CHEMICAL PATHOLOGY

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Information on CHOLINESTERASE Genotyping version 23.04.2018

GENOTYPING ASSAY

The routine screen consists of testing for butyrylcholinesterase (BCHE) activity and the following BCHE gene variants:

Traditional Name (abbreviation)	DNA variant HGVS nomenclature	Predicted Amino Acid Change	dbSNP entry
Dibucaine (A)	c.293A>G	p.Asp98Gly	rs1799807
Silent-1 (S)	c.435delTinsAG	p.Phe146delinsValfs*12	rs398124632
K-Variant (K)	c.1699G>A	p.Ala567Thr	rs1803274

Testing for Fluoride variations or rare variants by additional gene sequencing of the coding region may be performed if indicated. Testing of Dibucaine Number and Fluoride Number are no longer performed.

SPECIMEN & REQUEST

0.5 mL serum/heparinised plasma for BCHE activity (preferably collected prior to administration of anaesthetic or a minimum of 48 hours after) plus 5.0 mL EDTA whole blood for variation detection.

It is important to supply clinical details, medication and, for family studies, details of the relationship to the proband.

Transport and store refrigerated. Do not freeze. Please contact the laboratory for an estimate of turnaround times.

PRICE

The cost of measurement of BCHE activity is covered by the Medicare Schedule. The cost of detection of BCHE gene variations is not covered by the Medicare Schedule – the full cost may have to be paid by the patient.

The charge for testing the three variations in the routine screen is $100.00. Any extra investigations of the BCHE gene sequence to identify rarer variations will incur an additional charge of $100.00.

CLINICAL SIGNIFICANCE

There are two clinically important and related enzymes with the ability to hydrolyse acetylcholine:

Choline esterase I – true cholinesterase – red blood cell cholinesterase – acetylcholinesterase
Choline esterase II – pseudocholinesterase – serum cholinesterase – butyrylcholinesterase

Both enzymes are inhibited by organophosphate pesticides, the alkaloids prostigmine and physostigmine and a large variety of compounds, such as morphine, quinine, tertiary amines, phenothiazines, anti-neoplastic agents, MAO inhibitors, oral contraceptives, pyrophosphate, bile salts, citrate, fluoride and borate.

Only butyrylcholinesterase is inhibited by the muscle relaxants scoline (succinylcholine or suxamethonium) or mivacurium which may be administered during anaesthesia. Patients with persistently low BCHE activities may have deficient forms of the enzyme and an impaired ability to break down these agents. They may experience prolonged apnoea following surgery, requiring mechanical ventilation until the drugs are eliminated by other means. In a number of cases however, apnoea may entirely be due to factors other than BCHE deficiency.

The Dibucaine (*syn*. atypical) and Fluoride variants change the structure of the active centre of the enzyme and reduce substrate binding affinity compared to the usual form. The silent variants generally result in inactive enzyme or enzyme with minimal catalytic activity. The K-variant variant, which 90% of the time is in linkage with the Dibucaine variant, may cause a further quantitative 30% reduction in BCHE activity. However, in the absence of the Dibucaine variants or other contributing factors, the K variant does not usually cause clinically significant BCHE deficiency or apnoea.

The incidence of the BCHE variants and their apparent effect on enzyme activity (if known) are tabulated below:

Common Name	DNA variant	Percentage apparent reduction in enzyme activity in homozygotes	Percentage of carriers in European population
Dibucaine (A)	c.293A>G	60% (Yen et al)	2.0%*
Silent-1 (S)	c.435delTinsAG	>98%	0.22%
Fluoride-1 (F)	c.812C>T		0.51%
Fluoride-2 (F)	c.1253G>T		<0.5%
K-variant (K)	c.1699G>A	20 – 30%	19%

*When found the A variant is usually in linkage disequilibrium with the K variant.

Normal BCHE activity in healthy adults has a wide range (7-14kU/L for males and 6-14kU/L for females). Levels in children vary with age. Newborns have levels lower than adults but by 2 months these have increased to adult values. BCHE then continues to increase above adult values through childhood, peaking by approximately 6 years of age. Thereafter, BCHE decreases and by puberty is stabilised to the adult level.

Increases in BCHE activity may be observed in patients with nephrotic syndrome, essential hypertension, asthma, psoriasis, thyrotoxicosis, haemochromatosis, alcoholism, obesity, diabetes or with anxiety and other acute psychiatric states.

In addition to pesticide poisoning, BCHE activity may be reversibly decreased in a number of clinical conditions due to decreased synthesis in the liver. Acute hepatitis, chronic hepatitis of long duration and advanced cirrhosis can cause a 30-70% decrease in activity. Decreased activity may also occur secondary to hypothyroidism, malnutrition, pregnancy, acute infections, pulmonary embolism, muscular dystrophy, carcinoma and chronic renal disease, as well as after surgery and acute myocardial infarction.

Cocaine is metabolised by BCHE. Patients with a BCHE deficiency should avoid its use.

Interpretation of the DNA genetic test result should always be undertaken with the result of the phenotypic (biochemical) assay of enzyme activity.

PATIENT FOLLOW-UP when DNA variant(s) is/are found

For the patient who is heterozygous for a BCHE mutation

The patient is at risk of apnea following some muscle relaxants used in general anaesthesia e.g. succinylcholine and mivacurium. It is recommended that: (1) The patient seeks expert clinical advice regarding the risk involved, (2) Genetic family members particularly parents, siblings and children are tested to determine their risk.

Clinical interpretation of the above DNA genetic test result should be undertaken in conjunction with the BCHE biochemical test of enzyme activity. Note that environmental and other factors can alter the enzyme activity and DNA genetic tests on their own cannot predict clinical response.

For the patient who is homozygous or compound heterozygous for a BCHE mutation(s)

The patient is at significant risk of apnea following some muscle relaxants used in general anaesthesia e.g. succinylcholine and mivacurium. It is recommended: (1) The patient seeks expert clinical advice regarding the risk involved, (2) Genetic family members particularly parents, siblings and children are tested to determine their risk.

Clinical interpretation of the above DNA genetic test result should be undertaken in conjunction with the BCHE biochemical test of enzyme activity. Note that environmental and other factors can alter the enzyme activity.

REFERENCES

Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 4th Ed.
Davis L et al, Anaesthesia 1997 Mar; 52(3):244-260
Parnas M et al, American Journal of Clinical Pathology 2011:135:271-276
Yen T et al. Clinical Chemistry 2003;49:1297-1308.

ENQUIRIES

Clinical interpretation: A/Prof Peter Stewart (02) 9515 7162
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Laboratory issues: Dr Catherine Woolnough* (02) 9515 5359
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