Scientists discover mevalonate kinase gene mutations associated with disseminated superficial actinic porokeratosis

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A Chinese research team, led by Anhui Medical University and BGI, has found the strong genetic evidences of mevalonate kinase gene (MVK) mutations link to disseminated superficial actinic porokeratosis (DSAP). It is a major step toward discovering the genetic pathogenesisof DSAP, and sheds an eye-opening insight into its further molecular diagnosis and treatment. The latest study was published online in *Nature Genetics*.

DSAP is a rare, non-cancerous, non-contagious skin disorderthat causes dry, itchy lesions on the arms and legs. It usually begins to develop in adolescents and reach near-complete penetrance by the third or fourth decade of life. The accumulated sun exposure is a risk factor for DSAP. DSAP is a chronic disorder; it can be treated, but it cannot be cured.

In this study, Chinese researchers performed exome sequencing in two affected and one unaffected individuals who belong to a DSAP family. Through variants analysis and data filtering, they supposedthat MVK gene emerged as the only candidate gene located in previously defined linkage region linked to DSAP. Then they confirmed the co-segregation between the identified novel deleterious mutation and DSAP phenotype within the family.

To further identify novel MVK mutations, researchers conducted Sanger sequencing in other DSAP cases, which identified additional novel deleterious mutations. And none of which was detected in 676 unrelated

and ethnically matched controls. It provided strong evidence that these novel mutations were not polymorphisms. They did not found MVK mutations in other clinical subtypes of Porokeratosis, suggesting that MVK mutations may be specific to DSAP patients.

Mevalonate kinase, the protein encoded by MVK, is an important enzyme in the mevalonate pathway that is vital for multiple cellular processes by providing cells with essential bioactive molecules. In the investigation of the impact of MVK expression on the biological activities of keratinocytes, researchers indicated thatMVK plays a role in regulating calcium-induced keratinocytes differentiation and the MVK expression could protect keratinocytes from UVA-caused apoptosis.

Tao Jiang, senior scientist of this project at BGI, said, "Considering the high genetic heterogeneity of DSAP, It is fortunate for us to find the causative gene MVK by sequencing only three exomes and using previous genome-wide linkage results. Our study provides new insights into the pathogenesis of DSAP, and the identified MVK mutations offer the best candidate targets for gene diagnosis and clinical treatment of the disease."

Xuejun Zhang, corresponding author of this study, President of Anhui Medical University, said, "The exome sequencing is an effective method for identifying disease gene of monogenetic diseases in recent years. In this study, the Chinese scientists found disease gene MVK for DSAP using exome sequencing plus functional study. It not only indicates China has step into the most advanced level in searchingthe disease genes for monogenetic disease in the world, but also provides scientific basis for revealing DSAP pathogenesis, genetic counseling, risk prediction, prenatal diagnosis, new drug development, clinical diagnosis and treatment."

Provided by BGI Shenzhen