ABSTRACT

Research included in my habilitation achievement was focused mainly on exploring novel aspects of the genetic pathogenesis of Tuberous Sclerosis Complex (TSC). TSC is a hereditary autosomal dominant syndrome with an incidence of ~1/6000 in the general population, which occurs due to loss-of-function variants in the tumor suppressor *TSC1* and *TSC2* genes. TSC is characterized by tumors/lesions in multiple organs, including the brain, heart, skin, lung, and kidney. Genetic mosaicism is a relatively common phenomenon in TSC, observed in 10-15% of TSC patients.

The general aim of the research included in my habilitation achievement was to characterize germline and somatic loss-of-function variants/mutations in *TSC1* and *TSC2* in patients with TSC and patients with various cancer types, as well as to determine their association with the phenotype. The most important results obtained as part of my habilitation achievement are as follows:

- Analysis of TSC mosaicism performed in the largest group of samples/patients analyzed to date (>300 samples from 95 patients) significantly enriches the knowledge on (i) the spectrum and frequency of *TSC1*/*TSC2* mosaic variants in various tissues and (ii) clinical symptoms in mosaic TSC patients. The obtained results provide a valuable compendium of knowledge, contributing to the reduction of the risk of inheriting variants and the introduction of preventive measures that alleviate TSC symptoms. The results are also highly relevant in the context of the investigation of mosaicism in other human genetic diseases, including other syndromes associated with the inactivation of tumor suppressor genes.

- Development of a new ultrasensitive Multiplex High-sensitivity PCR Amplification (MHPA) method and its application to the analysis of facial angiofibroma (FAF) skin tumors led to the discovery of a 'shower' of highly prevalent somatic mutations generated by the UV radiation in the *TSC2* gene in TSC patients' facial skin. The mutations represent thousands of subclinical precursor FAF lesions, a small proportion of which develop into clinically observable tumors. These observations highlight the importance of sunblock and other measures to limit facial UV exposure for TSC individuals of all ages.

My habilitation achievement includes a cycle of 7 publications, including 6 publications summarizing the results of original research and 1 review publication. The publications were prepared during my 5-year postdoctoral fellowship at Brigham and Women's Hospital and Harvard Medical School in Boston, in the research group of Dr. David Kwiatkowski, a leading expert in TSC and cancer genetics. Publications included in my habilitation achievement were published in renowned, prestigious journals in the field of human genetics (average Impact Factor per publication: 10.7). 3 publications from the cycle were prepared as part of the grant *Postdoctoral Fellowship Grant Award 2020,* funded by *TSC Alliance,* which I led as PI.

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