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Information for patients with a disease-causing variant in the Hepatocyte Nuclear Factor-1 Beta (*HNF1B*) gene

What is Hepatocyte Nuclear Factor-1 Beta (*HNF1B*)?

HNF1B is a gene which acts as a switch to turn other genes on and off in the body. It is involved in the development of several organs in the body including the kidneys, pancreas, reproductive tract, and liver. People with a disease-causing variant in the *HNF1B* gene can have a variety of problems associated with these organs. This is sometimes called the "Renal Cysts and Diabetes or RCAD syndrome" because these are the most common features.

How do variants in *HNF1B* affect the kidneys?

The kidney is the most common organ to be affected in people with a variant in the *HNF1B* gene. HNF1B is important for the control of kidney development before a baby is born. Variants in the *HNF1B* gene can affect this process to different degrees. The most common finding is cysts (fluid filled swellings) in the kidneys. These are usually seen when an ultrasound scan is performed to look at the size, shape and structure of the kidneys. Other features associated with a variant in the *HNF1B* gene include small kidneys or the presence of only one kidney which may be of normal or abnormal shape. Sometimes abnormalities in the kidneys of a baby with a variant in the *HNF1B* gene are noticed before the baby is born when the mother is having an antenatal scan. The abnormalities in the kidneys have a variable effect on how well the kidneys work. Some people are only mildly affected and may have cysts in their kidneys but they work normally. Other people may be more severely affected and their kidneys may fail in which case artificial kidney treatment (dialysis) or a kidney transplant is required. In rare cases the kidneys fail to develop at all which may lead to the death of a baby in the womb.

What about *HNF1B* and diabetes?

Variants in the *HNF1B* gene are associated with an increased risk of developing diabetes. Diabetes is the second most common problem in people with a variant in the *HNF1B* gene after kidney abnormalities. However not all people with a variant in the *HNF1B* gene develop diabetes. Diabetes can develop at any age but often develops in adolescence or young adulthood and sometimes in pregnancy. Patients with an *HNF1B* variant can be affected with diabetes but have no clinical signs or symptoms of renal disease. Diabetes caused by variants in *HNF1B* is more commonly treated with insulin injections although it may be possible initially to use diet or tablets.

Some people with variants in the *HNF1B* gene also have a pancreas that is smaller than usual. This can be picked up on different types of scans (CT, MRI and sometimes ultrasound). The pancreas is an organ found in the abdomen that produces important enzymes and hormones (including insulin) to help break down food. If people are not making enough of these enzymes, this can cause loose stools and unintentional weight loss because they can't digest their food properly. However, they can be replaced by taking tablets with their meals.

What about *HNF1B* and uterine abnormalities?

Women with a variant in the *HNF1B* gene can have abnormalities of the reproductive tract, especially uterine abnormalities. This usually means that the uterus is a different shape or there may be a double uterus. These problems may be picked up on an ultrasound scan. It is possible for a woman with a uterine abnormality caused by a variant in the *HNF1B* gene to have a successful pregnancy.

What else can variants in the *HNF1B* gene affect?

Some people with variants in the *HNF1B* gene have mild abnormalities on blood tests of liver function, or an abnormal looking liver when scanned. However this does not seem to cause significant liver disease.

Some people, including women and young adults, are prone to attacks of gout and high levels of uric acid can be found in the blood. This is a result of the kidneys being unable to remove uric acid from the body as efficiently as they should. It is possible to take tablets to prevent attacks of gout.

Some people have low levels of magnesium on blood tests. However, this does not usually cause any symptoms and only a small number of people will need to take magnesium supplements.

People who have an *HNF1B* deletion (they lack one copy of the gene) may have autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and/or learning difficulties. The severity of these conditions is variable and may fluctuate over time. Specialist assessment may be helpful.

Does this result explain why other members of my family have kidney problems and diabetes?

If other members of your family are known to have kidney abnormalities such as cysts and diabetes it is likely that they also carry the same variant in the *HNF1B* gene. The genetic variant can pass from generation to generation, although sometimes it occurs as a new variant (referred to as a *de novo* variant) so there may be no-one else in the family affected. The range and severity of the abnormalities often varies widely within one family.

Will this affect my children?

We know that anyone who has a variant in the *HNF1B* gene has a 50% chance of passing this on to their children. It is important to remember that the effects can vary widely; detailed antenatal scanning particularly of the kidneys can be helpful in detecting abnormalities.

Can my family be tested?

It is possible to test other family members for the familial *HNF1B* variant, but it is important to consider discussing this first with a genetic counsellor.

What do I do if I want to know more?

If you would like to know more, the best thing to do is ring between 0900 and 1700 to arrange to talk to Dr Coralie Bingham on 01392-406366. Alternatively you can write with any questions to the following address:

Dr Coralie Bingham
Exeter Kidney Unit
Royal Devon and Exeter Hospital (Wonford)
Barrack Road
Exeter
UK
EX2 5DW

Email: coralie.bingham@nhs.net

There are also two websites with further information: **www.diabetesgenes.org** and **www.rarerenal.org**.

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Information for clinicians – monitoring patients with a disease-causing variant in the Hepatocyte Nuclear Factor-1 Beta (*HNF1B*) gene

Background

Patients with pathogenic variants in the *HNF1B* gene can have a variety of clinical features[1]. We have summarised which tests may be helpful in the detection and monitoring of different aspects of the disease based on our centre's experience in monogenic diabetes; there is insufficient information in the literature currently for evidence-based guidelines.

Imaging

All patients should undergo a renal ultrasound scan to look for evidence of a renal structural anomaly. If abnormal, we would suggest this is repeated every 3-5 years.

If the initial ultrasound scan is unremarkable, we would suggest repeating this every 3-5 years throughout childhood. In adults, it should be sufficient to monitor renal function using serum creatinine and estimated glomerular filtration rate (eGFR).

Imaging may also detect genital tract malformations, which can be seen as part of the disease spectrum.

Renal function

All patients should have their renal function checked with a serum creatinine and eGFR measurement. If patients have evidence of chronic kidney disease (CKD), they should be monitored in accordance with the clinical guidelines set out by the National Institute for Health and Care Excellence[2].

Adults with normal renal function should have their serum creatinine and eGFR repeated annually. For children with normal renal function, the frequency of monitoring will depend on their clinical situation – every 2-3 years may be sufficient in some circumstances.

Diabetes tests

Patients develop diabetes at a mean age of 24 years but the age of diagnosis can vary widely (reported range 0-61 years)[3]. Patients with known diabetes will need regular monitoring of HbA1c levels.

In adults without a diagnosis of diabetes, we would suggest an annual check of HbA1c. In children without a diagnosis of diabetes, annual urinalysis to test for glycosuria may be helpful. We would also recommend monitoring HbA1c when routine blood samples are being collected. Although HbA1c measurement is not appropriate for diagnosing type 1 diabetes in children[4], diabetes associated with HNF1B disease usually has a more insidious onset. Families should also be educated on the development of diabetes symptoms (polyuria, polydipsia and unexpected weight loss).

Neurodevelopmental disease

This is only a feature in patients with an *HNF1B* deletion. Patients may have ASD, ADHD and/or learning disorder. Patients may benefit from psychiatric or psychological assessment to facilitate access to support services.

Other tests

The following table summarises other tests that are useful in HNF1B disease.

Clinical feature	Test	Comment
Pancreatic exocrine dysfunction	Faecal fat Faecal elastase	Pancreatic enzyme replacement therapy will be required if evidence of clinically significant malabsorption
Deranged liver function	Liver function tests	Increase in liver enzymes may be seen and is usually asymptomatic
Hypomagnesaemia	Serum magnesium	Hypomagnesaemia is usually asymptomatic and rarely requires treatment
Early onset gout/hyperuricaemia	Serum urate	Hyperuricaemia may predispose to gout

Further information

The following review article may be helpful:

Clissold R et al. HNF1B-associated renal and extra-renal disease—an expanding clinical spectrum. Nat Rev Nephrol 2015; 11: 102–112. Published online 23 December 2014; doi:10.1038/nrneph.2014.232

References:

1. Bingham C and Hattersley AT. Renal cysts and diabetes syndrome resulting from mutations in hepatocyte nuclear factor-1. Nephrol Dial Transplant 2004; 19: 2703-08

2. National Collaborating Centre for Chronic Conditions. Chronic kidney disease: national clinical guideline for early identification and management in adults in primary and secondary care. London: Royal College of Physicians, September 2008.

3. Chen Y et al. Systematic review of TCF2 anomalies in renal cysts and diabetes syndrome/maturity onset diabetes of the young type 5. Chin Med J 2010; 123: 3326-33

4. John WG. Use of HbA1c in the diagnosis of diabetes mellitus in the UK. The implementation of World Health Organization guidance 2011. Diabet Med 2012; 29: 1350-7

5. Clissold R et al. Chromosome 17q12 microdeletions but not intragenic *HNF1B* mutations link developmental kidney disease and psychiatric disorder. Kidney International 2016; 90: 203-211