Ultrasensitive profiling of mutations driving tumorigenesis in hereditary syndromes associated with tumor suppressor genes inactivation

Birt-Hogg-Dubé (BHD) syndrome is one of the hereditary syndromes associated with inactivation of tumor suppressor genes, i.e., genes that help to protect cells in our bodies from tumorigenesis. The key gene in BHD pathogenesis is a tumor suppressor gene called folliculin (*FLCN*). Individuals with BHD have tumors in several organs including the skin and kidney, and also develop cysts in lungs. **It is suspected that the skin tumors and lung cysts that develop in BHD are due to somatic mutations ('second hits') occurring in *FLCN* but the genetic patomechanism of their development is unknown.** BHD has similarities to **Tuberous Sclerosis Complex (TSC)** tumor suppressor syndrome, in which tumors occur due to somatic mutations in either *TSC1* or *TSC2* tumor suppressor genes. I have recently developed a method (i.e., **'MHPA' method**) for **ultrasensitive detection of somatic mutations**. Using this method, I performed an analysis of somatic mutations in facial skin samples from TSC patients. The analysis led to the discovery that the UV component of sunlight causes numerous *TSC2* somatic mutations in facial skin, generating >10,000 facial skin tumors in most TSC patients. Detection of these mutations was made possible thanks to high sensitivity of MHPA method.

I hypothesize that **UV in sunlight also causes mutations in the *FLCN* gene in the BHD skin tumors**, since BHD patients also develop a lot of skin tumors in sun-exposed body areas (face, neck, chest). In this project, we plan to use my new MHPA method to analyze *FLCN* in a large set of BHD skin tumors, to confirm this model or hypothesis of skin tumor development in BHD. Confirming this hypothesis would deliver **completely novel insights about how skin tumors develop in BHD**. I also plan to use MHPA method to analyze a large set of BHD lung samples. I hypothesize that **somatic mutations in *FLCN* also contribute to BHD lung cyst development**.

In addition, in this project I also plan to perform an **ultrasensitive profiling of mutations in skin in other syndromes associated with tumor suppressor gene inactivation**, i.e., **TSC and Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)**. The MHPA analysis will be performed for genes responsible for occurrence of the syndromes, i.e., *TSC1* for TSC, and *FH* for HLRCC. This will **expand our knowledge on the currently unknown somatic mutations spectrum and genetic pathomechanisms** for these two additional tumor suppressor syndromes, and enable comparison among findings for all three syndromes studied in this project.

In addition, using our own research findings and publicly available data, we will prepare **a catalogue of somatic mutations and genes frequently mutated in normal skin**, **benign skin tumors** (like skin tumors in BHD, TSC, and HLRCC), and **malignant skin tumors** (like basal cell carcinoma, squamous cell carcinoma and melanoma). This comparison and summary of these mutations and genes involved in skin tumorigenesis is very important since skin cancer is by far one of the most common types of cancer seen in Poland and other populations.