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Genetic landscape of adult Langerhans cell histiocytosis with lung involvement

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MAPK alterations are present in most lesions from adult pulmonary LCH patients. In patients with refractory progressive disease, the identification of these alterations, including *BRAF* deletions, is important to guide the choice of targeted treatment. <http://bit.ly/2Qoknsn>

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ABSTRACT The clinical significance of the *BRAF*^{V600E} mutation in adult Langerhans cell histiocytosis (LCH), including pulmonary Langerhans cell histiocytosis (PLCH), is not well understood. Similarly, the spectrum of molecular alterations involved in adult LCH has not been fully delineated. To address these issues, we genotyped a large number of adult LCH biopsies and searched for an association of identified molecular alterations with clinical presentation and disease outcome.

Biopsies from 117 adult LCH patients, 83 with PLCH (median age 36.4 years, 56 females, 38 multisystem disease, 79 single system disease, 65 current smokers) were genotyped for the *BRAF*^{V600E} mutation. In 69 cases, LCH lesions were also genotyped by whole-exome sequencing (WES) or targeted gene panel next-generation sequencing (NGS). Cox models were used to estimate the association of baseline characteristics with the hazard of LCH progression.

MAPK pathway alterations were detected in 59 out of 69 cases (86%) (*BRAF*^{V600E} mutation: 36%, *BRAF*^{N486_P490} deletion: 28%, *MAP2K1* mutations: 15%, isolated *NRAS*^{Q61} mutations: 4%), while *KRAS* mutations were virtually absent in PLCH lesions. The *BRAF*^{V600E} mutation was not associated with LCH presentation at diagnosis, including smoking status and lung function, in PLCH patients. *BRAF*^{V600E} status did not influence the risk of LCH progression over time.

Thus, MAPK alterations are present in most lesions from adult LCH patients, particularly in PLCH. Unlike reports in paediatric LCH, *BRAF*^{V600E} genotyping did not provide additional information on disease outcome. The search for alterations involved in the MAPK pathway, including *BRAF* deletions, is useful for guiding targeted treatment in selected patients with refractory progressive LCH.