ZRS SKELETAL DISORDERS  
(PPD2 OMIM 174500; SD4 OMIM 186200)

INTRODUCTION
The ZRS (ZPA-regulatory sequence) in an enhancer element that regulates the expression of SHH within the zone of polarising activity (ZPA) posteriorly in the developing limb bud. ZRS is a highly conserved 800bp sequence located approximately 1Mb upstream of SHH and lies within intron 5 of the LMBR1 gene on 7q11. In mouse models, mutations within the ZRS cause ectopic expression of SHH.

In humans, mutations are associated with two closely related autosomal dominant conditions causing digit abnormalities.

1) Preaxial polydactyly type II (PPD2) is characterised a triphalangeal thumb which is usually opposable and contains a normal metacarpal. The distal phalanx of the thumb is sometimes duplicated and the great toe can be duplicated. The majority of variants described have been point mutations although duplications of the region have also been reported.

2) Syndactyly type IV (SD4) is characterised by complete cutaneous syndactyly of the fingers of both hands and also polydactyly (6 metacarpals and 6 digits). There may also be cutaneous syndactyly of the feet and, in severe forms, tibial hypoplasia. Non-penetration has been described. This phenotype has been associated with large duplications of the ZRS region.

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

STRATEGY AND TECHNICAL INFORMATION
- For new diagnostic cases - bi-directional sequencing analysis of the entire region (3 amplicons) and Multiplex Ligation-dependent Probe Amplification (MLPA) to detect deletions/duplications.

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