**FLNA NEURONAL/SKELETAL DISORDERS—OMIM 300017**

X-linked periventricular heterotopia (300049), otopalatodigital syndrome types I (311300) and II (304120), frontometaphyseal dysplasia (305620), Melnick-Needles syndrome (309350), X-linked cardiac valvar dysplasia (314400), terminal osseus dysplasia (300244), X-linked chronic idiopathic pseudo-obstruction (300048)

**INTRODUCTION**

FLNA, localised to Xq28, consists of 48 exons that encode a 2647 amino acid protein called filamin A that cross-links actin filaments into orthogonal networks in the cortical cytoplasm and participates in the anchoring of membrane proteins. The protein consists of an N-terminal actin binding domain and 24 conserved filamin repeat domains, the last of which acts as a dimerization domain. FLNA mutations can cause the following disorders:

1) **X-linked periventricular heterotopia (PVNH)** - associated with loss of function mutations spread throughout the gene. Heterozygous females present with seizures at an average age of 14-15 years. Hemizygous males generally show either pre- or neonatal lethality, although a small number of cases have been described with a phenotype that is similar to, or milder, than that of females.

2) **Otopalatodigital syndrome (OPD) spectrum disorders**

These four phenotypically related disorders arise from gain of function mutations in FLNA. All mutations described to date are missense, or small deletions that conserve the reading frame, and tend to be clustered in particular regions of the gene exhibiting genotype/phenotype correlation.

a) **Otopalatodigital syndrome type I (OPD1)** is the mildest phenotype in males and consists of conductive deafness, cleft palate, and mild skeletal anomalies. Mutations have been identified in exons 3-5.

b) **Otopalatodigital syndrome type II (OPD2)** leads to disabling skeletal anomalies that are often lethal in males.

Female carriers of OPD1 and OPD2 usually present with a milder or similar phenotype to males, although this can be variable.

c) **Frontometaphyseal dysplasia (FMD)** is characterised by generalised skeletal dysplasia, deafness and urogenital defects in males with females more mildly affected.

d) **Melnick-Needles syndrome (MNS)** is the most severe of these disorders causing malformations in affected males similar to those observed in individuals with OPD2 resulting in prenatal lethality or death in the first few months of life. Female carriers have a small chin, prominent eyes and bowed bones leading to thoracic hypoplasia. The majority of mutations have been identified in exon 22.

3) **X-linked cardiac valvar dysplasia (CVD1)** is a rare X-linked recessive form of heart disease characterised by mitral and/or aortic valve regurgitation. Penetrance appears to be complete in males but incomplete in females who are usually asymptomatic but have variable expression of the valve abnormalities. The mutations are usually missense mutations at highly conserved residues within flamin repeat domains 1, 4, and 5.

An in-frame deletion of 182 residues has also been described.

4) **Terminal osseus dysplasia (TOD)** is a dominant male-lethal disease characterised by skeletal dysplasia of the limbs, pigmentary defects of the skin, and recurrent digital fibroma with onset in female infancy. It has been associated with a single recurrent FLNA variant in exon 31.

5) **X-linked chronic idiopathic intestinal pseudo-obstruction (CIIPX)** is caused by a severe abnormality of gastrointestinal motility. Affected males have intestinal pseudo-obstruction due to diffuse abnormal layering of the small intestinal smooth muscle. It is associated with whole and partial duplications of FLNA, as well as other mutations within the FLNA gene.

6) **FLNA-associated congenital lung disease**: a small number of patients have been described with congenital lung disease in whom FLNA mutations have been identified. Other clinical features present can include, PVNH, hypotonia, cardiac anomalies and hyperlaxity.

Information is not available on the prevalence of the above disorders.

**TESTING**

- **Diagnostic:** Clinically affected patients
- **Familial mutation test:** Relatives of clinically affected patients (known mutation)
- **Prenatal:** At risk of having an affected child (known mutation)

**REFERRALS**

- From Geneticists, Paediatricians, Antenatal Services, Neurologists, Cardiologists, Respiratory Consultants or Dysmorphologists
- Prenatal referrals must be discussed with the laboratory and, where possible, arranged in advance.

**STRATEGY AND TECHNICAL INFORMATION**

- **For new diagnostic cases:** Mutation screening is undertaken by bidirectional fluorescent sequencing according to the following strategy:
  - PVNH: all coding exons are screened (exons 2-48)
  - OPD1: exons 3-5 are screened. The remaining coding exons can be screened on request.
  - OPD2: all coding exons are screened (exons 2-48)
  - MNS: exon 22 is screened. The remaining coding exons can be screened on request.
  - FMD: all coding exons are screened (exons 2-48)
  - CVD1: all coding exons are screened (exons 2-48)
  - TOD: exon 31 is screened. The remaining coding exons can be screened on request.
  - CIIPX: all coding exons are screened (exons 2-48)
  - Lung disease: All coding exons are screened (exons 2-48)

N.B. Sequencing will not identify whole exon duplications or deletions. As duplications have been reported in association with some of the above phenotypes, a dosage test is being developed.

**TARGET REPORTING TIMES**

- **Diagnostic test:** 40 days
- **Familial mutation test:** 10 days
- **Prenatal test (includes maternal contamination check):** 3 days

N.B. Details correct for the date of printing only – last updated 27/05/2016