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CURRENT PRACTICE

Antenatal diagnosis of inborn errors of metabolism

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The introduction of experimental treatment for lysosomal storage disorders and the increasing understanding of the molecular defects behind many inborn errors have overshadowed the fact that for many affected families the best that can be offered is a rapid, accurate prenatal diagnostic service. Many conditions remain at best only partially treatable and as a consequence the majority of parents seek antenatal diagnosis in subsequent pregnancies, particularly for those disorders resulting in a poor prognosis in terms of either life expectancy or normal neurological development.

The majority of inborn errors result from a specific enzyme deficiency, but in some the primary defect is in a transport system or enzyme cofactor. In some conditions the biochemical defect is limited to specific tissues only and this serves to restrict the material available for antenatal diagnosis for these disorders. Fortunately for many inborn errors the metabolic defect is generalised and both amniotic and chorion villus cells can be used as a diagnostic tissue.

Before contemplating prenatal diagnosis it is essential that a firm biochemical diagnosis has been established in the index case. It is unsafe to rely only on a clinical or histological diagnosis as many of the inherited disorders share a similar phenotype. To ease interpretation of results obtained on the fetus it is necessary to know the heterozygote levels of enzyme activity in the parents; occasionally these are remarkably low and can lead to difficulties in ascribing fetal genotype.

The properties of some enzymes are appreciably different when studied at different times of gestation. In addition, the activity obtained from chorion villus material may be very different from that obtained on amniotic fluid cells. It is essential that the correct tissue is collected at the most appropriate time. Liaison with the laboratory staff performing the test is mandatory if mistakes are to be avoided.

Prenatal testing by analysis of fetal DNA by either a gene specific DNA probe or gene tracking using restriction fragment length polymorphisms (RFLPs) requires proband DNA for comparison. This underlies the importance of establishing fibroblast cultures from all patients diagnosed as having a metabolic disorder as well as ensuring that blood is taken from all relevant family members for DNA extraction and storage.

Most prenatal testing for metabolic disease is performed in a few specialised laboratories.

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Sample requirement and techniques used in prenatal diagnosis

By far the majority of antenatal diagnoses are performed on samples obtained by either amniocentesis or chorion villus biopsy. For some disorders, however, the defect is not detectable in this material and more invasive methods have been applied to obtain a diagnostic sample.

FETAL LIVER BIOPSY

Fetal liver biopsy has been performed to diagnose ornithine carbamoyl transferase deficiency and primary hyperoxaluria type 1. Glucose-6-phosphatase deficiency (glycogen storage disease type I) could also be detected by this method. The technique, however, is invasive and can be performed by only a few highly specialised fetal diagnostic units.

FETAL BLOOD SAMPLING

Fetal blood sampling could be used for the antenatal diagnosis of many inborn errors. The sample, however, tends to be collected late in pregnancy and the technique is probably best reserved as a back up in case of failed amniotic fluid cell culture.

AMNIOCENTESIS

Amniocentesis has been the most common procedure for antenatal diagnosis of metabolic disease. Both the cell free amniotic fluid and cultured and uncultured amniotic fluid cells are useful in diagnosis.

The procedure is usually performed at 15–16 weeks' gestation and most analyses can be performed within two to three weeks of culture. First trimester amniocentesis has been attempted to allow earlier diagnosis, but the smaller sample size and possible variation in enzyme activity at the earlier stage of pregnancy have introduced variables that need to be studied before the technique can be widely applied.

(1) Cell free amniotic fluid can be used to detect a number of intermediary metabolites in many inborn errors. Where possible this technique should be backed by specific enzyme analysis, but for many conditions does allow a quick diagnosis. It is particularly relevant for organic acid disorders using stable isotope dilution gas chromatography with mass spectrometry and selected ion monitoring.

In mucopolysaccharide disorders the pattern

of excess glycosaminoglycan excretion can be detected by two dimensional electrophoresis and this can form the basis of a reliable antenatal test for this group of conditions.

(2) Amniotic fluid cells in culture are a common material used in antenatal diagnosis. In most cases the enzyme activity obtained in this tissue mirrors that obtained in cultured skin fibroblasts. As well as direct enzyme assay, radiolabelled incorporation studies can be performed on the cultured cells and a wide range of disorders detected. Contamination by mycoplasma or other organisms is the biggest threat to antenatal diagnosis by this method.

CHORION VILLUS BIOPSY

Chorion villus biopsy offers the advantage of first trimester diagnosis. Direct analysis of enzyme activity on fresh uncultured villus tissue usually allows a result to be available within 24–48 hours of the procedure. Problems associated with the technique include the possibility of maternal contamination and differences in enzyme activity in this tissue as compared with skin fibroblasts or cultured amniotic fluid cells. Despite these possible limitations most prenatal diagnoses for inborn errors are performed on chorion villus samples.

Specific inborn errors of metabolism

The appendix lists the specific inborn error, the biochemical defect, chromosome location of the gene mutation where known, and the test used for antenatal diagnosis. Where antenatal diagnosis has been successfully achieved the method used is clearly shown. For some disorders prenatal diagnosis is theoretically possible, although to the authors' knowledge not as yet successfully performed. In this case the most likely tissue and method are indicated with the rider, 'possible'. The key to the abbreviations used is shown at the end of the appendix.

Appendix

Specific inborn errors of metabolism

Condition	Enzyme deficiency	Chromosome location	Prenatal diagnosis
(A) CARBOHYDRATE METABOLISM			
(i) Galactose			
Galactokinase deficiency	Galactokinase	17q21-q22	AF, CVB
'Classical' galactosaemia	Galactose-1-phosphate-uridyltransferase	9p13	AF, CVB
Epimerase deficiency	UDP-Galactose-4-epimerase	1pter-p32	Poss CC
(ii) Fructose			
Hereditary fructose intolerance	Aldolase B	9q22	Poss DNA
Fructose 1–6 bisphosphatase deficiency	Frutose 1–6 bisphosphatase	—	No
(iii) Glycogen storage disease			
Ia Von Gierke	Glucose-6-phosphatase	—	Poss FT
b	Glucose-6-phosphatase translocase (T_1)	—	Poss FT
c	Glucose-6-phosphatase translocase (T_2)	—	Poss FT
II Pompe	Lysosomal acid glucosidase	17q23	AF, CVB
III Debrancher enzyme deficiency	Amylo-1-6-glucosidase	—	AF, CVB
IV Brancher enzyme deficiency	1-4-Glucan 6-glycosyl-transferase	—	AF, CVB
V McCardle	Muscle phosphorylase	11q13-qter	No
VI Liver phosphorylase deficiency	Liver phosphorylase	14	Poss FT
VII Phosphofructokinase deficiency	Phosphofructokinase	1cen-q32	No
IXa Phosphorylase kinase (recessive)	Phosphorylase kinase	16q12–q13·1	Poss FT
IXb Phosphorylase kinase (X linked)	Phosphorylase kinase	Xq12–q13	Poss FT
(B) AMINO ACID METABOLISM			
(i) Phenylalanine			
'Classical' phenylketonuria	Phenylalanine hydroxylase	12q22–q24·1	DNA
Tetrabiopterin homoeostasis	Dihydropteridine reductase	4p15·3	AF, CVB
Tetrabiopterin synthesis	Guanosine triphosphate cyclohydrolase	—	MET
	6-Pyruvoyltetrahydropterin synthase	—	MET

Condition	Enzyme deficiency	Chromosome location	Prenatal diagnosis
(ii) Methionine			
Homocystinuria	Cystathionine synthase	21q22–q22·1	AF, CVB
(iii) Tyrosine			
Tyrosinaemia I	Fumarylacetoacetate hydrolase	15q23–q25	AF, CVB
Tyrosinaemia II	Tyrosine aminotransferase	16q22–q22·1	No
(iv) Valine, leucine, isoleucine			
Maple syrup urine disease	Branched chain ketoacid dehydrogenase	19q13·1–q13·2	AF, CVB
(v) Glycine			
Non-ketotic hyperglycinaemia	Glycine cleavage system	9p22	CVB
(vi) Lysine			
Hyperlysinaemia	Aminoadipic semialdehyde synthase	—	UNK
(vii) Proline			
Hyperprolinaemia I	Proline oxidase	—	UNK
Hyperprolinaemia II	Pyrroline-5-carboxylate dehydrogenase	—	UNK
Hyperimidodipeptiduria	Prolidase	19q12–q13·2	Poss CC
(viii) Ornithine			
Gyrate atrophy of the choroid and retina	Ornithine aminotransferase	10q26	Poss CC
Hyperornithinaemia-hyperammonaemia-homocitrullinaemia (HHH syndrome)	Basic defect unknown	—	No
(C) UREA CYCLE DISORDERS			
N-acetylglutamate synthetase deficiency	N-acetylglutamate synthetase	—	UNK
Carbamyl phosphate synthetase deficiency (CPS)	Carbamyl phosphate synthetase	2p	Poss DNA/FT
Ornithine carbamyltransferase deficiency (OCT)	Ornithine carbamyltransferase	Xp21·1	Poss DNA/FT
Citrullinaemia	Argininosuccinic acid synthetase	9q34	AF, CVB
Argininosuccinic aciduria (ASA)	Argininosuccinate lyase	7p21-cen	AF, CVB
Argininaemia	Arginase	6q23	Poss DNA/FT
(D) ORGANIC ACID DISORDERS			
(i) Propionate and methylmalonate metabolism			
Propionic acidaemia	Propionyl-CoA carboxylase:		
	α-subunit	13	AF, CVB
	β-subunit	3q13·3–q22	AF, CVB
Multiple carboxylase deficiency	Holocarboxylase synthetase	—	MET
	Biotinidase	—	MET
Methylmalonic acidaemia	Methylmalonyl-CoA mutase	6p12-p21·2	AF, CVB
	Adenosylcobalamin synthesis:		
	cblA	—	AF, CVB
	cblB	—	AF, CVB
	(see also cobalamin metabolism)		
(ii) Pyruvate and lactate metabolism			
Lactate dehydrogenase deficiency	Lactate dehydrogenase	11p15·4	UNK
Pyruvate dehydrogenase deficiency	Pyruvate dehydrogenase complex:		***
	E_1 (decarboxylase) component	α-Xp22·1–22·2	Poss DNA
		β-3p13-q23	
	E_2 (dihydrolipoyl transacylase)	—	
	E_3 (dihydrolipoyl dehydrogenase)	7p15–q35	
	Pyruvate dehydrogenase phosphatase	—	
Pyruvate carboxylase deficiency	Pyruvate carboxylase	11q	AF
Phosphoenolpyruvate carboxykinase deficiency	Phosphoenolpyruvate carboxykinase	—	UNK

Condition	Enzyme deficiency	Chromosome location	Prenatal diagnosis
(iii) Respiratory transport chain defects			
The components of the respiratory transport chain are composed of many polypeptide subunits some of which are encoded by mitochondrial DNA			
Complex I	NADH CoQ reductase		###
Complex II	Succinate CoA reductase		
Complex III	$CoQH_2$-cyt c reductase		
Complex IV	Cytochrome oxidase		AF, CVB
Complex V	Oligomycine sensitive ATPase		
(iv) Branched chain organic acidaemias			
Isovaleric acidaemia	Isovaleryl-CoA dehydrogenase	15q14–q15	MET, AF
Isolated 3-methyl crotonyl CoA carboxylase deficiency	3-Methylcrotonyl carboxylase	—	Poss CC
3-Methylglutaconic aciduria	3-Methylglutaconic hydratase	—	Poss CC
3-Hydroxy-3-methylglutaryl CoA lyase deficiency	3-Hydroxy-3-methylglutaryl-CoA lyase	AF, CVB —	
Mevalonic aciduria	Mevalonate	—	AF
2-Methylacetoacetyl-CoA thiolase deficiency	2-Methylacetoacetyl-CoA thiolase	—	Poss CC
(v) Disorders of the γ-glutamyl cycle			
5-Oxoprolinuria	Glutathione synthetase	—	Poss CC
γ-Glutamylcysteine synthetase deficiency	γ-Glutamylcysteine synthetase	—	Poss CC
γ-Glutamylcysteine synthetase deficiency	γ-Glutamyltranspeptidase	—	Poss CC
5-Oxoprolinase deficiency	5-Oxoprolinase	—	Poss CC
(vi) Other organic acid disorders			
Alkaptonuria	Homogentisic acid oxidase	—	UNK
Glutaric aciduria type I	Glutaryl-CoA dehydrogenase	—	AF, CVB
Glutaric aciduria type II	Electron transfer flavoprotein (ETF) ETF:ubiquinone oxidoreductase	—	AF, CVB
Glycerol kinase deficiency	Glycerol kinase	Xp21·3–p21·2	AF, CVB
Hyperoxaluria type I (glycolic aciduria)	Alanine:glyoxylate aminotransferase	—	FT
Hyperoxaluria type II (glyceric aciduria)	Glyceric dehydrogenase	—	UNK
Canavan's disease	Aspartoacylase	—	Poss MET
(E) FATTY ACID OXIDATION DEFECTS			
Short chain acyl-CoA dehydrogenase deficiency (SCAD)	Short chain acyl-CoA dehydrogenase	12q22-qter	Poss CC
Medium chain acyl-CoA dehydrogenase deficiency (MCAD)	Medium chain acyl-CoA dehydrogenase	1p31	DNA/CVB
Long chain acyl-CoA dehydrogenase deficiency (LCAD)	Long chain acyl-CoA dehydrogenase	7	Poss CC
(F) LYSOSOMAL ENZYME DEFECTS			
(i) Mucopolysaccharidoses			
Type IH (Hurler's syndrome)	Iduronidase	4p16·3	AF, CVB
Type IS (Scheie's syndrome)	Iduronidase		
Type II (Hunter's syndrome)	Iduronate sulphatase	Xq28	AF, CVB
Type III (Sanfilippo's syndrome)			
A	Heparan N-sulphatase	—	AF, CVB
B	N-acetylglucosaminidase	—	AF, CVB
C	Acetyl-CoA-glucosaminide acetyltransferase	—	AF, CVB
D	N-acetylglucosamine 6-sulphatase	12q14	Poss CC
Type IV (Morquio's syndrome)			
A	Galactosamine 6-sulphatase	—	
B	β-Galactosidase	3p21-cen	Poss CC
Type VI (Maroteaux-Lamy syndrome)	N-acetylgalactosamine 4-sulphatase	5q11-q13	AF, CVB
Type VII (Sly's disease)	β-Glucuronidase	7q11·2–q22	Poss CC

Condition	Enzyme deficiency	Chromosome location	Prenatal diagnosis
(ii) Mucolipidoses			
Mucolipidosis II (I-Cell disease)	UDP-N-acetylglycosamine: lysosomal enzyme N-acetylglucosaminyl-l-phosphotransferase	—	AF, CVB
Mucolipidosis III (pseudo-Hurler polydystrophy)	Same as mucolipidosis II	—	AF, CVB
(iii) Glycoproteinoses			
α-Mannosidosis	α-Mannosidase	19p13·2–q12	AF, CVB
β-Mannosidosis	β-Mannosidase	—	Poss CC
Fucosidosis	α-Fucosidase	1p34	AF, CVB
Aspartylglycosaminuria	Aspartylglycosaminidase	4q21-qter	AF, CVB
Sialidosis type I (cherry-red spot-myoclonus syndrome)	Neuraminidase	6p21·3	AF, CVB
Sialidosis type II:			
Congenital and infantile	Neuraminidase	6p21·3	AF, CVB
Juvenile	Combined neuraminidase and β galactosidase deficiency	20	AF, CVB
(iv) Gm_2 gangliosidoses			
Tay-Sach's disease (variant B)	Hexosaminidase α-subunit	15q22–q25·1	AF, CVB
Sandhoff's disease (variant 0)	Hexosaminidase β-subunit	5q13	AF, CVB
Gm_2 activator deficiency (variant AB)	Gm_2 activator protein	5	Poss CC
(v) Other lysosomal storage disorders			
Metachromatic leucodystrophy	Arylsulphatase A	22q13	AF, CVB
Multiple sulphatase deficiency	Multiple lysosomal sulphatases	—	AF, CVB
Niemann-Pick disease:			
Type A	Sphingomyelinase	17	AF, CVB
Type B	Sphingomyelinase	17	AF, CVB
Type C	Cholesterol esterification		AF, CVB
Farbers	Ceramidase		AF, CVB
Gaucher's disease:			
Type 1 (non-neuronopathic)	Glucocerebrosidase	1q21	AF, CVB
Type 2 (acute neuronopathic)	Glucocerebrosidase	1q21	AF, CVB
Type 3 (Norrbottnian)	Glucocerebrosidase	1q21	AF, CVB
Krabbe's disease	Galactocerebrosidase	14	AF, CVB
Fabry's disease	α-Galactosidase	Xq22	AF, CVB
Schindler's disease	α-N-acetylgalactosaminidase	22q13–qter	Poss CC
Gm_1 gangliosidosis	β-Galactosidase	3p21–cen	AF, CVB
Wolman's disease	Acid lipase	10q	AF, CVB
Cholesterol ester storage disease	Acid lipase	10q	AF, CVB
Mucolipidosis type IV	?Ganglioside sialidase	—	HIST
(G) PEROXISOMAL DISORDERS			
Zellweger syndrome	Peroxisome biogenesis	7q11·23	AF, CVB
Neonatal adrenoleucodystrophy	Peroxisome biogenesis	—	AF, CVB
Infantile Refsum's syndrome	Peroxisome biogenesis	—	AF, CVB
(For disorders of peroxisome acyltransferase can be assayed)	biogenesis a peroxisomal enzyme—dihydroxyacetone		phosphate
Rhizomelic chondrodysplasia punctata	Multiple peroxisomal enzymes	—	AF, CVB
Pseudo-Zellweger syndrome	3-Oxoacyl-coenzyme A thiolase	3p23–p22	AF, CVB
Pseudo-neonatal adrenoleucodystrophy	Acyl-CoA oxidase	—	Poss CC
X linked adrenoleucodystrophy	Very long chain fatty acid ligase	Xq28	AF, CVB
Refsum's disease	Phytanic acid hydroxylase	11p13	Poss CC
Acatalasia	Catalase	—	UNK
(H) PURINE AND PYRIMIDINE METABOLISM			
Lesch-Nyhan syndrome	Hypoxanthine phosphoribosyl-transferase	Xq26-q27	AF, CVB
Adenine phosphoribosyl-transferase deficiency	Adenine phosphoribosyl-transferase	16q	AF, CVB
Adenosine deaminase deficiency	Adenosine deaminase	20q13·1	AF, CVB
Purine nucleoside phosphorylase deficiency	Purine nucleoside phosphorylase	14q13	AF, CVB

Condition	Enzyme deficiency	Chromosome location	Prenatal diagnosis
Myoadenylate deaminase deficiency	Myoadenylate deaminase	—	AF, CVB
Xanthinuria	Xanthine oxidase	—	UNK
Orotic aciduria	Uridine-5′-monophosphate synthase	3q13	Poss CC
Pyrimidine-5′-nucleotidase deficiency	Pyrimidine-5′-nucleotidase	—	UNK
(I) TRACE METAL METABOLISM			
Wilson's disease	Basic defect unknown	13q14	Poss DNA
Menke's disease	Basic defect unknown	Xq13	AF, CVB
Haemachromatosis	Basic defect unknown	6p21·3	UNK
Molybdenum cofactor deficiency	Molybdenum cofactor	—	AF, CVB
Isolated sulphite oxidase deficiency	Sulphite oxidase	—	Poss CC
(J) LIPID METABOLISM			
Abetalipoproteinaemia	Abnormal handling of apolipoprotein B	2p24	UNK
Lipoprotein lipase deficiency	Lipoprotein lipase	8p22	UNK
Lecithin:cholesterol acyltransferase deficiency (LCAT)	Lecithin:cholesterol acyltransferase	16q	UNK
Familial hypercholesterolaemia (hyperlipidaemia type IIA)	Deficient low density lipoprotein (LDL) receptors	19p13·1–13·3	AF
Dysbetalipoproteinaemia (type III, hyperlipidaemia)	Defective apolipoprotein E	19	UNK
Tangier disease	Defective high density lipoprotein (HDL) metabolism	—	UNK
Cerebrotendinous xanthomatosis	Mitochondrial 26-hydroxylase	—	UNK
Phytosterolaemia	Basic defect unknown	—	UNK
(K) VITAMIN METABOLISM			
(i) Folic acid			
Methylene tetrahydrofolate reductase deficiency	Methylene tetrahydrofolate reductase	—	AF, CVB
Glutamate formiminotransferase deficiency	Glutamate formininotransferase	—	No
(ii) Vitamin B_{12} (cobalamin)			
Transcobalamin II deficiency	Transcobalamin II	22q11·2qter	Poss CC
Defects in adenosylcobalamin (AdoCbl) synthesis:			
cbl A mutation	Basic defect unknown	—	AF, CVB
cbl B mutation	ATP:cob(I)alamin adenosyltransferase	—	AF, CVB
Both defects cause methylmalonic acidaemia as AdoCbl is an essential cofactor for the mutase enzyme			
Defects in methylocobalamin (MeCbl) synthesis:			
cbl E mutation	Basic defect unknown	—	AF
cbl G mutation	Basic defect unknown	—	Poss CC
Both disorders lead to a functional deficiency of N^5-methyltetrahydrofolate:homocysteine methyltransferase leading to homocystinuria, hypomethioninaemia without methylmalonic acidaemia			
cbl C mutation	Basic defect unknown	—	Poss CC
cbl D mutation	Basic defect unknown	—	Poss CC
cbl F mutation	Cobalamin transport from lysosome	—	Poss CC
(L) DEFECTS IN THE SYNTHESIS AND DEGRADATION OF HAEM PROTEINS			
(i) Porphyrias			
δ-Aminolevulinic acid dehydratase deficiency	δ-Aminolevulinic acid dehydratase	9q34	UNK
Acute intermittent porphyria	Porphobilinogen deaminase	11q23–qter	AF
Congenital erythropoietic porphyria	Uroporphyrinogen III cosynthase	—	MET
Porphyria cutanea tarda	Uroporphyrindecarboxylase	1qter–p21	No
Hereditary coproporphyria	Coproporphyrinogen oxidase	9	Poss CC
Variegate porphyria	Protoporphyrinogen oxidase	14q32	Poss CC
Erythropoietic protoporphyria	Ferrochelatase	—	Poss CC

Condition	Enzyme deficiency	Chromosome location	Prenatal diagnosis
(ii) Bilirubin metabolism			
Crigler-Najjar syndrome type I	UDP-glucuronyltransferase	—	No
Crigler-Najjar syndrome type II	UDP-glucuronyltransferase	—	No
Gilbert's syndrome	UDP-glucuronyltransferase	—	No
Dubin-Johnson syndrome	Basic defect unknown	—	No
Rotor syndrome	Basic defect unknown	—	No
(M) DISORDERS OF MEMBRANE TRANSPORT			
Cystinuria	Renal and intestinal transport defect	—	No
Lysinuric protein intolerance	Defect of cationic amino acid transport	—	No
Hartnup disease	Defect of neutral amino acid transport	—	No
Cystinosis	Lysosomal cystine transport	—	AF, CVB
Infantile free sialic acid storage disease	Lysosomal sialic acid transport	—	AF, CVB
Salla disease	Lysosomal sialic acid transport	—	AF
(N) MISCELLANEOUS DISORDERS			
Lowe's syndrome	Basic defect unknown	Xq25	UNK
Carbonic anhydrase II deficiency	Carbonic anhydrase II	8q22	No
Steroid sulphatase deficiency	Steroid sulphatase	Xpter–p22·32	AF, CVB
Hypophosphatasia	Alkaline phosphatase	1p	AF
Fumaric aciduria	Fumarase	—	Poss CC
Sjögren-Larsson syndrome	Fatty alcohol NAD oxidoreductase	—	Poss CC

AF: cell free amniotic fluid or cultured amniocytes. *CVB:* assay performed on either uncultured or cultured villus cells. *Poss CC:* as far as authors' are aware prenatal diagnosis has not been performed for these disorders. However, enzyme is expressed in fibroblast cells and theoretically could be used as the basis of a prenatal test. *Poss DNA:* the genetic mutation causing these disorders has been established and may be the most appropriate approach to prenatal testing. *Poss FT:* the enzyme deficiency can only be detected in fetal tissue. This would usually require a fetal liver biopsy, but in some instances direct fetal blood sampling by cordocentesis. *MET:* metabolites from fetal urine are detected in samples obtained by amniocentesis at 14–16 weeks' gestation. *UNK:* as far as the authors' are aware prenatal diagnosis has not been attempted. In a number of cases the exact biochemical defect is yet to be established. ***: assay of the total activity of the pyruvate dehydrogenase complex is possible, but as far as the authors' are aware has not been applied to prenatal testing. Partial deficiencies are common leading to difficulty in interpreting results. ###: only one component of the respiratory transport chain (complex IV, cytochrome oxidase) has been studied prenatally. In families with a deletion of mitochondrial DNA a molecular approach may be more appropriate. *HIST:* histological changes (usually abnormal lysosomal inclusions) within amniocytes have been used as a prenatal test. UDP: uridine diphosphate.