CAPN3, DCT, MLANA and TYRP1 are overexpressed in skin of vitiligo vulgaris Mexican patients

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Abstract. Vitiligo is a disorder causing skin depigmentation, in which several factors have been proposed for its pathogenesis: Environmental, genetic and biological aspects of melanocytes, even those of the surrounding keratinocytes. However, the lack of understanding of the mechanisms has complicated the task of predicting the development and progression. The present study used microarray analysis to characterize the transcriptional profile of skin from Vitiligo Vulgaris (VV) patients and the identified transcripts were validated using targeted high-throughput RNA sequencing in a broader set of patients. For microarrays, mRNA was taken from 20 skin biopsies of 10 patients with VV (pigmented and depigmented skin biopsy of each), and 5 biopsies of healthy subjects matched for age and sex were used as a control. A signature was identified that contains the expression pattern of 722 genes between depigmented vitiligo skin vs. healthy control, 1,108 between the pigmented skin of vitiligo vs. healthy controls and 1,927 between pigmented skin, depigmented vitiligo and healthy controls ($P<0.05$; false discovery rate, <0.1). When comparing the pigmented and depigmented skin of patients with vitiligo, which reflects the real difference between both skin types, 5 differentially expressed genes were identified and further validated in 45 additional VV patients by RNA sequencing. This analysis showed significantly higher RNA levels of calpain-3, dopachrome tautomerase, melan-A and tyrosinase-related protein-1 genes. The data revealed that the pigmented skin of vitiligo is already affected at the level of gene expression and that the main differences between pigmented and non-pigmented skin are explained by the expression of genes associated with pigment metabolism.

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Introduction

Vitiligo is a skin disease characterized by the lack of pigmentation in the skin, it affects approximately 0.1 to 2% of the world population. However, its prevalence varies considerably among populations and ethnic groups: 0.14% in Russia, 1% in USA, and 2.5% in Japan (1), although the highest incidence has been described in Mexico (4%) and India (8.8%) (1,2). The most common clinical variant of vitiligo is vitiligo vulgaris (VV), in which the patient presents asymptomatic, well-circumscribed, milky-white macules involving one or multiple body regions or segments (3). The lack of pigmentation could be attributed to two main causes: a) the absence of melanocytes, which are dendritic cells derived from the neural crest that migrates to the epidermis and then to the hair follicle during embryogenesis, or b) the inability of these cells to produce and store melanin in melanosomes in the process of melanogenesis (4). In this context, the pathological origin of vitiligo has not yet been fully understood. Several hypotheses and theories have been developed to explain these depigmentation processes (5-8).

Although melanocyte is responsible for the pigmentation process in vertebrates (9), the significance of the surrounding environment has been neglected, e.g., keratinocytes (8,10). Currently, it is known that the signaling mechanism that activates the route of melanogenesis is controlled by genes, whose products act as enzymes, structural proteins, transcriptional regulators, transporters, receptors and growth factors related