Novel *DNMT3A* Variant Associated With Multiple Tumors

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Background and Objective

The relationship between epigenetic modifications that influence gene regulation such as histone deacetylation, miRNA regulation and DNA methylation, and human diseases has been increasingly recognized. Dysregulation in DNA methylation patterns has been implicated in genomic imprinting and tumorigenesis. Several studies identified several epigenetic modifier genes that directly cause genomic DNA methylation such as DNA methyltransferases (DNMTs). In mammals, DNMTs such as DNMT1, DNMT3A and DNMT3B participate in DNA methylation to regulate normal biological functions. *DNMT*s aberrations usually affect genome-wide methylation profiles deactivating many tumor suppressor genes by methylation of their promotors. In this report, we describe a patient with several tumors, likely caused by a novel variant in *DNMT3A* gene.

Methods

To understand the possible cause for the multiple and apparently unrelated tumors, the patient underwent a comprehensive clinical, physical, biomedical and radiological examinations. The probands' gDNA was subjected to whole-exome sequencing (WES) and strict bioinformatics analysis. The identified variant was Sanger sequenced in all available patient's collected samples. The possible effect of the identified variant was investigated using multiple *in-silico* analysis tools and Protein 3D Modelling.

Results

A) Case Presentation

A middle-aged female who suffered from multiple recurrent and synchronous, mostly benign tumors. Tomography scan showed multiple right-sided enhancing tumors consistent with multiple meningioma. She had right thigh neuromesenchymal cyst and right breast mass of benign fibroadenoma. Ultrasound of the neck revealed that the thyroid gland was enlarged, with asymmetric enlargement of the right thyroid lobe.

CT scan and MRI of the abdomen and pelvis revealed an 11 mm-hyper-enhancing pancreatic uncinate process lesion, most likely representing neuroendocrine tumor without evidence of abdominal metastasis. Chest, cardiovascular, abdominal and musculoskeletal examination was normal. Neurological examination was unremarkable.

B) Identification of causal variant

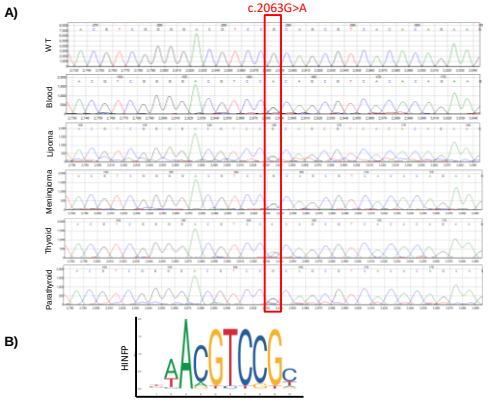

Figure 1. WES data analysis revealed a missense variant (c.2063G>A) in the *DNMT3A* gene that encodes a very important epigenetic enzyme. **(A)** Sanger sequencing of the different patient's samples confirmed the identified *DNMT3A* identified variant. **(B)** Functional annotation of the identified heterozygous missense variant in *DNMT3A* gene, using multiple *in-silico* analysis tools. Sites of DNaseI hypersensitivity, CHIP-seq defined transcription factor binding site (HINFP).

C) *In-silico* structural analysis of the R688H variant

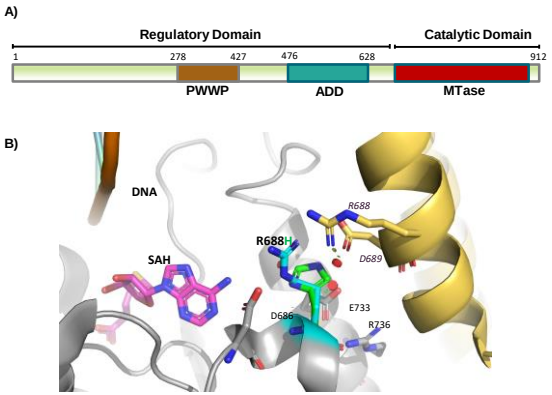

Figure 2 (A) Schematic diagram of the DNMT3A protein (912 aa), N-terminal domain contains two functional domains, a Pro-Trp-Trp-Pro (PWWP) and an ATRX-DNMT3A-DNMT3L (ADD) domains. C-terminal domain contains methyltransferase (MTase) domain. The identified variant p.R688H located in the first of the last three α-helices of the MTase domain. **(B)** Predicted effect of R688H mutation on human DNMT3A protein structure and function. The mutation R688H, which change the positive charged arginine to the uncharged histidine, would disrupt the intermolecular ion-bond interaction with D686, and hence would negatively affect the capability of DNMT3A to bind to S-adenosyl methionine (SAM) and to other DNMTs.

Conclusion

DNMT3A is an essential modifier gene in epigenetics. Here, we report the c.2063G>A, R688H variant as a potential cause of multiple and apparently unrelated tumors. This mono-allelic variant likely has a major consequence on the DNMT3A enzymatic activity and function. a mechanism that is not commonly recognized.