Haploinsufficiency of *GJB5* identified via exome sequencing causesa novel form of cutis laxa

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Abstract:

Cutis laxa is a clinically and molecularly heterogeneous genodermatosis. Mutations in five connexin genes (GJA1, GJB2, GJB3, GJB4, and GJB6) have been associated with a range of heritable skin disorders. HumanGJB5, GJB4 and GJA4 gene cluster maps within a 55 kb genomic region at chr.1p34.3. GJB5 is a novel gene, which is highly expressed in skin and placenta. Gjb5 null mice have reduced viability. So far, two large microdeletions encompassing GJB5 had been reported. A 4.8 Mb deletion was found in a patient with hypothyroidism, low birth weight, short neck, microtia, micrognathia, strabismus and speech delay while a 2.1 Mb microdeletion was reported in an unrelated child with mental retardation. We ascertained a 36 year old Caucasian female who originally presented with chronic arthralgia, osteopenia, cutis laxa and heart palpitations. Routine clinical evaluations showed persistent large joint hypermobility, significant cutis laxa and left ventricular dysfunction. She had several unsuccessful surgical corrections of her lax skin. Magnetic resonance angiography of her chest was normal. She was treated with beta blockade and intravenous bisphosphonate. Exome sequencing of her gDNA revealed a deleterious frame shift mutation[c.37delG; p.V13fsx26] in GJB5. Two unrelated additional variants [c.3193G>A, p.V10645I; c.96818G>A, p.R32273H] were identified in TTN gene, which is known to be associated with cardiomyopathies. These TTN variants provide a plausible explanation for the ventricular dysfunction in our patient. However, this is the first report of an apparently deleterious mutation in GJB5 causing cutis laxa. Functional studies using Hela cell scratch assays and patch clamp analyses are underway to characterize theGJB5 mutation