NOG SKELETAL DISORDERS – OMIM 602991

Multiple synostoses syndrome type 1 (186500); proximal symphalangism type 1A (185800); tarsal-carpal coalition syndrome (186570); stapes ankylosis with broad thumbs and toes (184460); brachydactyly type B2 (611377)

INTRODUCTION
NOG is localised to chromosome 17q22 and encodes noggin, a 232 amino acid secreted protein that inhibits BMP signalling pathways implicated in limb growth and patterning. There are several autosomal dominant disorders associated with mutations in NOG which have overlapping clinical features that range in severity.

1) Multiple synostoses syndrome type 1 (SYNS1) is characterised by joint fusions that commonly involve the proximal interphalangeal, carpal-tarsal, humeroradial, and cervical joints. A subpopulation also manifests characteristic facies and progressive conductive deafness due to fusion of the bony ossicles within the ear. The fusions begin in early childhood and are progressive. SYNS2 is associated with mutations in GDF5 (see separate information sheet).

2) Proximal symphalangism type 1A (SYM1A) is characterised by variable joint fusions of the proximal interphalangeal joints and occasionally the metacarpophalangeal joints in the hands. Joint fusions in the feet can also occur leading to a waddling gait. SYM1B is associated with mutations in GDF5 (see separate information sheet).

3) Tarsal-carpal coalition syndrome (TCC) is characterised by fusion of the carpals, tarsals and phalanges of the hands and feet, together with shortened first metacarpals, brachydactyly, and humeroradial fusion. Conductive deafness is not usually observed. Fusions are progressive.

4) Stapes ankylosis with broad thumbs and toes (SAFTT) is characterised by bilateral conductive deafness secondary to stapes ankylosis (fusion of bony ossicles within the ears), significant hyperopia (long-sight), broad thumbs and broad first toes. Fusion of the cervical vertebrae of the spine may be observed but there is no fusion of the carpals and tarsals.

5) Brachydactyly type B2 (BDB2) is characterised by hypoplasia or aplasia of the distal and/or middle phalanges (leading to shortened fingers/toes) together with proximal symphalangism (fusion of finger/toe joints), carpal synostosis (fusion of wrist bones) and syndactyly (fusion of two or more digits). BDB1 is associated with mutations in ROR2 (see separate information sheet).

TESTING
- Diagnostic: Clinically affected patients
- Carrier: Relatives of clinically affected patients in whom mutations have been identified
- Prenatal: At risk of having an affected child (known mutation(s) in family)

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

STRATEGY AND TECHNICAL INFORMATION
- For new diagnostic cases (all disease sub-types) - bi-directional sequencing analysis of the entire coding region (3 amplicons) and Multiplex Ligation-dependent Probe Amplification (MLPA) to detect deletions/duplications.
- Family tests: when a mutation has been identified in a family the individual is tested only for the familial mutation

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

N.B. Details are correct for the date of printing only – last updated 21/01/2014