# Circulating BRAF V600E levels as a biomarker for disease presence and activity in Langerhans Cell Histiocytosis

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## Background & objectives

Background

Langerhans Cell Histiocytosis (LCH) is a rare myeloid neoplasia with a vast range of clinical manifestations. The most severe form is a multi-system disease that can be life-threatening and mainly affects young children. Abnormal activation of the MAPK pathway is nearly universal and in approximately 60% of cases a BRAF V600E mutation is found. Treatment is adapted according to disease-extension at diagnosis and evaluations during therapy. BRAF inhibitors are not part of the current treatment protocol (LCH IV) but are sometimes used in patients who do not respond to standard treatment. BRAF inhibitors seem to rapidly cause clinical remission of the disease in most cases but the ideal length of treatment is unclear as the majority of patients relapse when the treatment is stopped.

Objectives

We aim to investigate the potential of circulating BRAF V600E levels as a biomarker for persistence of disease and disease activity in LCH.

## Methods

We conducted serial measurements of circulating BRAF V600E levels in 5 pediatric patients treated for BRAF V600E-positive LCH. Two patients were diagnosed during infancy and are treated with BRAF inhibitor dabrafenib as they did not respond to standard therapy. BRAF V600E levels in circulating cell-free DNA and in blood cells have been measured with targeted next generation sequencing. PCR-based barcoding was used to enhance the sensitivity of the analysis.

## Results

In two patients with multisystem disease under long-term treatment with the BRAF inhibitor, BRAF V600E was detected in blood despite clinical and laboratory parameters indicating complete remission of the disease. This is in line with the observation that the majority of patients relapse when BRAF inhibitor treatment is stopped.

## Conclusion

Levels of BRAF V600E in blood correlated with disease activity in pediatric patients with BRAF V600E positive LCH. In two patients under long-term treatment with BRAF inhibitor, BRAF V600E could be detected in blood despite complete clinical remission. Measurement of BRAF V600E in blood has potential to be a highly sensitive and specific biomarker for activity and presence of disease enabling accurate tailoring of treatment.