Oxford Molecular Genetics Laboratory

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PYRUVATE DEHYDROGENASE (PDH) DEFICIENCY

INTRODUCTION

Genetic defects in the pyruvate dehydrogenase (PDH) complex are among the most common causes of primary lactic acidosis and neurological dysfunction in infants and young children. Hence, PDH deficiency is one of the main causes of Leigh syndrome. Primary PDH deficiency is caused by mutation(s) in genes encoding subunits of the PDH complex, most commonly *PDHA1*. PDH deficiency has also been associated with defects in the PDH phosphatase, thiamine homeostasis, lipoic acid biosynthesis, and iron-sulphur cluster biosynthesis.

SERVICE

The laboratory provides a biochemical and genetic service for this group of disorders. Analysis of PDH enzyme activity in fibroblasts is typically the first step. Direct contact with the laboratory team is advised prior to sending fibroblasts (oxford.mitogenetics@nhs.net). Details of the main genetic testing options are also summarised under "Strategy" below.

This service is provided alongside our other mitochondrial disease services and is NHS Highly Specialised Services (HSS) funded for NHS referrals from England and Scotland.

TESTING

Diagnostic:	Clinically affected patients
Carrier or Presymptomatic:	Relatives of clinically affected patients
Prenatal:	At risk of having an affected child

REFERRALS

- From Hospital Consultants, mainly Clinical Genetics, Neurology, Paediatrics, Metabolic Medicine
- Prenatal referrals are only accepted from Clinical Genetics and / or Prenatal Diagnosis. They must be discussed with the laboratory and arranged in advance.

STRATEGY

- PDH enzyme activity in cultured fibroblasts (not part of our UKAS schedule of accreditation)
- Appropriate genetic testing dependant on PDH enzyme activity and clinical information:
  - Sanger sequencing of *PDHA1*
  - Sanger sequencing of subunits of the PDH complex (*PDHA1*, *PDHB*, *DLAT*, *DLD* & *PDHX*)
  - Next generation sequencing (NGS) of 24 genes: subunits of the PDH complex (*PDHA1*, *PDHB*, *DLAT*, *DLD* & *PDHX*) and other genes associated with PDH deficiency, mainly PDH regulation and co-factor biosynthesis genes (*BOLA3, ECHS1, FBXL4, GLRX5, HIBCH, IBA57, ISCA1, ISCA2, LIAS, LIPT1, LIPT2, LONP1, NFU1, PDP1, SLC19A2, SLC19A3, SLC25A19, SLC25A26, TPK1*)

TARGET REPORTING TIMES

PDH enzyme activity assay:	42 calendar days
Sanger sequencing of specific genes:	42 calendar days (high priority tests will be reported more quickly)
NGS of 24 gene panel:	84 calendar days (high priority tests will be reported more quickly)
Presymptomatic tests:	14 calendar days
Carrier tests:	42 calendar days
Prenatal testing (includes maternal contamination check):	3 calendar days

N.B. Details are correct for the date of printing only – last updated 31/10/2019