Inherited Metabolic Disorders

Biol 405 - Molecular Medicine
Inherited Metabolic Disorders

- Although originally related to defects in specific enzymes (e.g. phenylalanine hydroxylase) this category of genetic diseases now includes receptors (e.g. the insulin receptor), transporters (e.g. amino acid transport proteins) and structural proteins (e.g. dystrophin).

- Today about 200 disorders are known that are classified as inborn errors of metabolism (i.e. enzyme defects), at least a further 100 conditions are known where a non-enzymic protein is defective.
Phenotypic analysis

- Routine phenotypic screening of newborn infants for metabolic disorders was first introduced in the early 1960s.

- In many countries it is now standard for every newborn infant to be tested for phenylketonuria and hypothyroidism.

- More than 50 other tests can be performed on the same filter paper blood sample. The introduction of Tandem Mass Spectrometry allows considerable expansion of the range of disorders tested for.

- There are many social, ethical and legal implications associated with the use of these programmes.
Before a condition is considered suitable for mass screening it should **ideally** meet the following criteria:

- it should be frequent and severe enough to be a public health concern;
- it should cause a known spectrum of symptoms;
- the screening test should be simple and reliable and should have a low incidence of false-positive and false-negative results;
- the condition should be amenable to treatment;
- appropriate diagnostic tests must be available and arrangements for follow-up treatment should be in place;
- there should be a positive **cost-benefit ratio** to society.
Screening Practice

- Parental education and consent (educational material for parents, informed consent, informed dissent).

- Ensure screening of every infant (early discharge, births out of hospital, < 1% missed in UK).

- Timing of test (before discharge, before 72 hours of age and after at least 24 hours of normal protein and lactose feeding; rescreening?).

- Type of blood sample (cord blood not acceptable because most metabolites do not accumulate until after birth; infant heel blood sample). Fate of blood sample?
Genotypic analysis (analysis of DNA)

Molecular-based techniques can be used for:

- the preclinical diagnosis of individuals at risk;
- the identification of carriers;
- the safe, prenatal diagnosis of numerous genetic conditions;
- the confirmation of biochemical screening tests;
- the prediction of phenotypic severity of a disorder.
Direct mutation analysis

With this approach, the gene responsible for the condition has been characterised and the mutation identified.

- These mutations may consist of major structural rearrangements detectable by Southern blotting.

- The mutations may be base pair substitutions, small insertions or deletions that can be detected by PCR-based methods.

- Fundamental problems with the use of genotypic analysis as a newborn screening procedure are the occurrence of genetic heterogeneity and spontaneous mutation.
Indirect analysis

- When the gene responsible for a condition has not been identified, or when the gene is known but the mutations are too heterogeneous to be tested for directly, the presence of the mutation can be inferred by linkage analysis.

- When the gene responsible for the condition is known, RFLPs in and around the gene can be used to follow the segregation of the mutant allele in the family.
There are limitations with this approach:

- Numerous family members must be analysed;

- There is the possibility of prediction error because of recombination (i.e. two markers separated by $1 \times 10^6$ base pairs recombine in 1% of meiosis);

- Affected individuals for an autosomal dominant condition or carriers for a recessive condition must be heterozygous for at least one marker in order for the normal allele to be differentiated from the mutant allele.
DNA microarray technology for neonatal screening

- Newborn blood provides high quality DNA for use in highly multiplexed PCR. Archived blood spots stored 15-25 years can yield high-quality genomic DNA.

- Microarrays allow numerous amplification products to be co-analysed in a single assay.

- New manufacturing processes have reduced the cost of microarray technology to the point where it is practical for population screening of genetic diseases.

- High throughput is achieved by automation at every step.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
<th>Symptoms</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylketonuria (phenylalanine hydroxylase)</td>
<td>1/12,000</td>
<td>Mental retardation</td>
<td>Variants not uncommon.</td>
</tr>
<tr>
<td>Maple Syrup Urine Disease (branched chain ketoacid dehydrogenase)</td>
<td>1/250,000</td>
<td>CNS damage, death</td>
<td>Rapid onset of symptoms.</td>
</tr>
<tr>
<td>Homocystinuria (cystathionine synthase)</td>
<td>1/250,000</td>
<td>Late onset mental retardation</td>
<td>Methionine may not be elevated in all forms of the disease.</td>
</tr>
<tr>
<td>Tyrosinemia (fumarylaceto-acetase)</td>
<td>1/150,000</td>
<td>Liver, kidney damage</td>
<td>Transient tyrosinemia of newborn is common.</td>
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<tr>
<td>Hypothyroidism</td>
<td>1/4,000</td>
<td>Mental retardation, growth delay</td>
<td>Late onset of disorder is common.</td>
</tr>
<tr>
<td>Galactosemia (hexose 1-phosphate uridylyltransferase)</td>
<td>1/60,000</td>
<td>Liver, kidney, CNS damage, death</td>
<td>Galactose only rises after lactose ingestion.</td>
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<tr>
<td>Galactokinase Deficiency</td>
<td>1/250,000</td>
<td>Cataracts</td>
<td></td>
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<tr>
<td>Biotinidase Deficiency</td>
<td>1/250,000</td>
<td>Acidosis, skin rashes, growth failure, death</td>
<td>Enzyme affected by heat, storage and transfusions.</td>
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<tr>
<td>Sickle Cell Diseases</td>
<td>1/400</td>
<td>Anaemia, bone, kidney damage death</td>
<td>Specimens must be obtained before transfusions. Heterozygote detection can create problems of follow-up and counselling.</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>1/2,500</td>
<td>Pancreatic and respiratory dysfunction, malnutrition, death</td>
<td>High incidence of false positive and false-negative results.</td>
</tr>
<tr>
<td>Congenital Adrenal Hyperplasia (steroid 21-hydroxylase)</td>
<td>1/12,000</td>
<td>electrolytic imbalances, shock death</td>
<td>Rapid onset of shock in severe cases.</td>
</tr>
</tbody>
</table>
Summary

- About 200 disorders are known as inborn errors of metabolism, at least a further 100 conditions are known where a non-enzymic protein is defective.

- Phenotypic screening of newborns for metabolic disorders was introduced in the early 1960s. A condition should meet a number of criteria before it is considered suitable for mass screening.

- Genotypic analysis can be used for preclinical diagnosis of individuals at risk, identification of carriers, prenatal diagnosis, confirmation of biochemical screening tests and the prediction of phenotypic severity.

- Problems with genotypic analysis as a newborn screening procedure include genetic heterogeneity and spontaneous mutations.

- There are many social, ethical and legal implications associated with the use of these programmes.
References


