An activating mutation (V600E) in the serine/threonine kinase BRAF was recently described in LCH biopsy samples (Badalian-Very et al, 2010). LCH biopsy samples were collected, cells were sorted into CD3+ and CD207+ fractions, and purified RNA was amplified into cDNA. Sanger sequencing and BRAF allele-specific PCR were performed for each sample. Categorical clinical data were compared with BRAF genotype to evaluate clinical significance of the mutation. Transcriptomes of CD207+ cells were also compared (wild-type BRAF vs V600E) with the Affymetrix U133Plus2.0 platform to determine the impact of the BRAF mutation on gene expression. The BRAF V600E mutation was identified in cDNA generated from CD207+ cells in 31 (58%) of 53 LCH biopsy samples. In 8 cases of recurrent disease or multiple lesions, BRAF status was consistent in the presenting and the relapse CD207+ cells and in each of the multiple lesions. However, mutation status did not correlate significantly with age, sex, CNS risk, low- vs high-risk organs, single lesion vs multifocal/systemic, or future recurrent/refractory disease in this series. Unsupervised clustering gene expression profiles showed some segregation of data sets based on BRAF status (292 genes significantly up-regulated or down-regulated as a result of the V600E; only 4 genes significantly up-regulated). In this study, we validate the observation that it occurs with high frequency and definitively localize the pathologic CD207+ cell as the source of the mutation in LCH lesions. Interestingly, while the frequency of the mutation implies some functional significance, in this series, there is no statistically significant clinical difference between patients with wild-type or mutated BRAF lesions and only a minor difference between transcriptomes of LCH CD207+ cells with wild-type vs V600E BRAF. While the role for BRAF in LCH pathogenesis remains to be defined, this is an important molecular foothold from which to investigate the biology of LCH.

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