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Poster Presentations

P79-Cardiospondylocarpofacial syndrome as a distinct hereditary connective tissue disorder: novel missense variant in MAP3K7 in two unrelated patients

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Introduction: Cardiospondylocarpofacial syndrome (CSCFS, ORPHA: 3238) firstly delineated by Sousa et al. (2010) is an autosomal dominant multisystemic condition to date reported in few cases, even after the causative has been identified (Le Goff et al., 2016): MAP3K7 that encodes TGF-β-activated kinase 1, an important regulator of p38 mitogen-activated protein kinase signaling pathway. We describe two patients from unrelated families (7th and 8th reported) with the same novel missense variant and expand the phenotypic spectrum.

Clinical report: A 12-year-old Portuguese male presented at birth with hypotonia, bilateral inguinal hernia, cryptorchidism, facial dysmorphisms (myopathic-like facies, puffy eyes, ptosis, hypertelorism, downslanting palpebral fissures) and hands with loose and wrinkled skin resembling cutis laxa. Subsequently, he had motor and speech delay and at 4 years a bilateral conductive hearing loss was diagnosed. The cardiac follow-up revealed a myxomatous mitral and tricuspid valves. At last examination, he had normal intellect and growth, pectus excavatum, flat foot, significant joint laxity, and maintained the skin, hands and facial features. Retrospective X-rays analysis revealed cervical vertebral fusions. Trio WES identified a de novo heterozygous missense variant in MAP3K7 gene, c.629G>A (p.Cys210Ser), absent in control databases and only reported in one case from DDD project at Decipher database. This patient is an 8-year-old British patient with short stature, dysmorphic features, mitral insufficiency, conductive hearing loss, carpal fusion and also connective tissue features: joint laxity, soft velvety skin, hands with redundant skin, flat foot and pectus excavatum.

Discussion: CSCF is likely underdiagnosed. WES unveiled this diagnosis in both our patients who presented significant connective tissue features, not highlighted in the initial patients described. Underlying molecular mechanisms will also be discussed, CSCF is caused by loss-of-function heterozygous MAP3K7 non-recurrent missense variants or in-frame deletions, while frontometaphyseal dysplasia type 2 is caused mainly by a recurrent gain-of-function MAP3K7 frameshift variant.

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