

Oxford Molecular Genetics Laboratory

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Myhre Syndrome – OMIM 139210, 600993 (*SMAD4*)

INTRODUCTION

Myhre syndrome is a developmental disorder characterised by: developmental delay, short stature, facial dysmorphism, generalised muscle hypertrophy, deafness, stiff skin and skeletal abnormalities. The skeletal abnormalities include: square body shape, broad ribs, iliac hypoplasia, brachydactyly, flattened vertebrae, and thickened calvaria. Congenital heart defects and cryptorchidism can also occur. All cases of Myhre syndrome reported to date have arisen *de novo* in the proband and the disorder is autosomal dominant.

Myhre syndrome is associated with specific missense mutations at codon p.Ile500 in the *SMAD4* gene. Mutations reported so far include: p.Ile500Thr, p.Ile500Val and p.Ile500Met.

A phenotypic variant of Myhre syndrome, known as LAPS syndrome, is also caused by missense mutations at p.Ile500 in *SMAD4*. The most notable symptoms of LAPS are laryngotracheal stenosis, arthropathy, prognathism and short stature. Both syndromes are rare.

TESTING AND REFERRALS

Diagnostic:

- Clinically affected patients accepted from Clinical Genetics only

Carrier testing for a familial mutation:

- Parents of confirmed Myhre patients may be tested for mosaicism for the variant
- Referrals from Clinical Genetics only

Prenatal:

- Prenatal testing may be requested for the future siblings of confirmed Myhre patients, as the risk of germline mosaicism in a parent cannot be excluded
- Prenatal requests would only be accepted from Clinical Genetics and must be discussed with the laboratory and arranged in advance

STRATEGY & TECHNICAL INFORMATION

- Mutation screening in diagnostic referrals is undertaken by fluorescent sequencing analysis of exon 13 of *SMAD4* to interrogate the p.Ile500 codon (sequence ENST00000342988/NM_005359.3. exon 13 is also known as exon 11 in the literature according to some transcripts).
- When a pathogenic mutation has been identified in an individual, subsequent testing of the parents for the familial mutation may be requested.

TARGET REPORTING TIMES

Diagnostic test:	10 working days
Familial Mutation test:	10 working days
Prenatal testing (includes maternal contamination check):	3 working days

CLINICAL SENSITIVITY

Le Goff et al, Nature Genetics 2012 and Caputo et al, American Journal of Human Genetics, 2012, identified 11/11 and 8/8 cases of Myhre syndrome to have a mutation at *SMAD4* p.Ile500. Therefore clinical sensitivity approaches 100%.

N.B. Details are correct for the date of printing only – last updated 11/06/2015