

THE INCIDENCE, PREVALENCE, AND PATHOGENESIS OF MONOGENIC DIABETES SYNDROME

AUTHOR

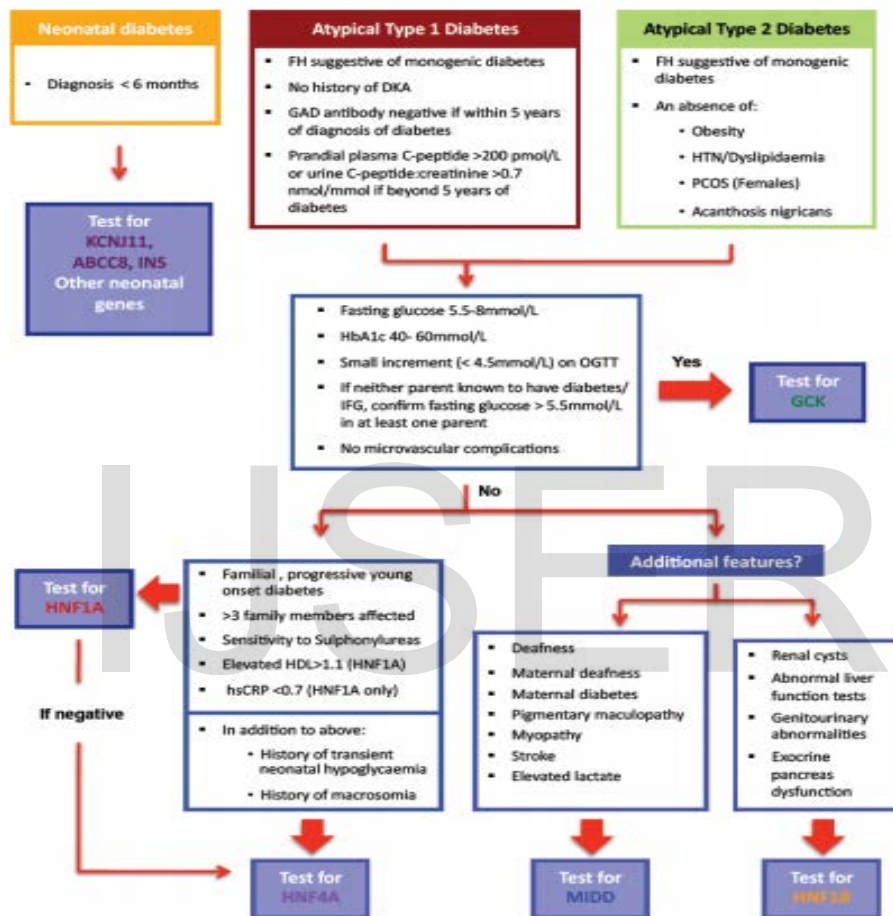
¹RAJESH JAIN, ¹SUSANNE OLEJAS, ¹ANI RASHEL FEH, ¹ALEXANDER EDWARDS, ¹HINA ALI, ¹ZOONIFER KHAN, ¹SATRUPA RAGOONANAN, ¹NISHA BENOY, ¹SHARMIN BADIEI, ¹RACHEL DAVIES

Correspondence Author: ¹Dr Rajesh Jain MD, Project Manager, Diabetes Prevention Control Project, National health Mission with World Diabetes Foundation, Denmark. 108 B Gandhi Gram, Vinobha Nagar, Kanpur, UP, India..Email:drrajeshjain@diabetesasia.org

Abstract

Monogenic diabetes syndromes result from a mutation of a single gene involved in the regulation of pancreatic beta-cell function. It is a rare condition, accounting for 1-4% of all paediatric diabetes cases. This gene defect is usually inherited, either autosomal or recessive, but a small percentage of spontaneous mutations have been found. There are over 40 subtypes of genetic mutations identified, each with its unique phenotypical characteristics (Rubio-Cabezas et al., 2014). Overall, it can be subdivided into two main categories: Maturity onset diabetes of the Young (MODY) and Neonatal diabetes (NDM). This report will discuss the incidence, prevalence, and pathogenesis of the MODY and NDM syndromes.

Diagnostic algorithm for assessment of suspected monogenic diabetes: diabetes diagnosed at < 35 years (Richard W 2013).



MODY 3: Mutation HNF1a

MODY-3 is caused by mutation in the Hepatocyte Nuclear Factor-1 Alpha (HNF1A). It constitutes about 30 to 70% of all MODY cases and is the most common type of MODY.

Geographical distribution plays an important role in the incidence of MODY-3, with the United Kingdom (UK), Netherlands and Denmark being regions with the highest incidence of MODY-3 (Ovsyannikova et al., 2017).

HNF-1A is a transcription factor that is important for beta cells differentiation (Karaca et al., 2017). The gene encoding transcription factor, HNF-1A, is essential to the underlying metabolic control exerted by beta-cells in regulating insulin secretion (Yamagata et al., 1996). The mutations in HNF1A cause a progressive pancreatic beta-cell dysfunction and hyperglycaemia (Anik et al., 2015).

HNF -1A is associated with the regulation of lipid and carbohydrate metabolism, thus mutations can lead to dyslipidaemia and cardiovascular complications (Ovsyannikova et al., 2017). Patients develop glycosuria even at normal blood glucose levels due to reduced renal reabsorption (Kim, 2015). HNF-1A mutations also predispose patients to an increased risk of liver neoplasms (Zucman-Rossi et al 2006). MODY-3 is characterized by young age at onset and family history of young onset diabetes (Iwabuchi et al 2013).

MODY 1 & 5: Mutation HNF4a, and 1b

HNF-4A makes up about 10% of MODY cases (Orpha.net, 2014). Children of a parent with HNF-4A have a 50% risk of inheriting the mutant gene (Diabetes UK, 2016). Diabetes caused by mutations in the HNF1b gene is a less common type of MODY, accounting for 1-5 % of cases (Orpha.net, 2014).

Research has demonstrated that prevalence varies in different regions in the UK.

Accurate prevalence data is difficult due to the cost of genetic diagnosis, and many countries lack a comprehensive testing program. The variation in referral rate in the UK demonstrates that many MODY cases are missed (Shields et al, 2010).

Individuals with mutations in HNF4A, (MODY1) present with a mild form of diabetes, however over time, hyperglycaemia is likely to increase. Pancreatic beta-cell dysfunction, not insulin resistance, is the primary defect of MODY-1, and manifests as decreased insulin secretion in response to glucose (Byrne et al, 1995). People with MODY may have a broad range of diabetic complications, including microvascular complications, particularly involving the retina and kidneys (Hamosh, 2014).

The most common clinical features of HNF1B, (MODY-5) are renal abnormalities and early onset diabetes, as well as uterine malformations, male genital tract malformations and hyperuricemia. The main pathophysiology related to the HNF-1B phenotype is reduced insulin secretion owing to beta-cell dysfunction, which may be associated with pancreatic atrophy (Bingham et al, 2004).

MODY 2: Glucokinase (GCK) Mutations

Glucokinase mutations (MODY-2) are the second most common subtype and accounts for 32% of MODY cases (Shields et al, 2010). Geographical distribution plays a role here also. Similar percentages were detected in European countries such as Italy with 41% cases and a

high number of de novo cases (Massa et al., 2001) and 31% in Czech Republic (Pruhova et al., 2003). In Asian countries, there is lower prevalence of MODY -2 (Kanthimathi et al., 2014).

GCK is a glycolytic enzyme present in the pancreatic beta-cell, liver, brain and many other tissues in mammals. GCK acts as a key sensor of the pancreatic beta-cells by regulating the rate of entry of glucose in the glycolytic pathway and its subsequent metabolism. GCK also stores glucose as glycogen in the liver (Murphy et al., 2013). The glycolytic pathway of GCK converts glucose to glucose-6-phosphate at glucose levels of above 4.0mmol/L and producing adenosine triphosphate (ATP), which then causes the extracellular release of insulin that helps to regulate plasma glucose.

Individuals with heterozygous inactivating GCK mutations present with mild fasting hyperglycaemia (5.5-8.3mmol/l and HbA1c 5.8%-7.6% = 40-60mmol/mol) and normal postprandial glucose levels. There is very mild deterioration with age and many patients do not require hypoglycaemic agents during their lifetime (Ajala et al., 2016). This is because they regulate plasma glucose level at its highest set point (Kavvoura and Owen, 2014).

MODY: Other mutations

Other mutations that cause MODY are rare, with ten other identified genetic mutations, and many more unidentified (Hamosh and O'Neill, 2016). These genes are expressed in the pancreatic beta-cell and are involved in glucose homeostasis. Heterozygous mutations cause diabetes related to beta-cell dysfunction (Polonsky and Burant, 2016).

Neonatal diabetes mellitus (NDM)

NDM is a rare monogenic form of diabetes defined as persistent hyperglycaemia requiring insulin, within first six months of life (Shah et al., 2014). The genetic defect grossly affects the development of Beta-cell numbers and function leading to poor feeding, failure to thrive and hyperglycaemia (Nansseu et al., 2016).

NDM has two variants: transient (TNDM), which accounts for 50-60% of cases and resolves by early infancy although it may relapse in early childhood; and permanent (PNDM), which is less prevalent and requires lifelong treatment (Polak and Cavé, 2007).

Many epidemiological studies have looked at the incidence of NMD and reported this as 1 in 300,000 to 400,000 (Grulich-Henn et al., 2010). The SEARCH study estimated the incidence of PNDM in the US as 1: 225000, which is similar to the UK, Netherlands and Poland (1: 260,000) (Shankar et al., 2012).

The common mutations in PNDM include a defect in the KCNJ11 gene, ABCC8 gene and INS gene. These account for 30%, 20% and 20%, respectively of patients with PNDM. The KCNJ11 and ABCC8 genes provide instructions in making subunits of ATP-sensitive potassium channel (K-ATP channel). Each K-ATP channel consists of 8 subunits: four produced from KCNJ11 gene and four from ABCC8 gene. K-ATP channels are found across cell membranes in the pancreatic beta cells. The K-ATP channels open and close in response to the amount of glucose in the blood stream. Closure of channels, in response to increased blood sugar, triggers

the release of insulin out of beta-cells into the blood stream. Mutations in KCNJ11 or ABCC8 genes result in K-ATP channels that do not close, leading to reduced insulin secretion from beta-cells and impaired blood sugar control (Genetics Home Reference, 2018).

INS gene provides instructions for making insulin. The insulin is produced in a precursor form called proinsulin, which consists of a single chain of amino acids. The proinsulin chain is cleaved to form A and B chains which are joined together by disulphide bonds to form insulin. Mutations in the INS gene disrupt the cleavage of proinsulin chain or the binding of A and B chains to form insulin leading to impaired blood sugar control. (Genetics Home Reference, 2018)

Clinical features include intrauterine growth retardation, persistent hyperglycaemia (>150 -200mg/dl) in infants younger than six months, glycosuria, osmotic polyuria, ketonuria, hyperketonaemia, dehydration, and failure to thrive. In some cases, individuals have developmental delay and epilepsy in addition to neonatal diabetes. A small number of individuals with PNDM have an under developed pancreas which can result in digestive problems such as fatty stools and inability to absorb fat-soluble vitamins (DeLeon et al., 2016).

TNDM is diabetes beginning in the first six weeks after birth, owing to a lack of insulin production. This remits by the 18th month of life. However, despite this remission, most children will develop diabetes later in life. This occurs in 50% of patients and corresponds with periods of growth, and thereby increased insulin demand, such as puberty or pregnancy (Flanagan, 2014).

The signs and symptoms of TNDM are as follows. Infants often have very stunted intrauterine growth, and are small at birth, falling in the third percentile or below. In some cases macroglossia, umbilical herniation, epilepsy and learning difficulties have also been present (Wessex Imprinting Group, not dated). Prevalence of TNDM in the UK was initially estimated at 1:400,000 (Shield et al 1997), but more recent calculations estimate total NDM incidence of 1:215,000 to 1:400,000 (Stanik et al 2007, Wiedemann et al 2010).

TNDM occurs due to overexpression of an imprinted paternally expressed gene on chromosome 6q24, in the *ZAC* and *HYMAI* regions. *ZAC* functions as a regulator of cell cycle arrest and apoptosis and overexpression affects the absolute number and efficiency of beta islet cells during pancreatic development. *ZAC* also affects islet cell responsiveness to PACAP-receptor1 (Pituitary Adenylate Cyclase Activating Polypeptide), a potent insulin secretagogue (Temple and Shield, 2002).

Clinical Investigations

When MODY is suspected, evaluation should be done to determine appropriate selection of patients for genetic testing (Naylor and Philipson, 2011). MODY can be misclassified as T1DM or T2DM, and subsequently, the patient may be administered the wrong treatment.

In T1DM, autoantibodies, including autoantibodies to islet cells, GAD, insulin, the tyrosine phosphatases IA-2 and IA-2 β , should be obtained before considering genetic testing (Borg et al., 2002). FPG, insulin and C-peptide levels can distinguish between MODY and T2DM

with hyperinsulinemia and high or normal C-peptide in T2DM. Some subtypes of MODY may also have a distinct pattern on oral glucose tolerance test (OGTT), like a small incremental increase between FPG and 2hPG in MODY-2 versus a large increase in MODY-3(Naylor and Philipson, 2011).

Urinary C-peptide: creatinine ratio can further distinguish subtypes MODY-1 and MODY-3 from T1DM, if duration of disease has been more than 5 years (Besser et al., 2011). These diagnostic tools may facilitate selection of patients for genetic testing. Molecular genetic testing should be pursued in individuals fitting a clinical phenotype of MODY using certified laboratories (Naylor and Philipson, 2011).

Conclusions: MD (Monogenic diabetes) should be always considered for differentiating from other diabetes, though not common but should be considered as differential diagnosis, and should go for Genetical testing so that outcomes can be improved, It is not as rare as considered previously. Genetic testing will be more cost effective as the cost of the test decreases, In developing Nation cost is biggest factor for diagnosis in public health facilities where testing is virtually absent in public institutions and available in private domain. likelihood of diagnosis of a monogenic cause increases with available facilities and treatment for life long benefit to patient.

REFERENCES

- Ajala, O., Huffman, D. and Ghobrial, I. (2016) 'Glucokinase mutation—a rare cause of recurrent hypoglycemia in adults: a case report and literature review'. *Journal of Community Hospital Internal Medicine Perspectives*, 6(5), p.32983.
- Anık, A., Çatlı, G., Abacı, A. and Böber, E. (2015) 'Maturity-onset diabetes of the young (MODY): an update'. *Journal of Pediatric Endocrinology and Metabolism*, 28, pp.3-4.
- Besser, R., Shepherd, M., McDonald, T., Shields, B., Knight, B., Ellard, S. and Hattersley, A. (2011) 'Urinary C-Peptide Creatinine Ratio Is a Practical Outpatient Tool for Identifying Hepatocyte Nuclear Factor 1- /Hepatocyte Nuclear Factor 4- Maturity-Onset Diabetes of the Young from Long-Duration Type 1 Diabetes'. *Diabetes Care*, 34(2), pp.286-291.
- Bingham, C. (2004) 'Renal cysts and diabetes syndrome resulting from mutations in hepatocyte nuclear factor-1'. *Nephrology Dialysis Transplantation*, 19(11), pp.2703-2708.
- Borg, H., Marcus, C., Sjoblad, S., Fernlund, P. and Sundkvist, G. (2002). Insulin autoantibodies are of less value compared with islet antibodies in the clinical diagnosis

of autoimmune type 1 diabetes in children older than 3 yr of age'. *Pediatric Diabetes*, 3(3), pp.149-154.

- Byrne, M., Sturis, J., Fajans, S., Ortiz, F., Stoltz, A., Stoffel, M., Smith, M., Bell, G., Halter, J. and Polonsky, K. (1995) 'Altered Insulin Secretory Responses to Glucose in Subjects with a Mutation in the MODY1 Gene on Chromosome 20'. *Diabetes*, 44(6), pp.699-704.
- DeLeon, D. and Standley, C. (2016) Permanent Neonatal Diabetes Mellitus. Available online at: www.ncbi.nlm.nih.gov/books/NBK1447. (Accessed 23th March 2018)
- Diabetes UK (2016). Rare diabetes type called MODY 1 needs alternative treatment, say researchers. Available online at: <https://www.diabetes.co.uk/news/2016/mar/rare-diabetes-type-called-mody-1-needs-alternative-treatment,-say-researchers-93761284.html> [Accessed 25 March. 2018].
- Flanagan, S. (2014). Transient neonatal diabetes (revision number 23). Diapedia. Available online at: <https://www.diapedia.org/41040851198/rev/23> [Accessed 26 March. 2018].

- Genetics Home Reference (2018). Permanent neonatal diabetes mellitus. Available online at: <https://ghr.nlm.nih.gov/condition/permanent-neonatal-diabetes-mellitus#genes> [Accessed 19 March 2018].
- Grulich-Henn, J., Wagner, V., Thon, A., Schober, E., Marg, W., Kapellen, T., Haberland, H., Raile, K., Ellard, S., Flanagan, S., Hattersley, A. and Holl, R. (2010) 'Entities and frequency of neonatal diabetes: data from the diabetes documentation and quality management system (DPV)'. *Diabetic Medicine*, 27(6), pp.709-712.
- Hamosh, A. (2014). Hepatocyte Nuclear Factor 4-Alpha: HNF4A. Available online at: <https://www.omim.org/entry/600281> [Accessed 17th March 2018].
- Hamosh, A. and O'Neill, M. (2016). OMIM Entry - # 606391 - MATURITY-ONSET DIABETES OF THE YOUNG; MODY. Available online at: <https://www.omim.org/entry/606391#title> [Accessed 22th March 2018].
- Iwabuchi, A., Kamoda, T., Shinohara, H. and Sumazaki, R. (2013) 'Japanese boy with maturity-onset diabetes of the young type 3 who developed diabetes at 19 months old'. *Pediatrics International*, 55(2), pp.e32-e34.

- Kanthimathi, S., Jahnavi, S., Balamurugan, K., Ranjani, H., Sonya, J., Goswami, S., Chowdhury, S., Mohan, V. and Radha, V. (2014). 'Glucokinase Gene Mutations (MODY 2) in Asian Indians'. *Diabetes Technology & Therapeutics*, 16(3), pp.180-185.
- Karaca, E., Onay, H., Cetinkalp, S., Aykut, A., Göksen, D., Ozen, S., Atik, T., Darcan, S., Tekin, I. and Ozkınay, F. (2017) 'The spectrum of HNF1A gene mutations in patients with MODY 3 phenotype and identification of three novel germline mutations in Turkish Population'. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, 11, pp.S491-S496.
- Kavvoura, F. and Owen, K. (2014) 'Monogenic diabetes'. *Medicine*, 42(12), pp.692-697.
- Kim, S. (2015) 'Maturity-Onset Diabetes of the Young: What Do Clinicians Need to Know? *Diabetes & Metabolism Journal*, 39(6), p.468.
- Massa, O., Meschi, F., Cuesta-Munoz, A., Caumo, A., Cerutti, F., Toni, S., Cherubini, V., Guazzarotti, L., Sulli, N., Matschinsky, F., Lorini, R., Iafusco, D., Barbetti, F. and Diabetes Study Group of the Italian Society of Paediatric Endocrinology and Diabetes (SIEDP).

IJSER

(2001). 'High prevalence of glucokinase mutations in Italian children with MODY.

Influence on glucose tolerance, first-phase insulin response, insulin sensitivity and BMI'.

Diabetologia, 44(7), pp.898-905.

- Murphy, R., Carroll, R. and Krebs, J. (2013) 'Pathogenesis of the Metabolic Syndrome: Insights from Monogenic Disorders'. *Mediators of Inflammation*, 2013, pp.1-15.
- Nansseu, J., Ngo-Um, S. and Balti, E. (2016) 'Incidence, prevalence and genetic determinants of neonatal diabetes mellitus: a systematic review and meta-analysis protocol'. *Systematic Reviews*, 5(1).
- Naylor, R. and Philipson, L. (2011). 'Who should have genetic testing for maturity-onset diabetes of the young?'. *Clinical Endocrinology*, 75(4), pp.422-426.
- Orpha.net (2014). Orphanet: MODY. Available online at:
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=552 [Accessed 25th March. 2018].

- Ovsyannikova, A., Rymar, O., Ivanoshchuk, D., Mikhailova, S., Shakhtshneider, E., Orlov, P., Malakhina, E. and Voevoda, M. (2017) 'A Case of Maturity Onset Diabetes of the Young (MODY3) in a Family with a Novel HNF1A Gene Mutation in Five Generations'. *Diabetes Therapy*, 9(1), pp.413-420.
- Polak, M. and Cavé, H. (2007) 'Neonatal diabetes mellitus: a disease linked to multiple mechanisms. *Orphanet Journal of Rare Diseases*, 2(1), p.12.
- Polonsky, K.S. and Burant, C.F. (2016) Type 2 Diabetes (in Williams Textbook of Endocrinology). 13th edn. Philadelphia. Chapter 31. Available online at: www.sciencedirect.com/science/article/pii/B978032329738000319 (Accessed 22th March 2018)
- Pruhova, S., Ek, J., Lebl, J., Sumnik, Z., Saudek, F., Andel, M., Pedersen, O. and Hansen, T. (2003). 'Genetic epidemiology of MODY in the Czech republic: new mutations in the MODY genes HNF-4 α , GCK and HNF-1 α '. *Diabetologia*, 46(2), pp.291-295.
- Richard W. Carroll, Rinki Murphy (2013) 'Monogenic Diabetes: A Diagnostic Algorithm for Clinicians', *Genes*, 4, 522-535

- Rubio-Cabezas, O., Hattersley, A., Njølstad, P., Mlynarski, W., Ellard, S., White, N., Chi, D. and Craig, M. (2014) 'The diagnosis and management of monogenic diabetes in children and adolescents'. *Pediatric Diabetes*, 15(S20), pp.47-64.
- Shah, B., Kataria, A., Palliyil Gopi, R. and Mally, P. (2014). 'Neonatal diabetes mellitus: current perspective'. *Research and Reports in Neonatology*, p.55.
- Shankar, R., Pihoker, C., Dolan, L., Standiford, D., Badaru, A., Dabelea, D., Rodriguez, B., Black, M., Imperatore, G., Hattersley, A., Ellard, S. and Gilliam, L. (2012). 'Permanent neonatal diabetes mellitus: prevalence and genetic diagnosis in the SEARCH for Diabetes in Youth Study'. *Pediatric Diabetes*, 14(3), pp.174-80.
- Shields, B., Hicks, S., Shepherd, M., Colclough, K., Hattersley, A. and Ellard, S. (2010). 'Maturity-onset diabetes of the young (MODY): how many cases are we missing?'. *Diabetologia*, 53(12), pp.2504-2508.
- Shield, J., Gardner, R., Wadsworth, E., Whiteford, M., James, R., Robinson, D., Baum, J. and Temple, I. (1997). 'Aetiopathology and genetic basis of neonatal diabetes' *Archives of Disease in Childhood - Fetal and Neonatal Edition*, 76(1), pp.F39-F42.

- Stanik, J., Gasperikova, D., Paskova, M., Barak, L., Javorkova, J., Jancova, E., Ciljakova, M., Hlava, P., Michalek, J., Flanagan, S., Pearson, E., Hattersley, A., Ellard, S. and Klimes, I. (2007). 'Prevalence of Permanent Neonatal Diabetes in Slovakia and Successful Replacement of Insulin with Sulfonylurea Therapy in KCNJ11 and ABCC8 Mutation Carriers' *The Journal of Clinical Endocrinology & Metabolism*, 92(4), pp.1276-1282.
- Stride, A., Vaxillaire, M., Tuomi, T., Barbetti, F., Njølstad, P., Hansen, T., Costa, A., Conget, I., Pedersen, O., Søvik, O., Lorini, R., Groop, L., Froguel, P. and Hattersley, A. (2002). 'The genetic abnormality in the beta cell determines the response to an oral glucose load' *Diabetologia*, 45(3), pp.427-435.
- Temple, I. and Shield, J. (2002). 'Transient neonatal diabetes, a disorder of imprinting'. *Journal of Medical Genetics*, 39(12), pp.872-875.
- Wessex Imprinting Group: Transient neonatal diabetes. Available online at: www.southampton.ac.uk/geneticimprinting/informationpatients/transientneonataldiabetes.page [Accessed 26th March 2018].

- Wiedemann, B., Schober, E., Waldhoer, T., Koehle, J., Flanagan, S., Mackay, D., Steichen, E., Meraner, D., Zimmerhackl, L., Hattersley, A., Ellard, S. and Hofer, S. (2010). 'Incidence of neonatal diabetes in Austria: calculation based on the Austrian Diabetes Register' *Pediatric Diabetes*, 11(1), pp.18-23.
- Yamagata, K., Oda, N., Kaisaki, P., Menzel, S., Furuta, H., Vaxillaire, M., Southam, L., Cox, R., Lathrop, G., Boriraj, V., Chen, X., Cox, N., Oda, Y., Yano, H., Le Beau, M., Yamada, S., Nishigori, H., Takeda, J., Fajans, S., Hattersley, A., Iwasaki, N., Hansen, T., Pedersen, O., Polonsky, K., Turner, R., Velho, G., Chèvre, J., Froguel, P. and Bell, G. (1996). 'Mutations in the hepatocyte nuclear factor-1 α gene in maturity-onset diabetes of the young (MODY3)' *Nature*, 384(6608), pp.455-458.
- Zucman-Rossi, J., Jeannot, E., Van Nhieu, J., Scoazec, J., Guettier, C., Rebouissou, S., Bacq, Y., Leteurtre, E., Paradis, V., Michalak, S., Wendum, D., Chiche, L., Fabre, M., Mellottee, L., Laurent, C., Partensky, C., Castaing, D., Zafrani, E., Laurent-Puig, P., Balabaud, C. and Bioulac-Sage, P. (2006). 'Genotype–phenotype correlation in hepatocellular adenoma: New classification and relationship with HCC'. *Hepatology*, 43(3), pp.515-524.