Quality Control and Telemedicine for BRAF V600E Mutations in Papillary Thyroid Carcinomas: Image Analysis and Classification and Regression Trees

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ABSTRACT

The assessment of BRAF V600E mutations is important for prognosis and treatment of Papillary Thyroid Carcinomas (PTC), the standard methods for their identification are molecular biology techniques. In this study, the potential of image morphometry applied to cell nuclei and sequentially the use of a Classification And Regression Tree (CART) is investigated, in order to: identify morphometric features useful to characterize BRAF mutations, and to eventually produce an algorithm identifying BRAF mutation status. The 140 studied cases had histological confirmation and known BRAF mutation status identified via real-time PCR. The analysis revealed that nuclear features contributing to BRAF mutation status identification via the CART model are related mostly to nuclear color. According to the results there is evidence that BRAF V600E mutations can be identified by measurable image features. Therefore, the proposed method is useful for quality control of BRAF V600E mutations on cytological slides, can serve as alternative to PCR method and may be used for remote assessment.

Keywords: BRAF, Classification and Regression Trees, Cytopathology, Image Analysis, Image Morphometry, Mutations, Papillary Thyroid Carcinoma, Quality Control, Telemedicine, Thyroid

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INTRODUCTION

A number of genetic alterations have recently been linked to papillary thyroid carcinomas; BRAF activating mutations being the most common, amounting from 35% to 83% (Cohen et al., 2004; Cohen et al., 2003; Finkelstein et al., 2012; Y. E. Nikiforov, 2011; Trovisco et al., 2006). More than 90% of these involve a thymine to adenine mutation in exon 15, resulting in a valine to glutamine substitution in the BRAF protein (V600E).

The assessment of the BRAF status contributes to prognosis and treatment of papillary carcinoma (Kabaker et al., 2012; Lassalle et al., 2010; Nucera et al., 2012; Pizzolanti et al., 2007; Xing et al., 2009), since it has been shown to relate to lymph node or distant metastasis, higher tumor staging, recurrence and treatment failure (He et al., 2014; Mekel et al., 2010; Rossi et al., 2013; Xing et al., 2005). Moreover, in cytological material, detection of BRAF mutations is useful in the diagnosis of papillary carcinoma. Because BRAF test has high specificity for PTCs, especially for classic and tall cell variants, in contrast BRAF mutations are not found in benign lesions and follicular neoplasms (Y. Nikiforov, 2012).

Recently, in histological sections it has been shown that specific morphologic characteristics could be correlated to BRAF activated PTCs (Finkelstein et al., 2012; Virk et al., 2014; Virk et al., 2013). However, there is no experience in cytological material, neither involvement of morphometric evaluation nor application of machine-based classification.

The aim of this study was to investigate if in ThinPrep® cytopreparations from thyroid PTC Fine Needle Aspirations (FNAs), is feasible to identify significant morphometric characteristics related to BRAF mutations. Specifically, after applying image morphometry on cell nuclei, and subsequently, a Classification And Regression Tree (CART) algorithm, the focus was on three topics:

1. To identify the most appropriate morphometric features to use in order to characterize if a nucleus expresses BRAF mutations.
2. To quantify each individual criterion.
3. To produce an algorithm, that exploits morphometric criteria via CARTs in order to predict the BRAF status of a PTC case.

If there is evidence that this is feasible, then there is an open road for three applications:

1. Use of digital images to perform an examination that is currently based on molecular biology methods.
2. Use a telemedicine environment to remotely identify BRAF V600E mutations as digital images is possible to be transmitted via communication channels.
3. Application of quality control and assurance locally or at distance by comparing the results of PCR-based methods and the proposing digital methodology. Definitely, in order to ensure quality, all the steps of the process should be standardized. Thus, emphasis should be given to minimizing human intervention, in this study this ranged from the biological sample collection, and transportation down to the measurements evaluation by a computerized system.
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