GLI3 SKELETAL DISORDERS – OMIM 165240

GCPS – OMIM 175700; PHS – OMIM 146510; PAPA1/PAPB – OMIM 174200; PPDIV – OMIM 174700

INTRODUCTION

GLI3 encodes a 1580 amino acid zinc finger transcription factor localised to chromosome 7p14 and is an essential component of the Sonic Hedgehog signalling pathway in mammalian skeletogenesis. There are 2 main autosomal dominant skeletal dysplasias associated with mutations in GLI3:

1) Pallister-Hall syndrome (PHS) is caused by gain-of-function truncating mutations within the middle third of the gene and is characterised by insertional polydactyly and hypothalamic hamartoma.

2) Greig Cephalopolysyndactyly syndrome (GCPS) is caused by loss-of-function mutations located throughout the gene and is characterised by preaxial polydactyly and a range of other possible features including postaxial polydactyly, syndactyly, hypertelorism and macrocephaly. Approximately 20% of GCPS patients are due to large scale deletions/duplications of GLI3.

Other autosomal dominant disorders caused by loss-of-function mutations of GLI3 include:

3) Preaxial polydactyly type IV (PPDIV) and postaxial polydactyly type A1/B (PAPA1/PAPB) – isolated brachydactylies.

4) Oral-facial-digital syndrome (OFDS) – some patients with features overlapping GCPS/PHS and OFDS have been shown to have mutations within GLI3.

5) Acrocallosal syndrome (ACLS) is characterised by postaxial polydactyly, macrocephaly, agenesis of the corpus callosum and severe developmental delay. A couple of patients with a clinical diagnosis of ACLS have been reported to have mutations within GLI3.

There is some debate as to whether these loss-of-function disorders are independent clinical entities or all part of the same disease spectrum. As such, these conditions are often described collectively as the ‘GLI3 morphopathies’.

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, Endocrinologists or Dysmorphologists
- Prenatal referrals must be discussed with the laboratory and, where possible, arranged in advance.

STRATEGY AND TECHNICAL INFORMATION

- For new diagnostic cases:
  - PHS – bi-directional fluorescent sequencing analysis of GLI3 exons 12, 13, and the first half of exon 14. If negative, screening of the remaining GLI3 exons and dosage analysis of GLI3 may be carried out.
  - For GCPS and other GLI3 disorders – bi-directional fluorescent sequencing of the 14 coding exons and exon/intron boundaries of GLI3, and dosage analysis by MLPA.

CLINICAL SENSITIVITY

- GCPS: Mutations in the coding region and exon-intron boundaries of GLI3 are reported to account for approximately 68% of typically affected and 29% of patients with some clinical features of Greig syndrome.
- PHS: Mutations in the coding region and exon-intron boundaries of GLI3 are reported to account for approximately 91% of typically affected and 40% of patients with some clinical features of Pallister-Hall syndrome.
- OFDS: Mutations in the coding region and exon-intron boundaries of GLI3 are reported to account for approximately 29% of individuals with features of GCPS/PHS and one or more features of oral-facial-digital syndrome (OFDS).

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 10/09/2015