persistent hyperinsulinemic hypoglycemia of infancy: Concerns about interpretation of intraoperative frozen sections. *Pediatr. Dev. Pathol.* 4, 138-143.
- Snaith J.R., McLeod D., Richardson A. and Chipps D. (2020). Multifocal insulinoma secondary to insulinomatosis: Persistent hypoglycaemia despite total pancreatectomy. *Endocrinol. Diabetes Metab. Case Rep.* 2020.
- Snider K.E., Becker S., Boyajian L., Shyng S.L., MacMullen C., Hughes N., Ganapathy K., Bhatti T., Stanley C.A. and Ganguly A. (2013). Genotype and phenotype correlations in 417 children with congenital hyperinsulinism. *J. Clin. Endocrinol. Metab.* 98, E355-363.

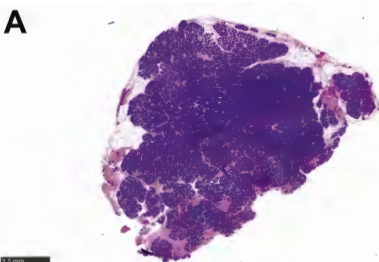
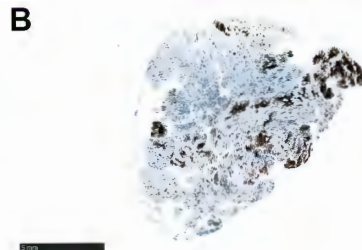
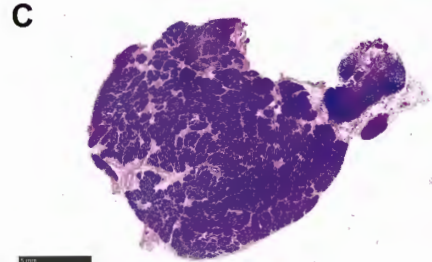
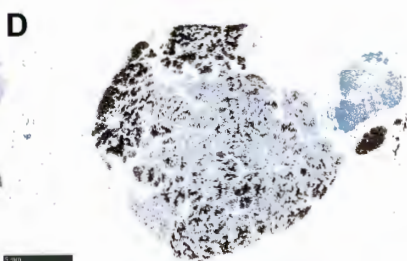
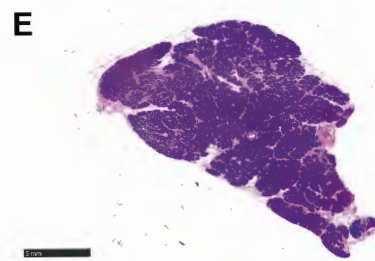
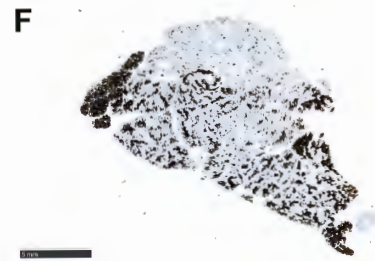
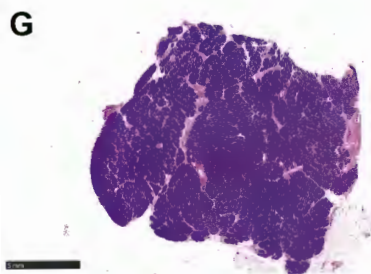
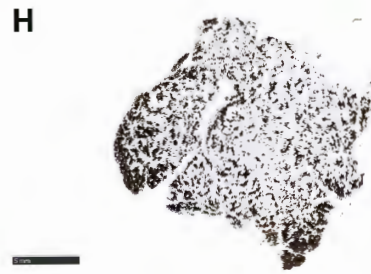
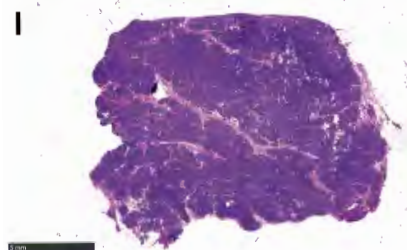
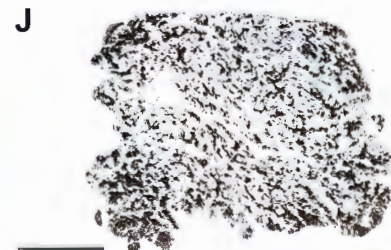
- Solcia E., Capella C. and Kloppel G. (1997). Tumors of the pancreas, Washington, DC: Armed Forces Institute of Pathology, 1997. Atlas of tumor pathology, third series, fascicle 20, 237-246.
- Stanescu D.E., Hughes N., Kaplan B., Stanley C.A. and De León D.D. (2012). Novel presentations of congenital hyperinsulinism due to mutations in the MODY genes: HNF1A and HNF4A. *J. Clin. Endocrinol. Metab.* 97, E2026-2030.
- Stanley C.A. (1997). Hyperinsulinism in infants and children. *Pediatr. Clin. North Am.* 44, 363-374.
- Stanley C.A., Lieu Y.K., Hsu B.Y., Burlina A.B., Greenberg C.R., Hopwood N.J., Perlman K., Rich B.H., Zammarchi E. and Poncz M. (1998). Hyperinsulinism and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene. *N. Engl. J. Med.* 338, 1352-1357.
- Stanley C.A., Fang J., Kutyna K., Hsu B.Y., Ming J.E., Glaser B. and Poncz M. (2000). Molecular basis and characterization of the hyperinsulinism/hyperammonemia syndrome: Predominance of mutations in exons 11 and 12 of the glutamate dehydrogenase gene. *HI/HA contributing investigators. Diabetes* 49, 667-673.
- Stanley C.A. (2004). Hyperinsulinism/hyperammonemia syndrome: Insights into the regulatory role of glutamate dehydrogenase in ammonia metabolism. *Mol. Genet. Metab.* 81 Suppl 1, S45-51.
- Stanley C.A. (2011). Two genetic forms of hyperinsulinemic hypoglycemia caused by dysregulation of glutamate dehydrogenase. *Neurochem. Int.* 59, 465-472.
- Starke A., Saddig C., Kirch B., Tschahargane C. and Goretzki P. (2006). Islet hyperplasia in adults: Challenge to preoperatively diagnose non-insulinoma pancreatogenic hypoglycemia syndrome. *World J. Surg.* 30, 670-679.
- Stefan Y., Grasso S., Perrelet A. and Orci L. (1983). A quantitative immunofluorescent study of the endocrine cell populations in the developing human pancreas. *Diabetes* 32, 293-301.
- Suchi M., MacMullen C., Thornton P.S., Ganguly A., Stanley C.A. and Ruchelli E.D. (2003). Histopathology of congenital hyperinsulinism: Retrospective study with genotype correlations. *Pediatr. Dev. Pathol.* 6, 322-333.
- Suchi M., Thornton P.S., Adzick N.S., MacMullen C., Ganguly A., Stanley C.A. and Ruchelli E.D. (2004). Congenital hyperinsulinism: Intraoperative biopsy interpretation can direct the extent of pancreatectomy. *Am. J. Surg. Pathol.* 28, 1326-1335.
- Suchi M., MacMullen C.M., Thornton P.S., Adzick N.S., Ganguly A., Ruchelli E.D. and Stanley C.A. (2006). Molecular and immunohistochemical analyses of the focal form of congenital hyperinsulinism. *Mod. Pathol.* 19, 122-129.
- Svensson E., Muth A., Hedenström P. and Ragnarsson O. (2022). The incidence of insulinoma in western Sweden between 2002 and 2019. *Ann. Gastroenterol.* 35, 434-440.
- Tartaglia A., Busonero G., Gagliardi L., Boddi V., Pieri F. and Nizzoli M. (2022). Complete remission of recurrent multiple insulin-producing neuroendocrine tumors of the pancreas with somatostatin analogs: A case report and literature review. *Discov. Oncol.* 13, 66.
- Thakker R.V., Newey P.J., Walls G.V., Bilezikian J., Dralle H., Ebeling P.R., Melmed S., Sakurai A., Tonelli F. and Brandi M.L. (2012). Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J. Clin. Endocrinol. Metab.* 97, 2990-3011.
- Thompson G.B., Service F.J., Andrews J.C., Lloyd R.V., Natt N., van Heerden J.A. and Grant C.S. (2000). Noninsulinoma pancreatogenous hypoglycemia syndrome: An update in 10 surgically treated patients. *Surgery* 128, 937-944; discussion 944-935.
- Thorburn M.J., Wright E.S., Miller C.G. and Smith-Read E.H. (1970). Exomphalos-macroglossia-gigantism syndrome in Jamaican infants. *Am. J. Dis. Child.* 119, 316-321.
- Thornton P.S., MacMullen C., Ganguly A., Ruchelli E., Steinkrauss L., Crane A., Aguilar-Bryan L. and Stanley C.A. (2003). Clinical and molecular characterization of a dominant form of congenital hyperinsulinism caused by a mutation in the high-affinity sulfonylurea receptor. *Diabetes* 52, 2403-2410.
- Thornton P.S., Stanley C.A., De Leon D.D., Harris D., Haymond M.W., Hussain K., Levitsky L.L., Murad M.H., Rozance P.J., Simmons R.A., Sperling M.A., Weinstein D.A., White N.H. and Wolfsdorf J.I. (2015).

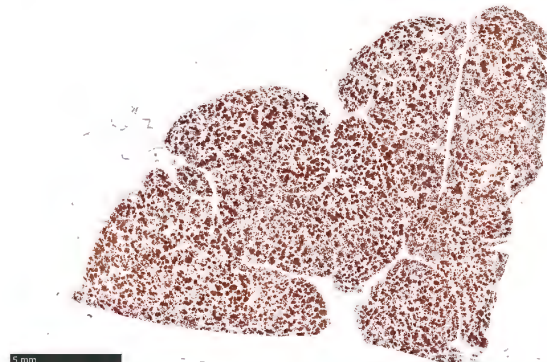
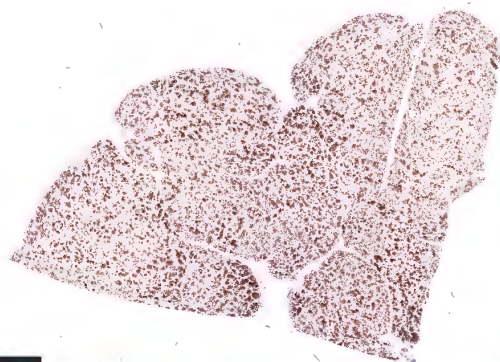
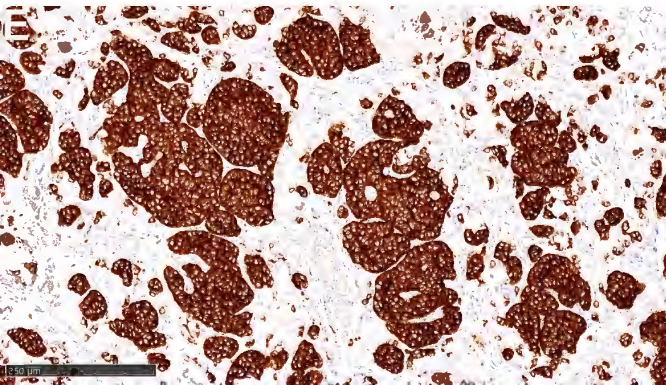
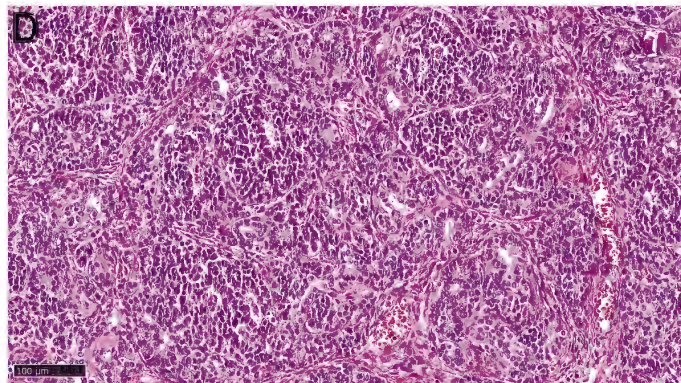
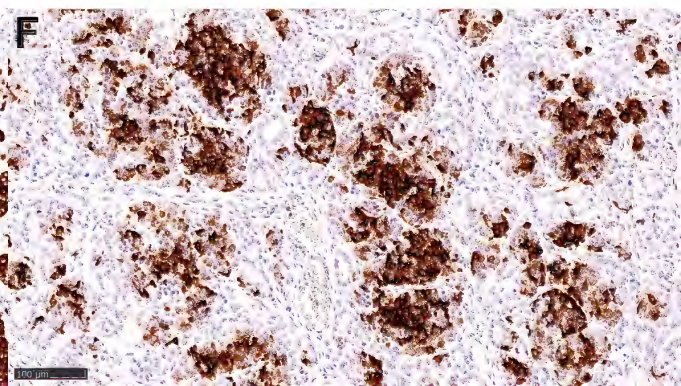
- Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. *J. Pediatr.* 167, 238-245.
- Toaiari M., Davì M.V., Dalle Carbonare L., Boninsegna L., Castellani C., Falconi M. and Francia G. (2013). Presentation, diagnostic features and glucose handling in a monocentric series of insulinomas. *J. Endocrinol. Invest.* 36, 753-758.
- Tragl K.H. and Mayr W.R. (1977). Familial islet-cell adenomatosis. *Lancet* 2, 426-428.
- Tung J.Y., Boodhansingh K., Stanley C.A. and De León D.D. (2018). Clinical heterogeneity of hyperinsulinism due to HNF1A and HNF4A mutations. *Pediatr. Diabetes* 19, 910-916.
- Valayannopoulos V., Vaxillaire M., Aigrain Y., Jaubert F., Bellanné-Chantelot C., Ribeiro M.J., Brunelle F., Froguel P., Robert J.J., Polak M., Nihoul-Fékété C. and de Lonlay P. (2007). Coexistence in the same family of both focal and diffuse forms of hyperinsulinism. *Diabetes Care* 30, 1590-1592.
- van Beek D.J., Nell S., Verkooijen H.M., Borel Rinkes I.H.M., Valk G.D. and Vriens M.R. (2020). Surgery for multiple endocrine neoplasia type 1-related insulinoma: Long-term outcomes in a large international cohort. *Br. J. Surg.* 107, 1489-1499.
- van der Steen I., van Albada M.E., Mohnike K., Christesen H.T., Empting S., Salomon-Estebanez M., Greve Rasmussen A., Verrijn Stuart A., van der Linde A.A.A., Banerjee I. and Boot A.M. (2018). A multicenter experience with long-acting somatostatin analogues in patients with congenital hyperinsulinism. *Horm. Res. Paediatr.* 89, 82-89.
- van der Wal B.C., de Krijger R.R., de Herder W.W., Kwekkeboom D.J., van der Ham F., Bonjer H.J. and van Eijck C.H. (2000). Adult hyperinsulinemic hypoglycemia not caused by an insulinoma: A report of two cases. *Virchows Arch.* 436, 481-486.
- Vanderveen K.A., Grant C.S., Thompson G.B., Farley D.R., Richards M.L., Vella A., Vollrath B. and Service F.J. (2010). Outcomes and quality of life after partial pancreatectomy for noninsulinoma pancreatogenous hypoglycemia from diffuse islet cell disease. *Surgery* 148, 1237-1245; discussion 1245-1236.
- Verkarre V., Fournet J.C., de Lonlay P., Gross-Morand M.S., Devillers M., Rahier J., Brunelle F., Robert J.J., Nihoul-Fékété C., Saudubray J.M. and Junien C. (1998). Paternal mutation of the sulfonylurea receptor (SUR1) gene and maternal loss of 11p15 imprinted genes lead to persistent hyperinsulinism in focal adenomatous hyperplasia. *J. Clin. Invest.* 102, 1286-1291.
- Vezzosi D., Bennet A., Fauvel J. and Caron P. (2007). Insulin, c-peptide and proinsulin for the biochemical diagnosis of hypoglycaemia related to endogenous hyperinsulinism. *Eur. J. Endocrinol.* 157, 75-83.
- Viljoen D. and Ramesar R. (1992). Evidence for paternal imprinting in familial Beckwith-Wiedemann syndrome. *J. Med. Genet.* 29, 221-225.
- Volk W.B.W., F.K. (1985). Quantitative studies of the islets of nondiabetic patients. *The Diabetic Pancreas* 117-125.
- Wabitsch M., Lahr G., Van de Bunt M., Marchant C., Lindner M., von Puttkamer J., Fenneberg A., Debatin K.M., Klein R., Ellard S., Clark A. and Gloyn A.L. (2007). Heterogeneity in disease severity in a family with a novel G68V GCK activating mutation causing persistent hyperinsulinaemic hypoglycaemia of infancy. *Diabet. Med.* 24, 1393-1399.
- Wang H., Bender A., Wang P., Karakose E., Inabnet W.B., Libutti S.K., Arnold A., Lambertini L., Stang M., Chen H., Kasai Y., Mahajan M., Kinoshita Y., Fernandez-Ranvier G., Becker T.C., Takane K.K., Walker L.A., Saul S., Chen R., Scott D.K., Ferrer J., Antipin Y., Donovan M., Uzilov A.V., Reva B., Schadt E.E., Losic B., Argmann C. and Stewart A.F. (2017). Insights into beta cell regeneration for diabetes via integration of molecular landscapes in human insulinomas. *Nat. Commun.* 8, 767.
- Wang K.H., Kupa J., Duffy K.A. and Kalish J.M. (2019). Diagnosis and management of Beckwith-Wiedemann syndrome. *Front. Pediatr.* 7, 562.
- Weksberg R., Shuman C. and Beckwith J.B. (2010). Beckwith-Wiedemann syndrome. *Eur. J. Hum. Genet.* 18, 8-14.

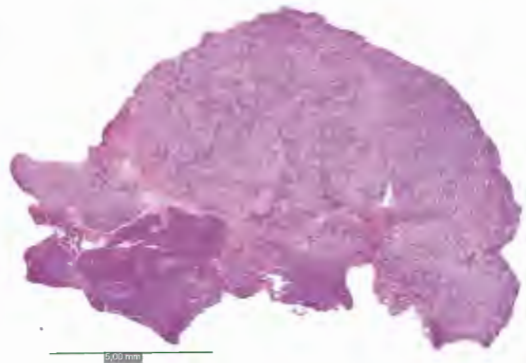
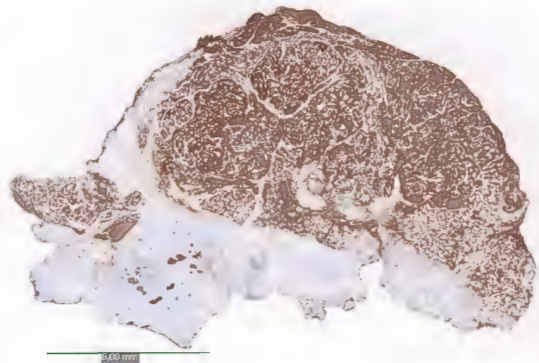
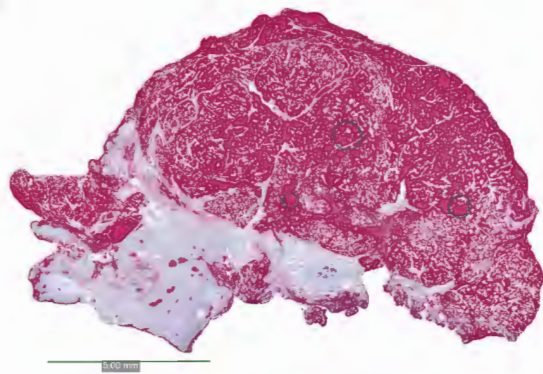
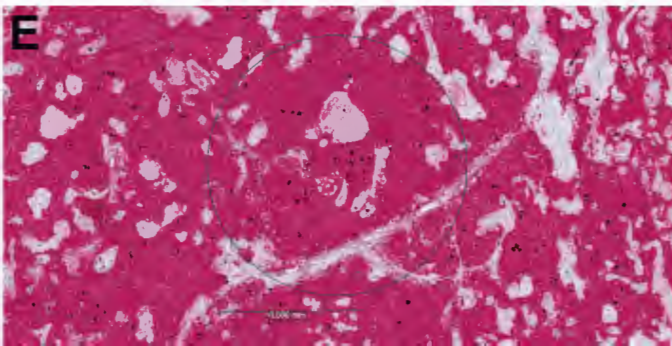
- Welters A., Lerch C., Kummer S., Marquard J., Salgin B., Mayatepek E. and Meissner T. (2015). Long-term medical treatment in congenital hyperinsulinism: A descriptive analysis in a large cohort of patients from different clinical centers. *Orphanet J. Rare Dis.* 10, 150.
- Whipple A.O. (1938). The surgical therapy of hyperinsulinism. *International de Chirurgie* 3: 237-276.
- Wieland I., Schanze I., Felgendreher I.M., Barthlen W., Vogelgesang S., Mohnike K. and Zenker M. (2022). Integration of genomic analysis and transcript expression of ABCC8 and KCNJ11 in focal form of congenital hyperinsulinism. *Front. Endocrinol. (Lausanne)* 13, 1015244.
- Wiesli P., Perren A., Saremaslani P., Pfammatter T., Spinaz G.A. and Schmid C. (2004). Abnormalities of proinsulin processing in functioning insulinomas: Clinical implications. *Clin. Endocrinol. (Oxf)* 61, 424-430.
- Wilson M., Peters G., Bennetts B., McGillivray G., Wu Z.H., Poon C. and Algar E. (2008). The clinical phenotype of mosaicism for genome-wide paternal uniparental disomy: Two new reports. *Am. J. Med. Genet. A* 146a, 137-148.
- Witte D.P., Greider M.H., DeSchryver-Kecsckemeti K., Kissane J.M. and White N.H. (1984). The juvenile human endocrine pancreas: Normal v idiopathic hyperinsulinemic hypoglycemia. *Semin. Diagn. Pathol.* 1, 30-42.
- Witteles R.M., Straus I.F., Sugg S.L., Koka M.R., Costa E.A. and Kaplan E.L. (2001). Adult-onset nesidioblastosis causing hypoglycemia: An important clinical entity and continuing treatment dilemma. *Arch. Surg.* 136, 656-663.
- Won J.G., Tseng H.S., Yang A.H., Tang K.T., Jap T.S., Lee C.H., Lin H.D., Burcus N., Pittenger G. and Vinik A. (2006). Clinical features and morphological characterization of 10 patients with noninsulinoma pancreatogenous hypoglycaemia syndrome (NIPHS). *Clin. Endocrinol. (Oxf)* 65, 566-578.
- Yakovac W.C., Baker L. and Hummeller K. (1971). Beta cell nesidioblastosis in idiopathic hypoglycemia of infancy. *J. Pediatr.* 79, 226-231.
- Yamada Y., Kitayama K., Oyachi M., Higuchi S., Kawakita R., Kanamori Y. and Yorifuji T. (2020). Nationwide survey of endogenous hyperinsulinemic hypoglycemia in Japan (2017-2018): Congenital hyperinsulinism, insulinoma, non-insulinoma pancreatogenous hypoglycemia syndrome and insulin autoimmune syndrome (Hirata's disease). *J. Diabetes Investig.* 11, 554-563.
- Yau D., Laver T.W., Dastamani A., Senniappan S., Houghton J.A.L., Shaikh G., Cheetham T., Mushtaq T., Kapoor R.R., Randell T., Ellard S., Shah P., Banerjee I. and Flanagan S.E. (2020). Using referral rates for genetic testing to determine the incidence of a rare disease: The minimal incidence of congenital hyperinsulinism in the UK is 1 in 28,389. *PLoS One* 15, e0228417.
- Yorifuji T., Muroi J., Uematsu A., Hiramatsu H. and Momoi T. (1999). Hyperinsulinism-hyperammonemia syndrome caused by mutant glutamate dehydrogenase accompanied by novel enzyme kinetics. *Hum. Genet.* 104, 476-479.
- Yorifuji T., Hosokawa Y., Fujimaru R., Kawakita R., Doi H., Matsumoto T., Nishibori H. and Masue M. (2011). Lasting 18F-DOPA PET uptake after clinical remission of the focal form of congenital hyperinsulinism. *Horm. Res. Paediatr.* 76, 286-290.
- Yu R., Nissen N.N., Hendifar A., Tang L., Song Y.L., Chen Y.J. and Fan X. (2017). A clinicopathological study of malignant insulinoma in a contemporary series. *Pancreas* 46, 48-56.
- Zhou C., Dhall D., Nissen N.N., Chen C.R. and Yu R. (2009). Homozygous P86S mutation of the human glucagon receptor is associated with hyperglucagonemia, alpha cell hyperplasia, and islet cell tumor. *Pancreas* 38, 941-946.
- Zobel M.J., McFarland C., Ferrera-Cook C.T. and Padilla B.E. (2020). Surgical management of medically-refractory hyperinsulinism. *Am. J. Surg.* 219, 947-951.



A**B****C****D**

A**B****C****D****E****F****G****H****I****J**

A**B****C****D****F**

A**B****C****D****E****F**