Genetic screening for ethnic minorities

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Why screen in primary care?

At least 5% of the British population consists of members of ethnic minorities at risk for haemoglobin disorders and glucose-6-phosphate dehydrogenase (G6PD) deficiency, and 10% of births in Britain occur in these groups.¹ A smaller group of people of Jewish ancestry are at risk for Tay-Sachs disease. The main objective of screening for carriers of haemoglobin disorders and Tay-Sachs disease is to identify couples at risk of having an affected child. Then they may have an informed choice among the available options,² which include prenatal diagnosis to avoid the birth of a seriously ill child and neonatal diagnosis to allow optimal management of affected infants from the outset. Because carrier screening and counselling must be offered to whole populations it needs to be based in primary care.

At present screening is done primarily in antenatal clinics, but informing people of a major genetic risk should not be left so late.¹ Couples at risk will then have to make undesirably hasty decisions about whether to have prenatal diagnosis or terminate an affected pregnancy and will miss the option of prenatal diagnosis in the first trimester.

Neonatal screening for sickle cell disease and trait is becoming standard practice in many inner city districts.³ When general practitioners are informed of carrier infants born to mothers on their list, they should ensure that the family receives adequate information (see below).

Secondary aims of carrier identification are to help reduce iatrogenic disease (for example, people with thalassaemia trait are often misdiagnosed as iron deficient and can develop haemochromatosis from long term iron treatment) and to increase community awareness of the disorders.

Epidemiology

To inform their patients general practitioners need to be aware of the epidemiology and clinical picture of the conditions being screened for.

Haemoglobin disorders

Table I gives the incidence of haemoglobin disorders and G6PD deficiency in different ethnic groups. For simplicity, all ethnic groups not of northern European origin should be viewed as at risk for all these disorders.

TABLE I—Ethnic groups in Britain at risk of haemoglobin disorders

	Numbers in Britain	Common haemoglobinopathies	% Carriers	Affected infants (births/1000)	% Males G6PD deficient
Afro-Caribbeans	750 000	S>C>βth>D	11-14	3-4.5	12
West Africans	99 000	S>C>βth	20-25	9.3-19.2	20
Indians	873 000	βth>D,E,S	3-10	0.23-2.5	7
Pakistanis	370 000	βth>D,E,S	6	2.0*	5
Bangladeshis	87 000	E>βth	5	0.4**	3
East African Asians	221 000	βth>D,E,S	6-10	0.9-2.5	27
Cypriots	180 000	βth>αth>S	17	7.2	7
Middle Eastern (Iranian, Lebanese, etc)	200 000	βth>S	?	?	5-10
Chinese (Hong Kong, Singapore)	>250 000	αth>βth	6	0.5	3
Italians	>250 000	βth>αth>S	1-6	?	0-6

αth=α thalassaemia, βth=β thalassaemia.

*Allows for high frequency of consanguineous marriage.

**Allows for fact that EE is not a pathological condition.

Combinations of different genes can lead to the major haemoglobinopathy syndromes shown in the box.

Major haemoglobin disorders

Thalassaemia

β thalassaemia major
Hb E/β thalassaemia
α⁰ thalassaemia (hydrops fetalis)
Haemoglobin H disease

Sickle cell disease

Hb SS (sickle cell anaemia)
Hb S/C disease
Hb S/β thalassaemia
Hb S/D disease

In the thalassaemias the production of haemoglobin is impaired. β Thalassaemia major is the commonest. Affected children present at around 6 to 12 months with pallor (haemoglobin concentration 40-70 g/l) and failure to thrive. Treatment consists of regular monthly blood transfusions to maintain normal haemoglobin concentrations and nightly subcutaneous infusion of the iron chelating agent desferrioxamine (Desferal) to prevent multiorgan toxicity from transfusional iron overload. Treatment is very burdensome, but when it is started early and faithfully maintained the quality of life is good, and patients are expected to survive at least 30 years.⁴ Prenatal diagnosis is highly acceptable to most couples at risk of having thalassaemic children: first trimester diagnosis is particularly important for British people of Pakistani origin.

Patients with sickle cell disease have structurally altered haemoglobin molecules. They suffer from anaemia (haemoglobin concentration approximately 80 g/l), but most symptoms arise because "sickled" red cells block capillaries. Affected children most often present with painful swellings of the hands or feet (the hand-foot syndrome). Unless they are diagnosed in the neonatal period or in the early months of life there is a more than 10% chance of death before the age of 7. Once a diagnosis has been made, prophylactic penicillin and folic acid 5 mg should be given daily, and patients should attend special clinics. Most survivors of the hazards of childhood suffer from recurrent, unpredictable, and very painful crises and other complications.⁶ Prenatal diagnosis is requested by between 30% and 50% of couples at risk for sickle cell disease.⁷ Neonatal diagnosis is always indicated.

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Tay-Sachs disease

In this recessively inherited condition the lysosomal enzyme hexosaminidase A is absent or severely deficient, and incompletely digested products of myelin breakdown accumulate in neurones and interfere with their functioning. Affected infants seem normal to about 6 months of age but then "go backwards" developmentally, becoming apathetic and floppy with an exaggerated startle reaction and loss of head control. They become blind and deaf by 12 to 18 months of age, have frequent fits, and usually die before the age of 5 from progressive paralysis leading to aspiration pneumonia.⁸ Prenatal diagnosis is possible by assaying the enzyme in chorionic villus material or cultured amniotic fluid cells and is highly acceptable to most couples at risk.

Initiating screening

Screening can be either purposive or incidental. Purposive screening entails motivating members of risk groups to ask for testing when they visit the surgery for any reason. Posters and leaflets giving the following key information are available (see Appendix for sources):

- The trait is common in healthy people; *you* could be a carrier
- Being a carrier does not affect your own health, but could affect that of your children
- Carriers can be detected by a simple blood test
- You can avoid serious problems if you know your risk.

Whenever a member of a risk group has a full blood count performed incidentally it will become apparent whether or not they carry a thalassaemia. Most black people are tested for sickle cell trait before receiving an anaesthetic, and jaundiced newborns are tested for G6PD deficiency. When reports of these tests are received by the practice the implications should be discussed with the patient or parents.

Diagnosis of carriers

Tests to identify carriers of haemoglobin disorders are simple and accurate.³ Usually 5 ml of blood anticoagulated with EDTA sent to the laboratory with a request for a "haemoglobinopathy screen" (box) will be adequate, but it is necessary to check the type of specimen required with the local haematological laboratory and to ensure that the laboratory will give a diagnosis as well as the test results.

The primary screen for a thalassaemia trait is a microcytic normochromic blood picture. A low mean cell haemoglobin in the presence of a normal haemoglobin concentration in an adult can only mean a thalassaemia trait (table II). All samples with a mean cell haemoglobin <25 pg should be investigated further. (A few people with an important thalassaemia trait have a mean cell haemoglobin of 25-27 pg. When screening for genetic counselling HbA₂ measurement on all samples with a mean cell haemoglobin <27 pg is

Screening tests for haemoglobinopathies

For thalassaemias:

Red cell indices. If mean cell haemoglobin <25 pg, measure HbA₂

For abnormal haemoglobins S, C, D, and E:

Hb electrophoresis

Specific for HbS (trait and homozygous):

Sickle solubility (Sickledex) test

recommended, but the realistic cut off point will depend on local circumstances and must be agreed with the local haematologist.) The important distinction between α and β thalassaemia trait is made by measuring the concentration of HbA₂: over 3.5% indicates β thalassaemia trait and 3% or less α thalassaemia trait.

The differential diagnosis of normochromic microcytosis with a normal concentration of HbA₂ can be difficult. Usually it indicates one of the two forms of α thalassaemia, α^+ or α^0 . α^+ Thalassaemia is nearly always harmless because even in the homozygous state there is still plenty of functioning α globin and only a slightly lowered haemoglobin concentration. It is the only form of α thalassaemia found in Africa and the Indian subcontinent, so α thalassaemia carriers of such ancestry should be reassured that they have only a harmless minor blood condition, with practically no genetic risk. By contrast, homozygous α^0 thalassaemia causes stillbirth or neonatal death. Both α^0 and α^+ thalassaemia occur among people from East Asia (from South China, Hong Kong, Singapore, Malaysia, etc) and the Mediterranean area. α Thalassaemia carriers of such ancestry should arrange for their partner to have a blood test before pregnancy is contemplated.

Thalassaemia and iron deficiency often coexist, especially in Asians, and each confuses the diagnosis of the other. In groups at risk for thalassaemia the diagnosis of iron deficiency requires measuring serum iron or ferritin. Pregnant women with thalassaemia trait should be given extra iron when indicated.

Carriers of Tay-Sachs disease can readily be identified by a lower than normal level of hexosaminidase A in serum or white blood cells. Testing is more reliable when done before pregnancy. It should be offered to everyone with a Jewish parent or grandparent, before they start their families.

Counselling carriers

The result of a haemoglobinopathy screen will probably be sent to the general practitioner together with a card supplied by the Department of Health to haematologists. Giving this card to the patient without adequate explanation can do more harm than good. Information for carriers should include:

- The high incidence of the trait, and the fact that carriers are healthy and will not develop the major disease—very important for patients to understand
- The recessive inheritance of the condition. It is not necessary to mention genes and statistics. Most people are satisfied with a simple explanation, such as the following: "Thalassaemia is an inherited characteristic, like skin or eye colour. In fact, you are half thalassaemic and half normal, but the normal half protects you. When you have children, you can only hand on thalassaemia or normal, but not both. If your partner is a non-carrier, some of your children will be carriers and some not, but no one will be ill. However, if by chance your partner is another carrier, one of your children could inherit thalassaemia from both of you,

TABLE II—Example of red cell indices (selected to show that anaemia is not a necessary feature of thalassaemia trait)

Index		Normal woman	Woman with β or α^0 thalassaemia trait
Haemoglobin	Hb (g/dl)	12.1	12.7
Red blood cells	RBC (μ l)	4.29	6.32
Packed cell volume	PCV (%)	36.5	39
Mean cell volume	MCV (fl)	86	63
Mean cell haemoglobin*	MCH (pg)	29.6	20.3
Mean cell haemoglobin concentration	MCHC (%)	33.6	32.3

*Normal range 27-32 pg; range in typical thalassaemia trait 18-25 pg.

and that child would be sick. But if you know about the problem beforehand, you can avoid it"

- The main points about the major disease (see above)
- The fact that the trait is advantageous: haemoglobinopathy traits and G6PD deficiency confer protection against malaria, and Tay-Sachs carriers may be protected against tuberculosis
- Knowledge of carrier state very rarely influences people's choice of partner, but may affect reproductive behaviour⁹
- Further information can be obtained from support associations.¹

It can be useful to give or send carriers an information booklet (see Appendix) to read before the discussion and to take home with them. It can be particularly difficult to inform people whose first language is not English. Some booklets are available in other languages.

Whom to refer?

Carriers should be encouraged to invite their partner to have a blood test at some time before becoming pregnant. If there is any abnormality in the partner the couple must be referred for genetic counselling, either at a specialist prenatal diagnosis centre or a sickle cell or thalassaemia centre or by a clinical geneticist, as appropriate (see Appendix).

G6PD deficiency

G6PD deficiency is not usually screened for in Britain, although the tests are relatively simple.¹⁰ This deficiency impairs the red cell's ability to cope with oxidative stress and can lead to neonatal jaundice or a life threatening haemolytic crisis when an affected person eats broad beans or takes certain drugs. Inheritance is X-linked. When a woman is a carrier half her sons inherit the mutant gene and half her daughters are carriers, on average. Homozygous women constitute 5-15% of patients.

General practitioners need to ensure that affected people are given correct information: the list of dangerous drugs (box) does not include many common medicines such as penicillin and paracetamol. Other members of the family should be tested.

Members of primary care teams working with patients from ethnic minorities will need to have a basic knowledge of the principles described above, and larger practices may find it useful to arrange for one member of the team to develop knowledge of this subject. This person, who will be available for intrapractice referral for counselling, need not be a doctor. The health visitor or practice nurse may in fact be a more appropriate counsellor.

Common drugs that can be associated with haemolysis in G6PD deficiency¹⁰

Antimalarial drugs:	Sulphonamides:
Primaquine	Dapsone
Pamaquine	
?Chloroquine	Antibiotics:
	Nitrofurantoin
	Nalidixic acid
	?Chloramphenicol

Appendix

Posters and simple leaflets to motivate people to be tested for the haemoglobin disorders are obtainable from the Press and Public Relations Department, North East Thames Regional Health Authority, 40 Eastbourne Terrace, London W2 3QR.

Leaflets for carriers of haemoglobin disorders can be obtained from the Sickle Cell Society, Green Lodge, Barretts Green Road, London NW10 7AP and (in English, Greek, Turkish, Urdu, Hindi, Gujarati, and Bengali) from the United Kingdom Thalassaemia Society, 107 Nightingale Lane, London N8 7QY.

Leaflets about Tay Sachs disease can be obtained from the Tay-Sachs Carrier Testing Centre, 8th Floor, Guy's Tower, Guy's Hospital, St Thomas Street, London SE1 9RT.

A list of sickle cell or thalassaemia centres is given in Appendix 4 of the Royal College of Physicians' *Report on Prenatal Diagnosis and Genetic Screening*,¹ or addresses may be obtained by telephoning the George Marsh Sickle Cell and Thalassaemia Centre at St Anne's Hospital, Tottenham: 081 809 1797.

Prenatal diagnosis with specialist counselling for couples at risk for haemoglobin disorders is available at University College and Middlesex School of Medicine Perinatal Centre, 86-96 Chenies Mews, London WC1E 6HX, or the Department of Haematology, King's College Hospital Medical School, Denmark Hill, London SE5 9RS.

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THE MEMOIR CLUB

Work does not come naturally to the young, human, male animal. Nor does the control of the instincts and passions which are so powerful at puberty. Hence the need for constructive teaching, compulsory learning, and effectively enforced discipline. Without these, civilised life and family happiness are for most people out of reach.

One group of people have remained almost entirely untouched and uninfluenced by the disastrous philosophy of permissiveness. Their realism and commonsense are saving the day. Men on the whole are delighted at the thought of respectable promiscuity. Most women regard it with disgust, based on their inherent understanding of the nature of family life and the extraordinarily hard work on which the successful family is built.

It has for a long time been possible, though not easy, for women to enter the learned professions, including medicine. Women have always

occupied special places in industry, for example in textiles and light engineering assembly. In the arts, as painters, novelists, and musicians, they have won their place on pure merit. But in the higher positions in politics, the civil service, and management, they have, with one or two exceptions, been most carefully kept out. It is one of the good things arising from the so called women's lib movement that women are at last starting to take their places as prime ministers, general managers, and prison governors. This may yet prove to be the most important social change of our time.

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