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The molecular characterization of Animal-Type Melanoma

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Background

Animal-type melanoma (ATM) is a rare melanoma subtype, classified as “pigmented epithelioid melanocytoma” in the latest edition of the WHO Skin Tumors. The histopathological features include hyperpigmented spindle, epithelioid cells with the presence of melanophages. In immunohistochemistry, the loss of cytoplasmic staining for the PRKAR1A protein is distinctive and loss of expression of the R1α subunit results in dysregulation of melanocyte function. However, studies on the genetic profile of this entity are limited and driver mutations in the pathogenesis of ATM are unknown. Our study aims to explore the genetic landscape of ATM and to identify gene variants as potential prognostic and therapeutic biomarkers.

Methods

We enrolled 26 patients with ATM from different IMI centers. The DNA extracted from paraffin-embedded tissue, was amplified with Next Generation Sequencing using an IMI-validated Somatic DNA (IAD79062) multi-gene panel. Target regions were analyzed by Ion Torrent Suite Software used as control for conventional melanoma.

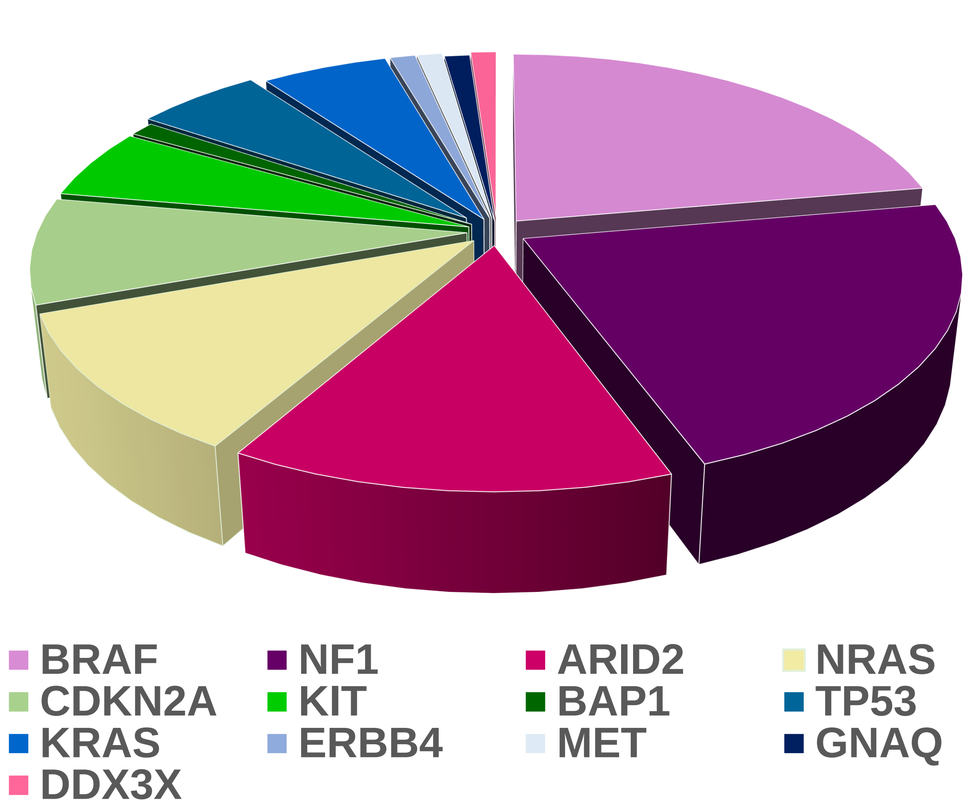

Fig. 1 Pathogenetic variants of our cohort

Results

40 pathogenetic variants were isolated: 20 % involved the BRAF gene and 20% NF1 gene. ARID2, NRAS and CDKN2A mutations were detected in 12.5%, 10% and 7.5% of cases, respectively. Mutations in KIT, TP53 and KRAS genes are present in two cases, while BAP1, CDK4, ERBB4, MET, GNAQ, and DDX3X variants were unique. Most of the variants are missense (82.5%) and nonsense (15%). Nonsense variants result in NF1 (10%), ARID2 (5%) alterations, or in a loss of function mutation in GRD region (GTPase-activating protein-related domain). In 50% of the patients analyzed, we found ‘UV signature’ (nucleotide variations of type C> T). In our cohort, BRAF variant was observed in not chronically UV-exposed melanoma, mainly in men (87.5%) without a correlation with age.

Sex	Age	Site	NF1 variant
M	77	Trunk	c.4084C>T
M	81	Head& Neck	c.3721C>T c.3826C>T
M	36	Limb	c.3883A>G
F	51	Limb	c.5248G>A c.7106G>A
M	59	Head& Neck	c.3907C>T
F	55	Conjuctiva	c.4532T>C

Tab 1: Characteristics of patients with NF1 pathogenetic variants

Conclusions

Our data provide additional information on ATM molecular landscape thus suggesting a more appropriate diagnosis and prognostic evaluation of these variant. However, further larger studies are required for understanding the genetic background and its correlation with outcome.

Sex	Age	Site	ARID2 variant
F	68	Head&Neck	c.2080C>T
M	59	Head&Neck	c.1718C>T
F	51	Uveal	c.3580C>T c.2852C>T c.1277C>T

Tab 2: Characteristics of patients with ARID2 pathogenetic variants

REFERENCES: Zembowicz A et al. Loss of expression of protein kinase a regulatory subunit 1alpha in pigmented epithelioid melanocytoma but not in melanoma or other melanocytic lesions. Am J Surg Pathol. 2007;31:1764–75.

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