

## BCOR Gene Analysis in OculoFacioCardioDental Syndrome (OFCD) and Lenz Microphthalmia Syndrome (LMS)

**Disorder also known as:** Syndromic Microphthalmia 2, MCOPS2, MAA2, ANOP2, Lenz dysplasia, Lenz dysmorphogenetic syndrome with multiple associated anomalies

### Clinical Features:

**OculoFacioCardioDental Syndrome (OFCD):** Patients with OFCD present with congenital ocular defects (unilateral/bilateral microphthalmia with congenital cataracts or just with congenital cataracts alone), facial anomalies (narrow face with a broad nasal tip, separated nasal cartilage, cleft palate), congenital heart defects (septal defects), and skeletal anomalies. A unique and cardinal diagnostic feature is dental root radiculomegaly and other dental abnormalities. Mild mental retardation and conductive or sensorineural hearing loss are less common. <sup>1,2,3,4</sup>

**X-linked Lenz Microphthalmia Syndrome (LMS):** LMS can be highly variable in its phenotypic presentation between families and even between members of the same family. The eyes are usually asymmetrically affected with ocular anomalies, such as microphthalmia/anophthalmia, coloboma and cataract. Mild-moderate mental retardation and urogenital anomalies (hypospadias, cryptorchidism, renal aplasia/hypoplasia, hydroureter) are the most common associated findings. Hearing loss has also been reported. <sup>1,2,3,4</sup>

### Genetics:

X-linked dominant with male lethality for OFCD, and X-linked recessive for LMS. <sup>1,2,3,4</sup> The BCOR gene is located on Xp11.4 and is hypothesized to be involved with determining laterality during fetal development. OFCD and LMS are allelic disorders in that they are both caused by pathogenic variants occurring in the BCOR gene. While loss-of-function variants in BCOR are associated with OFCD (haploinsufficiency), only a single missense variant (p.P85L) has been identified in patients with LMS1.

### Test Methods:

**OFCD syndrome:** Variant analysis of the BCOR gene in females is offered in 2 Tiers. Tier 1 consists of sequence analysis of select exons (partial exon 6, exons 9-13) and deletion/duplication testing by targeted array CGH analysis with exon-level resolution (ExonArrayDx). This Tier 1 test is expected to detect all variants reported to date. The Tier 2 test includes sequence analysis of the rest of the coding sequence of BCOR (remaining part of exon 6, exons 4-5, and 14-17). Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, quantitative PCR or another appropriate method.

**LMS:** This test is a targeted analysis for only the p.P85L variants, the only variants in the BCOR gene reported in patients with LMS.

**Test Sensitivity:**

**OFCD syndrome:** Our comprehensive test approach, combining sequencing of the entire coding sequence of BCOR (exons 4-17) with deletion/duplication analysis is expected to identify a pathogenic variant in ~99% of clinically diagnosed female patients.<sup>1</sup>

**LMS:** Data for BCOR analysis in LMS are scarce. It appears that BCOR is not a major gene for LMS as only one variant, p.P85L, was identified in 1 out of 21 patients with X-linked Lenz microphthalmia tested<sup>1</sup>.

**References:**

1. Hilton et al (2009) Eur J Hum Genet 1-11.
2. Horn et al (2005) Eur J Hum Genet 13: 563-569.
3. Martinez-Garay et al (2007) Eur J Hum Genet 15:29-34.
4. Ng et al (2004) Nat Genet 36;4:411-416.