Identification of genetic cause split hand and foot formation

Scientists at DBT's Centre for DNA Fingerprinting and Diagnostics (CDFD) at Hyderabad found a deleterious change in the DNA (mutation) in *BHLHA9* (Basic Helix-Loop-Helix A9) gene (p.Glu74Leu) as the likely cause of the disease Camptosynpolydactyly. The discovery was made using one of the cutting edge next generation sequencing technology, the exome sequencing, followed by DNA microarray analysis. Conventional sequencing confirmed the presence of this mutation in patient and tissues of terminated fetus. Both unaffected parents were found to be carriers for the same mutation.

Previous studies on zebra fish and mouse models demonstrated BHLHA9 involvement in regulation of fundamental limb developmental processes. Earlier, genetic mutations or variations were also reported in *BHLHA9* gene in association with various split hand and foot malformation diseases, although the manifestations of these diseases are remarkably different. The reason for this stark contrast in disease characteristics for different mutations in the same gene is not well understood till date.

The p.Glu74Leu mutation is located in a DNA binding domain of *BHLHA9* and Glu74 (glutamic acid) which is the only acidic amino acid residue in this region, when changed to amino acid leucine (Leu), it alters DNA binding properties of the gene that may lead to abnormal function of the protein. Further research is needed for confirmation of this hypothesis.

Complex Camptosynpolydactyly is severe abnormality of fingers in both the hands and feet. The phenotype was first reported in a marriage held within close relatives (consanguineous) in north Indian families back in 1999. So far, only one Indian family was reported by our group whereas three-year-old female child was affected and in subsequent pregnancy, a male fetus was found to be affected with same abnormality.

The discovery about the abnormal hand and foot formation will be helpful in future genetic testing of patients with similar abnormality and has also advanced scientific knowledge regarding the embryonic development of hand and foot in a fetus. The scientific work was published in the *American Journal of Medical Genetics*.

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