

NATIONAL CENTRE FOR MEDICAL GENETICS

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GUIDELINES

Guidelines for Primary Healthcare Professionals

Genetic Testing & Risk Assessment of Rare Disorders

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BACKGROUND

Authors & Funders

This handbook has been developed by staff at the National Centre for Medical Genetics (NCMG) and the National Children's Research Centre (NCRC), Dublin, Ireland.

The Health Research Board is supporting the development of this rare disease handbook through their Knowledge Exchange and Dissemination Award which aims to maximise the uptake of research findings into policy and/or practice (grant MRCG/2011/17/K).

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ABOUT THIS HANDBOOK

Rationale and Project Team

This handbook has been developed by members of the National Centre for Medical Genetics (NCMG) and the National Children's Research Centre (NCRC) as a guide for health practitioners, particularly general practitioners and midwives, in relation to common clinical genetic queries. It is hoped that the information contained herein will go some way towards bridging the information gap that exists in the context of these patient queries. The advice contained in this handbook has been developed and approved by clinical and laboratory-based experts on rare disorders and genetic testing.

The handbook provides information and guidance on best practice with respect to genetic testing, including a range of FAQ style sections on what to do in response to common scenarios. Similarly, the handbook describes the role of the National Centre for Medical Genetics, and how the Centre can be of assistance to primary healthcare professionals and midwives.

We also describe options for practitioners and patients with regard to genetic counselling. In response to feedback from practitioners, we have included information on genetic testing for cystic fibrosis; an area that is particularly relevant since the introduction of the new-born screen programme in July 2011.

We see this handbook as an evolving tool, and we very much welcome feedback as to how it might be improved and developed.

We are extremely grateful to the project team and contributors who wrote, compiled and developed the various sections within the handbook. We are also indebted to our funders, the Health Research Board (HRB), who recognised the provision of this information to healthcare practitioners as a priority and supported the development of the project.

Finally, this handbook forms just one part of our outreach and education efforts. We have developed a microsite – where all of this information is available to download in single section format, along with news and events – which is available to view at www.ucd.ie/medicine/rarediseases.

Thanks for reading,

Rare Disease Handbook Project Team

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KEY FACT

The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder.

Genetic Testing

What is Genetic Testing?

Genetic testing involves analysing blood samples for alterations in the DNA that can cause hereditary diseases.

What types of genetic disorders can be tested?

There are two main types of genetic disorders:

Chromosome disorders

Chromosome testing involves looking at all 46 chromosomes in the human cell

Single gene disorders

Single gene testing involves targeting the DNA specific to that gene to look for alterations in the DNA sequence that might lead to a genetic disorder

When would we do chromosome testing?

Chromosome testing is done on newborn babies with birth defects or on couples who have had recurrent (≥ 3) miscarriages. Chromosome testing of at-risk relatives is available if something is picked up in a family member. If their relatives are at risk of carrying the same chromosome finding, that might put them or their children at risk of having a child with significant health problems.

When would we do single gene testing?

Single gene testing is done on children and adults who present with features typical of a specific genetic disorder (e.g. Cystic Fibrosis; Tuberous Sclerosis). The test is performed to confirm the clinical diagnosis. Once confirmed, we can offer genetic testing to other at-risk members of the same family. Their relatives could carry the same DNA alteration that might put them, or their children, at risk of having a child with health problems.

What is carrier testing?

Carrier testing is done to determine:

- a. If someone carries a chromosome abnormality that is causing health problems in their family or
- b. If someone carries an alteration in a gene that might cause health problems for them or their (future) children

When would we ask a GP to take a blood sample for us?

As we are a National service we see families from all over the Republic of Ireland. Sometimes we need to offer cascade screening to elderly or sick relatives living far from Dublin. The result on this relative could have important implications for the wider family. We will ask GPs or practice nurses to help us with sample collection under these circumstances.

Sometimes we get referrals from GPs asking us to advise a family member of an affected individual. Depending on the condition (e.g. Cystic fibrosis), there are times when we, in turn, will ask the GP to help by arranging the genetic test, and we will offer the advice once the results are back.

The main reason we do this is to minimise appointments. Our staffing levels are between 10-15% equivalent European centres and our waiting times are > 1 year.

We have started a strict triage process to attempt to manage the waiting list and reduce waiting times. Part of this triage is to arrange genetic testing for certain conditions with the GPs help.

For certain genetic conditions, where the test is a predictive test, all relatives must be seen by a member of NCMG before genetic testing can take place (e.g. Huntington's Disease, cancer genetic tests).

Those that test negative do not require an appointment and are sent a letter of reassurance, thereby freeing up appointments for others.

What sort of blood samples do we request?

Sometimes we ask you to take blood to do carrier testing on an at-risk individual. We would send you details on how to go about this.

- a. If the disorder in the family is a chromosome problem then blood needs to be taken in lithium heparin tubes and sent to the chromosome laboratory at The National Centre for Medical Genetics, Our Lady's Children's Hospital Crumlin, Dublin 12
- b. If the disorder in the family is a single gene disorder then blood needs to be taken in EDTA tubes (the same as full blood count tubes) and sent to the molecular laboratory at NCMG, OLCHC, Crumlin, Dublin 12.

In both cases, we need to know the name of the affected relative and date of birth (if possible), which must be included on the form with the sample.



How do I go about arranging genetic testing?

Genetic testing is available for most genetic conditions, either locally at NCMG or abroad (arranged through NCMG).

However, for many conditions it is advised that they see someone from the Clinical Genetics Department prior to testing.

For example, Part IV of the disability act 2005 states that genetic testing (processing of data in legal terms) should not be done without providing information or without consent being obtained. NCMG tries to provide information to patients and clinicians regarding if, when and how to pursue genetic testing.

Please note that there are times when we cannot offer testing. For example, we always need a sample from the affected individual before being able to advise any at-risk relatives. If the affected relative has died, then we may not be able to identify the family's risk.

For families with whom we have worked previously, we do request that GPs and other health care professionals help us by taking bloods from at-risk family members. This is because many families cannot travel to us to have blood taken.

Why are the genetics laboratories so strict about documentation on blood samples?

The genetic laboratories adhere to the blood transfusion guidelines. They insist that names and dates of birth are exactly the same on blood bottles and the paperwork attached to the sample.

This is because a genetic test result not only has implications for the patient but also their relatives. If a sample mix up occurs the wrong risk could be given not only to the patient but also their relatives.

Any samples that do not meet their guidelines are discarded.



THE CLINICAL GENETICS SERVICE AT THE **National Centre for Medical Genetics** (NCMG)

What is the purpose of the NCMG?

NCMG was set up approximately twenty years ago to offer Genetic counselling services to all residents (adult and paediatric) of the Republic of Ireland.

Who are the team?

The Clinical service is staffed by four medical consultants and six full-time genetic counsellors. We have a further three genetic counsellors who are funded through charitable organisations who provide services to families with specific genetic disorders.

What sort of families do we see?

Children and adults with:

- Birth defects
- Unexplained intellectual disability
- Chromosomal disorders
- Single gene disorders (e.g. cystic fibrosis)
- Pregnant woman with an abnormality identified on antenatal scan, possible teratogenic disorders
- Sudden death syndrome (?SADs)
- Rare cancer syndromes or hereditary breast and/or bowel cancer

What are the roles within NCMG?

Clinical Genetic consultants see families (adults and children) with either complex or unknown disorders which are thought to have a genetic basis. Our role is to make a diagnosis if we can, discuss recurrence risks and advise on preventative options if available. We also advise on any new clinical trials that we are notified of.

Genetic counsellors are graduates with either a scientific or nursing background who train in genetic counselling. Genetic counsellors advise families on the risk of recurrence of the genetic disorder within the family where there is a known genetic diagnosis (mostly confirmed by a genetic blood test). They discuss preventative options including reproductive options and the importance of folic acid for those families who have a child with a genetic problem. The cancer Genetic counsellors discuss cancer screening including mammography and prophylactic surgery options. The cardiac Genetic counsellor, who is funded by the Children's Medical and Research Foundation (CMRF), Cardiac Risk in the Young (CRY) and Heart House, discusses genetic testing for disorders causing sudden adult death syndrome. Both of the latter two counsellors will arrange cascade genetic testing for at-risk relatives and any screening options. With increasing availability

of new genetic tests, we are finding an increasing number of referrals to help with interpretation of genetic test reports.

There is a genetic counsellor employed by the neurofibromatosis (NF) society who provides clinics to patients affected by NF1 and NF2. Shire pharmaceuticals have recently funded a Genetic counsellor to help with the volume of metabolic referrals from the National Centre of Inherited Metabolic Disorders (NCIMD) to NCMG.

How much does it cost and is it just Dublin based?

The service is free and is mainly out-patient based. Most clinics are held for adults and children at Our Lady's Children's Hospital in Crumlin but we do hold regular clinics in Temple Street Children's University Hospital as well as Cork University Hospital, Limerick Regional Hospital and Galway Regional Hospital.

What can NCMG offer my patients?

In the last twenty years, huge advances have been made in the field of Clinical Genetics. Isolation of many new disease genes has allowed us confirm diagnoses, offer cascade screening to at-risk relatives and offer preventative options to couples at high risk. Unfortunately, our service is not as comprehensive as we would wish and waiting lists far exceed European norms.

How do you manage referrals?

We process referrals through our triage process. Following triage, referrals are dealt with in a number of ways

- a. Accept to the waiting list
- b. Reject the referral if it is inappropriate and we cannot help
- c. We might ask you to do some blood tests up front to facilitate the referral
- d. We might ask you for more information on the affected individual in the family (this person might not be your patient so you might need to go back to your patient and ask them to gather further details)

We request steps (c) and (d) to help expediate appointments. In some cases the information provided means that we can reassure the family without the need for an appointment, thereby freeing up appointment times for those at risk and maximising efficiency of waiting lists.

For any predictive genetic tests, patients must be seen first prior to a blood test being taken.

Any referrals that are awaiting blood tests or further information are put on hold pending the results of the tests or the receipt of the information.

Service Provision

We introduced restrictions on our service in February 2012 as our waiting times were unsustainable and our staffing levels are inadequate (Figure 1). We no longer offer genetic counselling to parents of children with the following conditions: isolated cleft lip/palate, non-disjunction trisomy 21, isolated deafness and neural tube defects. Whilst we regret this restriction, we had no option. None of these disorders are rare diseases and there is some support for these families within the health care providers which can partly compensate. Rare disorders were prioritised as there is minimal to no support for many of the rare diseases. These restrictions will be reviewed on an ongoing basis. Should our staffing crisis improve in the future we will reconsider this decision.

What is a rare disease and why is it so special?

The EU council recommendation on rare diseases comes into force in October 2013. As 70-80% of rare diseases are genetic, this directly affects our service. Essentially, any patient with a rare disorder has a right to up-to-date information about their condition, regardless of the rarity of their disorder. They also have a right to travel within Europe to access advice, treatment and/or ongoing clinical trials if they cannot access a centre of expertise within their own country. We have had to prioritise these families as, often, we are the only centre that can provide the service required.

What is the rare disease paradox?

The diseases are rare, patients with rare diseases are many

The paradox of rare diseases is that, whilst each disease is individually rare, collectively there are thousands of rare diseases which means that overall they are common. In fact, there are approximately 160,000-200,000 people living with a rare disease in the Republic of Ireland. It is therefore not unusual to have a rare disease.

Where can I find further information?

Our website www.genetics.ie provides information on our service including how to make a referral, consent forms, instructions for sending samples, waiting times for clinics and cancer questionnaires.



Genetic Counselling

FOR GENETIC DISORDERS

Focus on families who are planning pregnancies or who are currently pregnant.

1 Management of women in pregnancy or considering a pregnancy when there is a known genetic disorder in the family

Ideally, pre-pregnancy planning is recommended where there is a family history of a genetic disorder. It is better if we can establish family relationships and confirm diagnosis prior to a pregnancy. This allows the team time to establish if the patient

- a. is at risk
- b. if they are at risk whether there is any testing the medical team can offer in current or future pregnancies

Those who are not at risk can be reassured and discharged. We understand that the National Centre for Medical Genetics (NCMG) waiting list is long and frustrating for our patients, referrers and NCMG staff (Figure 1A/B). This sometimes leads to a pregnancy occurring prior to us being able to offer genetic counselling and pre-conceptual advice.

Before testing an at-risk individual, ideally we first need to identify the specific genetic alteration in their affected relative.

Confirming diagnoses in relatives can take time - consent is often required. We understand it may not be easy to get consent of diagnoses from close relatives. If the at-risk patient is already pregnant it may not be possible to establish risks or offer genetic testing as there may not be enough time to gather consent and the necessary information.

Some genetic conditions are caused by common DNA alterations which can be easily screened for. For example, if the affected relative has cystic fibrosis, they can undergo routine genetic testing of a panel of common disease-causing alterations in the cystic fibrosis gene to identify which specific genetic alteration they have. Once clarified that the affected relative has a common DNA alteration, we can offer genetic testing to the couple considering pregnancy or confirm whether or not they carry the family genetic disorder.

However, for other disorders (e.g. Duchenne muscular dystrophy), the genetic alterations which cause the condition may be unique to the particular family and may not be identified during routine genetic testing. In this instance, further work is required to identify the specific family mutation in the affected relative before establishing carrier status in the pregnant relative.

In order to establish a genetic diagnosis, we need a blood sample from the affected individual. Genetic reports on parents are only requested where a genetic abnormality is identified in the affected child and there is a risk that it might be hereditary. Note, not all genetic disorders are hereditary. An affected child may have a genetic alteration that was not present in or inherited from either parent, but arose for the first time in the affected child. The parents' samples are analysed and then compared to their child's. The report will include a comparison of both results.

Whilst routine pre-conceptual genetic testing can take up to 4 months, testing is expedited during an ongoing pregnancy. If there is a known genetic alteration in the family, results can be made available within two weeks during a pregnancy. However, if the genetic alteration is not known, there is no guarantee that this will be possible within the time-frame of a current pregnancy. This is why pre-conceptual referral is so important. There are 23,000 different genes (3,674 known disease genes) and testing for only ~20 is available at NCMG. Therefore many genetic tests are sourced from accredited laboratories abroad. DNA is extracted in NCMG and an aliquot is sent for testing to the foreign laboratory. Some genetic tests take longer than others to complete and for some disorders there is no genetic testing available.



Prenatal testing

NCMG co-ordinates pre-natal testing for families known to have a genetic disorder.

The fetal assessment unit does not request the assistance of NCMG when prenatal testing is carried out because of advanced maternal age.

The Genetic counsellors co-ordinate approximately 100 prenatal tests for families annually. This number is increasing year on year. Most families are known to us and self refer to access antenatal testing.

Others are referred in pregnancy and we can establish risks in time for a pre-natal test in some cases. The majority of couples opting for testing face a high risk (25% or greater) of recurrence.

However, up to 25% of requests for pre-natal testing to NCMG are for disorders where there is a low recurrence risk (<1% to ~<5%). These requests tend to come from families who have had a child with a severe genetic disorder and the couple cannot contemplate a recurrence.

The Genetic counsellor liaises with the family before testing to ensure a complete understanding of what the testing process entails and how the couple wish to learn of the result.

The Genetic counsellor requests an appointment with one of the three Dublin fetal assessment units based on the date of the patients last menstrual period (LMP).

As many samples need to go abroad and timing is of utmost importance, all pre-natal tests organised by NCMG are performed in Dublin.

We aim to get a result back to the couple as soon as possible to allow an option regarding decisions on rest of pregnancy care and management.



Most of the pre-natal tests we request are done by chorionic villus sampling (CVS) as this gives a sample that produces good quality DNA that can be extracted speedily. The optimal time to perform this test is between 11-13 weeks.

Antenatal tests carried out before week 11 risk higher rates of maternal cell contamination (MCC) and failure due to sample dissection difficulties. NCMG cytogenetic and molecular laboratories process the CVS samples. A result on an at-risk fetus can be reported back to the couple within 2-3 weeks in most cases.

The cytogenetic laboratory analyses the chromosomal complement of the fetus (termed karyotyping). The main antenatal referral requests to the cytogenetics laboratory come directly from obstetricians because of concerns on antenatal scanning or the sample has been taken for maternal age/anxiety.

The clinical team at NCMG do not get involved with these referrals. NCMG clinical staff co-ordinate testing for between 30-40 families who have had a previous child with a rare chromosomal anomaly (e.g. unbalanced chromosomal translocation). These require liaison with the cytogenetics laboratory as often special Fluorescent In Situ Hybridisation (FISH) probes are required for the genetic analysis. These are high risk cases and the analysis is targeted at the familial abnormality- it is not a routine chromosome analysis.

There are some chromosomal disorders where an amniocentesis is preferred to a CVS because of the quality of the chromosome test. We advise the fetal assessment unit accordingly.

The molecular laboratory processes samples for single gene genetic testing (cystic fibrosis, spinal muscular atrophy, sickle cell anaemia). Whilst the latter three disorders can be analysed locally (they are the most common requests for pre-natal testing we handle), we also get requests for testing of other less common genetic disorders.

As we cannot test for all genetic conditions in-house, testing for these conditions takes place in up to 200 different foreign diagnostic laboratories. Samples are couriered with appropriate documentation to avoid delays in customs.

The molecular laboratory also performs Maternal cell contamination testing on all of our pre-natal tests to ensure that the sample that has been tested is derived from fetal DNA, and not from the mother which would give an erroneous result.

2 Management of couples where a diagnosis of a genetic disorder is reached in a pregnancy or in the postnatal / neonatal period

- Sometimes the fetal assessment teams will involve us in ongoing pregnancies where abnormalities are identified on scan or on amniocentesis.
- If the amniocentesis identifies a rare chromosomal anomaly we will see the family and advise of the likely outcomes. We source our information from the latest literature and the patient organisation "Unique" (www.rarechromo.org).
- If the scan identifies a specific genetic disorder (e.g. osteogenesis imperfecta) or an abnormality with a possible genetic explanation we are asked to help meet with the family and discuss possible diagnoses and outcomes.
- If a baby is identified on ultrasound scan to have multiple abnormalities with a normal karyotype but with a likely poor prognosis, then we may be able to "bank" DNA for future analysis. This can be useful for counselling a diagnosis in future pregnancies.
- After the birth of the child with a genetic disorder, follow-up is offered to discuss recurrence risk and options for future pregnancy and management of the wider family.

Ireland has a high birth rate and also has double the liveborn malformation rate of other European countries. The neonatal teams are well experienced in the investigation of babies with malformations. The Clinical Genetics team are asked to see neonates with multiple malformations, to see if we can make a diagnosis that might influence management.

Follow up appointments involve discussion on the disorder and possible outcomes. We also discuss:

- Recurrence risk and preventative options including limiting family size, pre-natal testing, ovum or sperm donation and pre-implantation genetic diagnosis in the future if appropriate.
- Risks to other family members.
- If the child has a disorder where the risk to more distant relatives is high (e.g. chromosomal translocation or X-Linked gene), we do try to help our families disclose this information by providing our patients with information letters or leaflets that they can pass on to the wider family. However it is the responsibility of the person we see in clinic to disclose this information to their relatives.
- The at-risk relative just needs to contact our department directly (with the name of the affected patient) and we can organise an assessment. Alternatively, if you are referring such a case, let us know the name of the affected individual and we will arrange an appointment as soon as possible.
- Where birth defects occur as sporadic events and relatives are not at increased risk, we request couples to inform other family relatives to reassure them.



Hereditary Haemochromatosis

FOR GPs

What is haemochromatosis?

Haemochromatosis is iron overload of the liver, pancreas, heart, joints and other organs impairing their structure and function.

Hereditary Haemochromatosis (HHC) is a common inherited disorder characterised by the genetic predisposition to absorb excess dietary iron. In Northern Europe, 95% of patients with HHC will have mutations in the HFE gene.

HHC is an adult onset disease, children do not need to be tested. We advise that children of affected parents attend their GPs when they are adults themselves to arrange for genetic testing at this stage.

Secondary iron overload is seen in a variety of conditions including alcoholic liver disease, cirrhosis from any cause, haemolytic anaemia and transfusional/parenteral iron overload.

The genetics of HHC

In Northern Europe 10% of people are carriers of one of the two main alterations (called mutations) in the HFE gene; C282Y and H63D. Carriers (also known as heterozygotes) have one altered HFE gene and one normal HFE gene and are generally not affected by iron overload.

Iron overload can arise when both copies of an individual's HFE gene (also known as homozygous affected) are altered/mutated.

A blood-based genetic test can be arranged to screen for the HFE C282Y and H63D mutations. Many large teaching hospitals around Ireland offer this service. Please contact your local unit for details of the nearest hospital that will offer genetic testing.

Currently there is some debate regarding the H63D variant, some centres argue that the effect of this variant is so small that it should not be regarded as a HHC susceptibility finding at all. As this debate is ongoing, we have included H63D in our table but the advice may change as the involvement of H63D in HHC is clarified.

HFE Gene Copy 1	HFE Gene Copy 2	Genotype	% of Irish population	Risk of developing clinically significant iron overload
Normal	Normal	Homozygous normal	57.2%	None
C282Y	Normal	Heterozygous carrier of C282Y	14.9%	Unlikely to develop HHC but may have mild symptoms (lethargy, joint pain, weakness)
H63D	Normal	Heterozygous carrier of H63D	22.8%	None and unlikely to have symptoms. No need to offer testing to other relatives
C282Y	C282Y	Homozygous for C282Y	1.2%	Increased risk of developing HHC
C282Y	H63D	Compound heterozygous	2.5%	Increased risk of developing clinically milder form of HHC; not as severe as C282Y homozygotes
H63D	H63D	Homozygous for H63D	1.5%	Slightly increased risk of developing HHC; usually mild

Not everyone who inherits two HFE mutations will develop iron overload and fewer will develop the clinical syndrome.

The majority of Irish HHC patients have two copies of the C282Y mutation (homozygous affected) but clinical and biochemical features vary

- 90% have high plasma iron (raised Transferrin Saturation)
- only 50- 70% have high tissue iron (raised serum ferritin)
- only 35% develop organ damage (with ferritin > 1000ng/ml)

There are several factors known to influence expression of the disease in those patients that are genetically susceptible. Women tend to have a later and less severe onset because of menstruation and pregnancy. Alcohol, a diet high in iron, obesity and hepatitis B and C increase the chance of clinical symptoms.

There are ~54,000 people in the Republic of Ireland with the genetic predisposition to HHC. We don't diagnose everyone with the genetic predisposition because only some will develop symptoms. Nevertheless, there is also evidence suggesting that many individuals who are clinically affected and are symptomatic are not identified.

What are the symptoms?

Symptomatic organ involvement, when it does occur, tends to begin in middle age. No two people are alike and symptoms will vary from person to person.

The most common symptoms noticed by people with HHC are:

- fatigue, general weakness and lethargy
- joint pain
- abdominal pain
- sexual dysfunction – loss of sex drive
- discolouration or bronzing of the skin
- mood swings and irritability

The early bio-chemical signs of HHC tend to be:

- hepatomegaly (enlarged liver)
- abnormal liver function tests (LFTs)
- increased ferritin and transferrin saturation

If not treated early, people with HHC can develop diabetes mellitus, cirrhosis, cardiac problems and hepatocellular carcinoma.

Diagnosis of HHC

Early diagnosis is not easy, since presenting symptoms are relatively common and non-specific. Consider diagnosis, especially if two or more of the following:

- Men aged 40-50 years
- Type 2 diabetes mellitus, especially those diagnosed at an early age, with elevated LFT, hepatomegaly, early-onset sexual dysfunction or abnormal iron markers
- Unexplained liver disease or liver disease with abnormal iron markers

- Chronic unexplained fatigue, weakness and abdominal pain
- Asymptomatic patients with incidental elevated LFT, ferritin or hepatomegaly
- Early onset arthralgia (joint pain), atypical arthropathy
- Early onset male impotency, early menopause and loss of libido in women
- Early onset arrhythmias and cardiomyopathy
- Unexplained increasing skin pigmentation or 'permanent tan'
- First degree relatives over 18 years of age of a confirmed case of HHC

What are the tests?

Transferrin Saturation (TS) and Ferritin

Non-fasting test initially if considering the diagnosis and/or as part of a general screen. Both TS and ferritin are required as patients in the early stages of clinical disease can have normal ferritin, but raised TS. In addition, ferritin is an acute phase protein which can be raised in intercurrent illness.

If the TS is >50% a fasting TS and ferritin is needed as it avoids effect of diet and diurnal variation.

If the fasting TS is >55% (in men or post menopausal women) or >50% in premenopausal women, this indicates a need for HFE genetic testing, regardless of the ferritin level.

These tests may need to be done on a serial basis if the genetic test reveals someone has two susceptibility mutations.

HFE Genetic Testing

A serum ferritin >300mcg/l in men and postmenopausal women or >200mcg/l in premenopausal women, suggests that the patient may be iron overloaded. This should prompt a fasting TS. If this is abnormal (see above) HFE genetic testing should be done and a referral to the liver centre once the genetic test result is available. If the patient is negative for the HFE mutations, further investigations will be needed.

A ferritin of 1000mcg/l should prompt a fasting TS. If this is abnormal, a referral to gastroenterology should be made at the same time as the blood is sent for genetic testing.

Genetic testing for HFE mutations is positive in over 95% of those affected in our population. A genetic test never needs to be repeated.

Liver biopsy

Secondary care will consider the need for liver biopsy and advanced genetic testing.

A liver biopsy will not be needed if the patient:

- is aged <40 yr
- does not have hepatomegaly
- has a normal alanine aminotransferase test (ALT)
- has ferritin <1000mcg/l

Management Considerations

Monitoring

- Asymptomatic C282Y homozygote with normal ferritin level at diagnosis: annual TS and ferritin recommended
- Asymptomatic C282Y/H63D compound heterozygote with normal ferritin level at diagnosis: 3 yearly testing of ferritin and TS is satisfactory
- If cirrhosis is present: surveillance for hepatocellular carcinoma with 6 monthly ultrasound scan and alpha feto protein levels

Dietary Advice

Avoid iron supplements. No other dietary advice. It is important to continue to eat the high iron leafy vegetables as these have health benefits.

Cascade (family) Screening

Once a person with Haemochromatosis is diagnosed, family screening is recommended for all first-degree relatives. If patients with HHC are worried about their children, it is useful to perform genetic testing on the other parent to predict whether the children will need to be considered for genetic testing. If your patient tests positive for two HFE mutations, further iron study tests (transferrin saturation and ferritin) will be required.

Relationship to affected individual	Risk of having two non-working HFE genes	Risk of developing disease	Advice
Sibling (brother/sister)	~27%	5.4%	Genetic test*
Son or daughter	11%	2.2%	Genetic test*
Parent	9%	2%	Genetic test*
Spouse	Population risk ~0.5-1%	Population	Genetic test if concerned about risk to children
All other 2° degree relatives (uncle/nephew/cousin)	Slightly higher than population risk	Slightly higher than population	No need to test unless family history of HHC on both sides

*assuming spouse is of Irish ancestry.

If spouse is not from Europe then the risks reduce substantially as the likelihood that the spouse carries an altered HFE gene decreases.

Treatment -Venesection

Once the serum ferritin is above the normal range venesection will be started in secondary care. The aim is to keep ferritin <100mcg/l. Some patients may consider blood donation if they are well and fulfil donation criteria.

If venesection is needed and is started before 35 yr, all major hepatic morbidity can be avoided.

Once a person is affected clinically, some signs and symptoms respond more readily to venesection:

- Fatigue, abdominal pain, hepatomegaly and skin pigmentation respond very well
- Joint pain, glucose intolerance, NIDDM and cardiac signs improve in 40%
- Hypogonadism and impotence respond poorly
- Cirrhosis and insulin-dependent diabetes are irreversible, but venesection can reduce portal hypertension and reduce insulin requirements
- Risk of hepatocellular carcinoma is not removed if cirrhosis is already present

Useful Information

- European Association for the Study of the Liver. EASL Clinical Practise Guidelines for HFE Hemachromatosis. Journal of Hepatology (2010) doi: 10.1016/j.jhep.2010.03.001 http://www.easl.eu/assets/application/files/03d32880931aac9_file.pdf
- Irish Haemochromatosis Association www.haemochromatosis-ir.com/home.html
- British Haematology Society www.bcsghguidelines.org
- The Haemochromatosis Society www.haemochromatosis.org.uk

Regional Contacts

Dr Stephen Stewart, Hepatology, Mater Misericordiae University Hospital





Common Clinical Genetic Scenarios

We have identified five possible scenarios that GPs and Midwives might encounter in their surgeries and advise on how to approach issues that might come up when taking the family history.

SCENARIO 1

A woman tells you she has a relative with an X-linked disorder and is worried about her risks of having an affected child. The risk to this lady depends on (i) the type of X-linked disorder, (ii) who the affected relative is and (iii) how she is related to them.

- If the relative is on the fathers side of the family (e.g. brother/cousin of her father), and her father is **healthy** then she is **not at risk**.
- If a woman's father is affected by an X-linked condition then she is an obligate carrier of that disorder and has a 1 in 4 risk of having an affected child or a 1 in 2 risk if the fetus is known to be male. For example, haemophilia in a man means that all of his daughters will be carriers.

Relationship to affected relative with X-linked disorder	Risk of being a carrier	Risk of having an affected pregnancy	NCMG advice
Sister of affected male	Risks vary depending on the disorder	Significant	Find out name of affected relative and contact NCMG for specific risk and advice
Aunt of affected male	Risks vary depending on the disorder	Significant	Find out name of affected relative and contact NCMG for specific risk and advice
Niece with the affected uncle being on her mothers side (mother's brother affected)	Risks vary depending on the disorder	Significant	Find out name of affected relative and contact NCMG for advice

SCENARIO 2

A patient / pregnant woman tells you he/she (or his/her partner) has a relative with cystic fibrosis (CF). As CF is so common in Ireland, we do offer carrier testing if there is a family history. However, whilst parents of a child with CF have a 1 in 4 risk of recurrence, more distant relatives overall have a <1% chance of having an affected child unless their partner also has a family history.

Prior to testing, the risks to relatives are detailed in the table below.

Relationship to affected relative	Risk of being a carrier	Risk of having an affected child
Sibling	2/3	<1% (assuming their partner does not have a family history of CF)*
Aunt/uncle	1/2	<1% (assuming their partner does not have a family history of CF)*
Grandparent	1/2	n/a
First cousin	1/4	<1% (assuming their partner does not have a family history of CF)*

* the risks are greater if the partner has CF or has a family history of CF

ACTION

What can you do?

Offer genetic testing if they wish.

Carrier testing is available to anyone over the age of 16 who has a relative or partner who has CF or carries a CF mutation.

What type of blood sample is needed?

A 2-3ml peripheral blood sample in an EDTA bottle is required. This is the same bottle used for full blood count (FBC) analysis.

Does the blood sample need to be refrigerated?

If possible, please refrigerate the sample however it should be fine at ambient temperature for several days.

How do I send the sample?

If you have an arrangement with your local hospital they may be able to deliver the sample to us. Otherwise you can send it by regular post. Guidelines for packaging of specimens for transport can be downloaded at www.genetics.ie/pir/sending_samples.pdf

What information needs to be included with the referral?

- your patient's name and DOB
- the name and DOB of the family member or partner who has CF or is a carrier of a CF mutation and their relationship to your patient*.
- the ethnic background of the patient as different mutations are responsible for CF in different ethnic groups
- your own contact details

* If the mutation in the affected relative is not known, testing can be done for common CF mutations. A report can be issued but it will contain a caveat and the result may not be as definitive as one would like.

Go to www.genetics.ie/pir/CF_pir.pdf to download a CF request form

SCENARIO 3

A patient / pregnant woman tells you he/she (or his/her partner) has a relative (**not his/her own child**) with Down syndrome. The patient / pregnant woman wants to know about whether there is an increased risk of having a child with Down syndrome. This scenario describes a situation where a more distant family member (not the patient's child) has Down syndrome.

Parents of children with Down syndrome do have an increased risk above population and these families should be dealt with by the local maternity unit. NCMG will see those families with high risk Down syndrome due to translocation.

Down syndrome can be caused by:

- non-disjunction [47,XY +21 or 47,XX + 21], (95% of cases) where there is no increased risk to more distant relatives (Fig. 3A)
- translocations involving chromosome 21 (~3%), where the chromosome report clearly states this and recurrence risk can be increased for more distant family members
- mosaic Down syndrome (~2%) where there is no increased risk to more distant family relatives

Translocation Down syndrome

Translocation Down syndrome occurs when part of chromosome 21 becomes attached (translocated) onto another chromosome, before or at conception. Children with translocation Down syndrome have the usual two copies of chromosome 21, but they also have additional material from chromosome 21 attached to the translocated chromosome (Fig. 3B).

Chromosome laboratories alert clinicians looking after a child with a translocation form of Down syndrome of the increased risk. NCMG make a concerted effort of follow up these families. However, disclosure of personal information is only through the family so it is possible that an at-risk relative will not have been informed if communication within a family is difficult.

How to deal with a family history of Down syndrome

Attain the name of the affected relative so that NCMG can check if there is any record of that child on their system and advise you whether your patient is at risk or not.

However, NCMG will not have the records of all cases of Down syndrome in Ireland as the laboratory only started in the 1990's and many prenatal tests for Down syndrome are sent abroad.

What if there is no record of the relative's chromosome report?

If your patient is particularly worried, they need to go back to the family of the affected relative and gain information on what type of Down syndrome their relative has. Without this information, accurate advice cannot be given. The approach to the family with the affected individual has to be through the individual concerned and not by the midwife/clinician/medical team.

Family history of non-disjunction Down syndrome

Relationship to affected relative with Down syndrome	Type of Trisomy 21 in affected relative 47,XY + 21 or 47, XX +21	Risk of having an affected child
Parents	No need for parental bloods	Slight increase above population and maternal age
Sibling, aunt, uncle or cousin	No need for bloods	Same as population, use maternal age graphs

Family history of translocation Down syndrome

Relationship to affected relative with Down syndrome	Translocation Down syndrome	Risk of having an affected child
Parents	Parents chromosomes required to work out risk	May be significant- depends on type of translocation. Family should be seen by NCMG for advice
Sibling, aunt, uncle or cousin	Chromosomes may be required to work out risk	May be significant- depends on type of translocation. Family should be seen by NCMG for advice

SCENARIO 4

A patient/pregnant woman tells you he/she (or his/her partner) has a relative with an intellectual disability (ID). There are numerous causes of intellectual disability and it might not be possible to identify a cause. Many families have been given diagnoses in the past which are erroneous. The Clinical Genetics team can only give advice when a diagnosis is confirmed by medical notes (+/- laboratory test). The closer the relationship to the individual with ID, the higher the risk that the couple may have an affected child.

ID can be due to:

- Non genetic causes
- Genetic causes

The genetic causes can be due to a

- Chromosomal anomaly or
- Single gene anomaly

Both of these anomalies can occur as a sporadic event (new mutation) in a family with negligible recurrence risk to at-risk relatives. However, some inherited forms can occur (chromosomal translocations, X-linked genes causing ID in males etc), so there may be a risk to your patient.

NCMG advice would be to find out

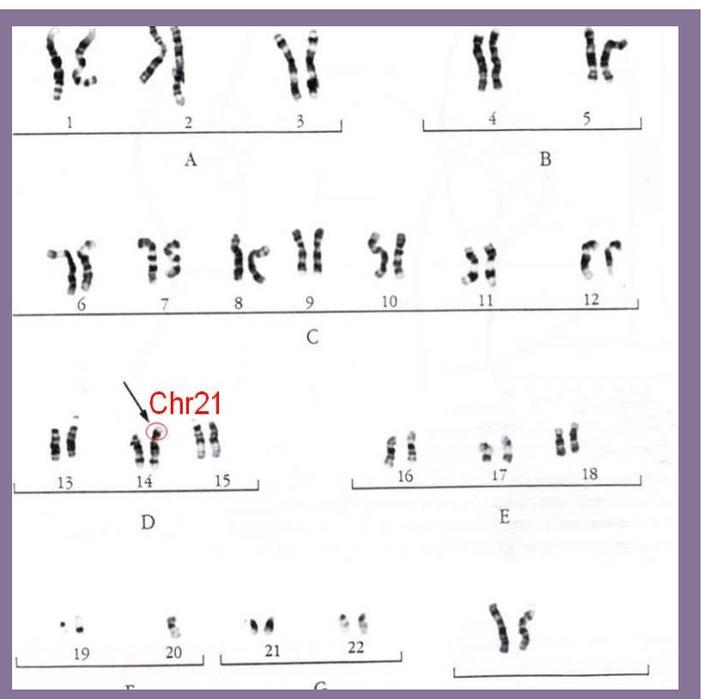
- Who was affected in the family and how they are related to the couple in the antenatal clinic?
- Was the affected individual(s) a male or female?

If your patient was very concerned and wanted to take it further and you would appreciate our advice, we would need details (name, date of birth) of the affected relative(s). We could search to see if there are any records of the affected relatives, and outcomes would be as follows:

- If we could find no records- we cannot help. Depending on the pedigree structure we could give an estimate on recurrence risks (after weighing up all possible modes of inheritance)
- The records are found but indicate that no diagnosis had been reached. Depending on the pedigree structure we could give an estimate on recurrence risks (after weighing up all possible modes of inheritance). We might suggest more updated tests on the affected individual that could be offered, but this is only appropriate if your patient is the parent of an affected child. We cannot re-investigate other people's children (to help establish their relative recurrence risk) without their consent.
- The records are found and NCMG is able to establish a diagnosis from the records. Under these circumstances, we would be able to give accurate risks to your patient. Ultimately, this could mean-
 - a. Negligible risk to your patient; no tests required; reassure your patient
 - b. Increased risk established; NCMG will advise accordingly and arrange assessment



(Fig. 3A) Karyotype of individual with non-disjunction Down syndrome showing three copies of chromosome 21 (called trisomy 21) instead of the normal two copies.



(Fig. 3B) Karyotype of individual with translocation Down syndrome showing the two normal copies of chromosome 21 plus extra material from chromosome 21 attached to the translocated chromosome 14.

SCENARIO 5

CONSANGUINITY AND RISK OF AUTOSOMAL RECESSIVE DISORDERS

We all carry two copies of every gene. Autosomal recessive disorders occur when both copies of a particular gene are not working. Both parents are carriers of this recessive gene, but are healthy because they have one working copy of the gene. If each parent passes on a copy of the non-working gene to a child, the child will be affected by the disorder. Autosomal recessive disorders are more common in consanguineous communities.

Risk of recessive disorder to a pregnancy where consanguinity exists	
Degree of relationship to pregnant woman	Increased risk to baby above population
Father/brother	30%
Uncle	~10%
First cousin	3%
Second cousin	1%
First cousin once removed	1%
Double first cousins	~5-10%

What should you do if a patient tells you he/she is related to his/her partner and they wish to have children?

- Find out how they are related
- Find out if there are multiple consanguinity loops in the family (describes situation where relationship is more than just a once off cousin marriage- where cousin marriages have been occurring throughout the family tree- increasing the risk of autosomal recessive disorders)

How should one advise couples who are related to each other?

- This depends on the ethnicity of the couple
- If the couple are ethnically Irish we offer detailed antenatal ultrasound scans and Cystic fibrosis carrier testing
- If the couple are from the Irish Traveller population, there are distinct genetic disorders that are known (see table below)
- Members of the Irish Traveller population are a group at high risk of having a child with an autosomal recessive disorder. We do welcome referrals into our service from this population as we can offer specific genetic testing which will help define the couple's risk.

Below we have listed some of the disorders we find amongst the Irish Traveller population. In taking a family history you might consider asking specifically about whether any of these conditions are seen within their family.

Disorder	Carrier frequency in the Irish Traveller population	Genetic carrier test
Hurler syndrome	1 in 10	Yes – UK laboratory
Galactosemia	1 in 11	Yes – UK laboratory
I Cell	1 in 10	Yes – UK laboratory
Fanconi's anaemia	Unknown*	Yes – UK laboratory
Osteogenesis Imperfecta (brittle bone)	Unknown*	Yes – NCMG
Bylers	Unknown	Yes – NCMG
Friedreich ataxia	Unknown*	Yes – NCMG
ACTH resistance with natural killer cell deficiency	Unknown*	Yes – NCMG hope to offer this test by end of 2013
Congenital adrenal hyperplasia	Unknown*	Yes – UK laboratory
Infantile liver dysfunction with anaemia and developmental delay (+/- seizures)	Unknown	Yes – NCMG hope to offer this test by end of 2013
Micro-anophthalmia	Unknown	Yes – NCMG hope to offer this test by end of 2013
McArdle disease (Glycogen storage disease type V)	Unknown	Yes – UK laboratory
Primary ciliary dyskinesia (sinusitis and bronchiectasis)	Unknown	Not yet available

- If the couple are not ethnically Irish, we can offer targeted genetic testing depending on the ethnicity:
 - Pakistani couple: offer Beta thalassemia carrier screen and detailed ultrasound scan
 - Chinese couple: offer alpha thalassemia carrier screen and detailed ultrasound scan
 - Couple from elsewhere- contact NCMG and we can advise accordingly

DATA AND STATISTICS

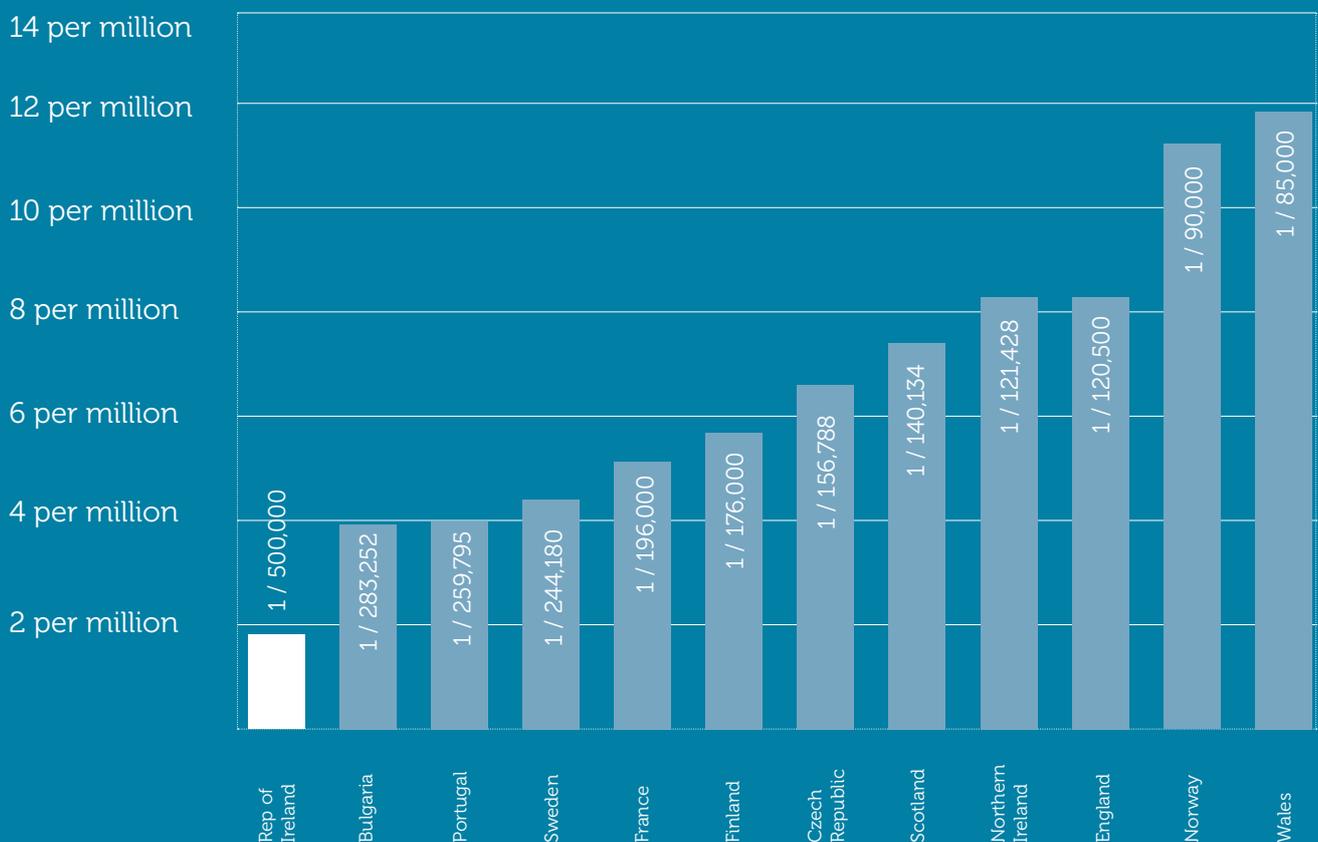


Figure 1A. comparison of the Genetic consultant staffing levels across twelve European countries.

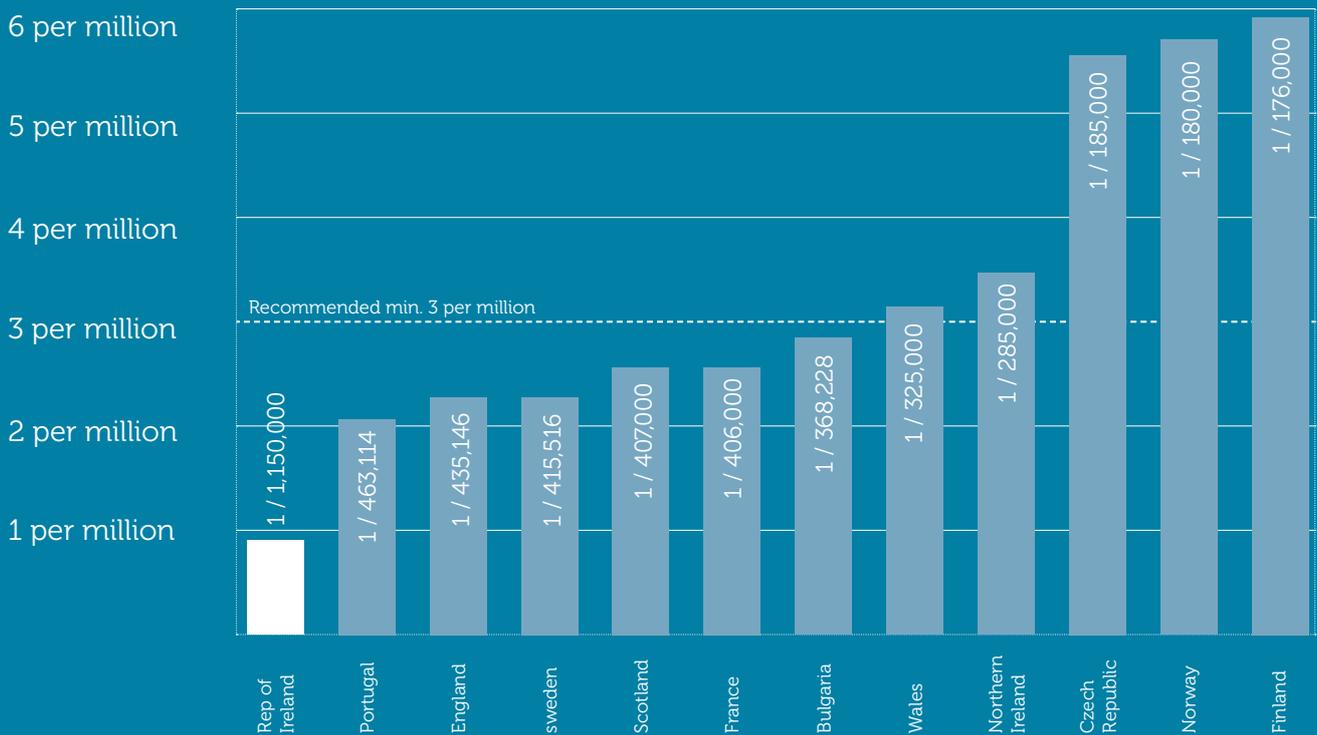


Figure 1B. Number of Genetic consultants per population. A comparison of the Genetic consultant staffing levels across eleven European countries. The Royal College of Physicians UK recommend a minimum of 3 Consultant Geneticists per million. Based on these recommendations, the Republic of Ireland should have 14 Consultant Geneticists for its population of 4.6 million. There are currently 4 Consultant Geneticists in the Republic of Ireland.

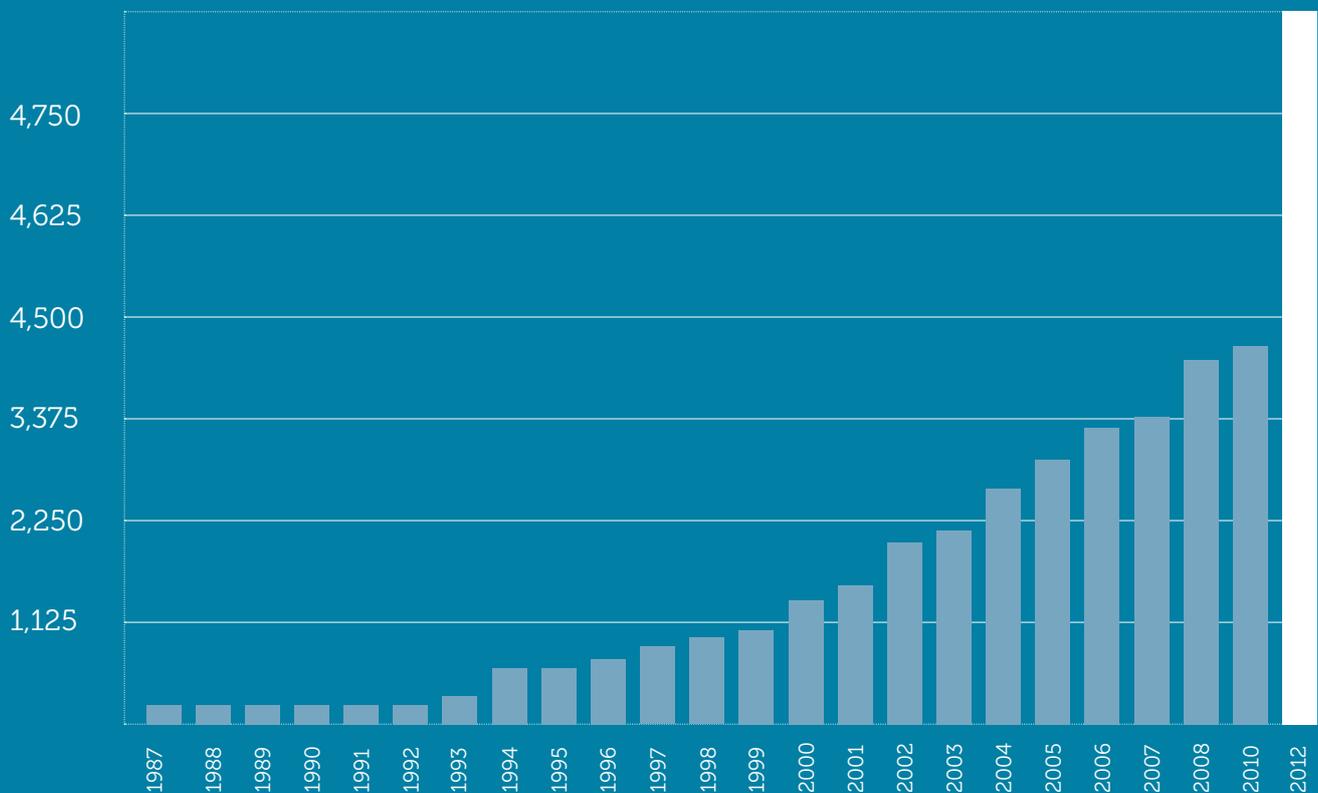


Figure 2. Identification of disease-causing genes. The number of clinical phenotypes for which the molecular basis is known is presented. The figures were taken from <http://omim.org/statistics>.

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