PTPN11 Gene Analysis in Metachondromatosis

Clinical Features:
Metachondromatosis (MC) is a hereditary disorder characterized by benign cartilage-capped tumors (exostoses) (ostechondromas), commonly of the hands and feet, and enchondromas of long bone metaphyses and iliac crest. The majority of patients have multiple hard and painless nodules on multiple digits, which can be sometimes calcified. In addition develop irregularities on the metaphyses of the long bones and the iliac crest, which are histologically enchondromas. MC exostoses may regress or even resolve over time, and short stature is not characteristic of MC. The clinical features of MC overlap with another autosomal dominant disorder, hereditary multiple exostoses (HME). However, the location, orientation and duration of exostoses differ between both disorders. For instance, the exostoses in HME usually do not resolve and may cause permanent deformity. While the osteochondromas in HME point away from the adjacent epiphysis and rarely affect the hands and feet, those in MC point toward the epiphysis and are preferentially located on the hands and feet [1]. In contrast to HME, which is in 1-5% of patients associated with development of malignant chondrosarcoma [2], no increased risk for malignancies has been reported in MC. Metachondromatosis was shown to be caused by loss-of-function variants in the PTPN11 gene [1, 3].

Inheritance Pattern/Genetics:
Autosomal dominant.

Test Methods:
Using genomic DNA obtained from the submitted biological material, all coding exons of the PTPN11 gene and their splice junctions are PCR amplified. Bi-directional sequence is obtained and analyzed to evaluate for a variant. If desired, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is also available as a separate test to evaluate for an intragenic deletion or duplication of one or more exons of the PTPN11 gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
In one study, two families with a clinical diagnosis of the MC were proven to segregate distinct loss-of function variants in the PTPN11 gene [1]. In a second study, disease-causing loss-of-function variants were identified in 11 out of 17 (~65%) families with a clinical diagnosis of MC [2].

References:

1. Sobreira NL., et al., (2010) PLoS Genet. Jun 17;6(6): e1000991
2. Vink JR et al., (2005) Eur J Hum Genet 13:470-474.
3. Bowen ME., et al., (2011) PLos Genet. Apr 7(4):e1002050