Table II. Comparison of patient characteristics of livedoid vasculopathy according to the methylenetetrahydrofolate reductase (*MTHFR*) C677T genotypes

Variable*	MTHFR genotypes			*P* value
	CC homozygote (n = 4)	CT heterozygote (n = 13)	TT homozygote (n = 7)	
Onset age, y	27.0 ± 9.6	40.8 ± 15.7	33.7 ± 14.8	.244
Disease duration, y	9.8 ± 8.7	9.2 ± 8.0	7.0 ± 2.6	.913
Disease severity score (range 0-9)	4.5 (3-6)	5.3 (3-9)	5 (3-8)	.499
Homocysteine, μmol/L	7.0 ± 2.8	8.6 ± 2.8	11.9 ± 5.5	.105

MTHFR, Methylenetetrahydrofolate reductase.
*The results are presented as mean ± SD or as median (range).

When patient characteristics of LV were compared against different MTHFR C677T genotypes, MTHFR polymorphism was not related with any patient characteristics (Table II). Theoretically, the MTHFR C677T polymorphism might be related only with the incidence of LV, not with further progression of the disease.

This study has some limitations, including its retrospective nature and the small number of patients due to the rarity of LV. However, the present study is the largest study, to our knowledge, to demonstrate the associated hypercoagulable conditions in Korean patients with LV, as well as the first study worldwide to find that the MTHFR C677T polymorphism increases the risk of LV by comparison with non-LV control.

In summary, more than one-third of Korean patients with LV had hypercoagulable abnormalities, of which MTHFR C677T polymorphism was the most frequent. Female sex and MTHFR C677T TT genotype were independent risk factors of LV. In contrast, the homocysteine level was normal in most patients.

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Clinical, histopathologic, and molecular profiles of *PRKAR1A*-inactivated melanocytic neoplasms

To the Editor: Protein kinase A regulatory subunit-α (PRKAR1A) is inactivated in a subset of melanocytic neoplasms, including pigmented epithelioid melanocytoma (PEM), melanotic schwannoma (MS), and the exceptionally rare pigmented epithelioid melanoma.[1,2] The genomic profiles of PEM and MS have been well described; PEM typically lacks genomic alterations (GAs) in the *TERT* promoter or *CDKN2A* gene or significant chromosomal copy number alterations, whereas MS shows monosomies of chromosomes 1, 2, and 17. Cohen et al[2] recently described histopathologic findings of a single case of

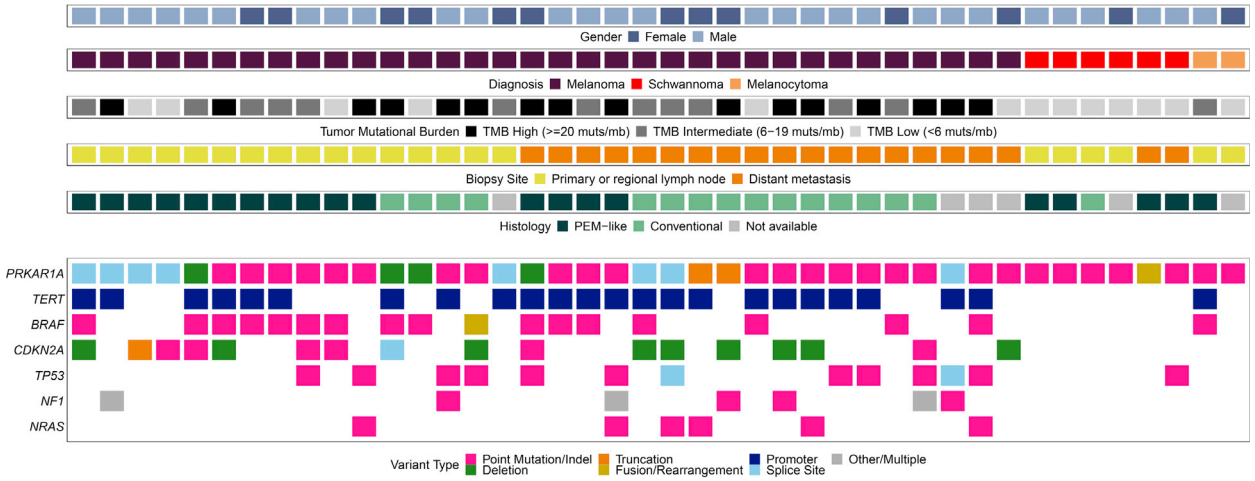

Fig 1. Clinical features and molecular alterations in *PRKAR1A*-mutant melanocytic neoplasms. Each column represents a unique patient's neoplasm. *PEM,* Pigmented epithelioid melanocytoma; *TMB,* tumor mutational burden.

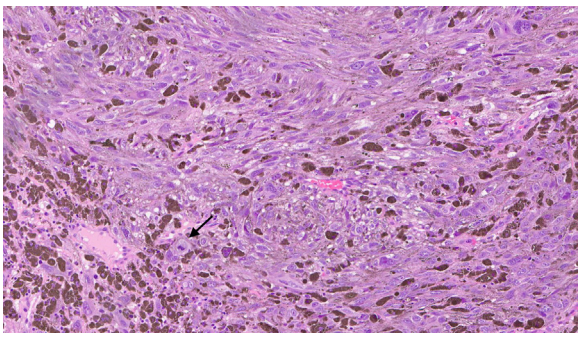

Fig 2. Histopathology of *PRKAR1A*-inactivated melanomas. Examination shows fascicles and vague nests of large, epithelioid cells with cytoplasmic melanin pigment and prominent nucleoli. Mitotic figures (arrow) and admixed melanophages are readily identifiable. (Hematoxylin-eosin stain; original magnification: × 200.)

heavily pigmented epithelioid melanoma with loss of PRKAR1A expression.[2]

Here, we used comprehensive genomic profiling (CGP) to identify the characteristics of *PRKAR1A*-inactivated melanomas.

We searched our archive of 255,008 clinical samples that had undergone CGP using a hybrid capture-based DNA sequencing platform[3] for melanocytic neoplasms with inactivating GAs in *PRKAR1A*. Approval for this study, including a waiver of informed consent and a Health Insurance Portability and Accountability Act waiver of authorization, was obtained from the Western Institutional Review Board (protocol no. 20152817).

Inactivating *PRKAR1A* GAs were detected in 42 of 4770 melanocytic neoplasms (0.9%). Of these, 34 cases were melanoma (primary sites: 32 nonacral cutaneous, 1 acral, and 1 anal mucosal), 6 were MS, and 2 were melanocytomas. Disease classifications were based on diagnoses submitted by the clinician, pathology reports, histology, and GAs. Cases showed truncating variants (n = 29), splice-site variants (n = 8), and homozygous deletions (n = 5) in *PRKAR1A*.

In the melanoma cohort, median age was 59 years (range, 18-87 y), 68% were male, and 94% had documented advanced disease. Specimen sites included primary sites (n = 9), regional lymph nodes (n = 7), and distant metastases (n = 18).

Overall, 94% of melanomas harbored a pathogenic GA in *TERTp*, *CDKN2A*, or both; 50% were *BRAF* mutant (10/17 were *BRAF V600E*), 28% were *NRAS* mutant, 18% were *NF1* mutant, and 18% were triple wild type (Fig 1). Genomic profiles showed no significant differences between primary and metastatic sites. Among melanomas, the median tumor mutational burden was 15.0 mutations/megabase (range, 1.7-187 mut/Mb). PD-L1 tumor immunohistochemistry was performed on 9 melanoma cases, with positive staining (>1%) identified in 3 cases (33%), similar to the 31.3% rate of PD-L1 positivity in all melanomas in the CGP database.

Half (15/30) of the melanomas with available histology showed large epithelioid and dendritic melanocytes with prominent nucleoli, gray-blue cytoplasm, and abundant melanin pigment, arranged in large confluent nests and fascicles, consistent with features described in PEM (Fig 2). Melanomas sequenced from primary tumors or regional lymph nodes showed a significant correlation with PEM-like histology compared with

those sequenced from distant metastasis (73% vs 27%, $P = .027$). The remaining cases showed unremarkable smaller epithelioid and/or fusiform cells with no consistent architecture.

Inactivation of *PRKAR1A* is known to increase cyclic adenosine monophosphate–stimulated protein kinase A activity and has been shown to promote tumorigenesis and modulate the tumor microenvironment.[4] Preclinical data have shown possible targeted treatment strategies.[5] Although the current study is limited by its retrospective nature, enrichment for clinically advanced tumors, and the lack of follow-up data and patient-paired primary/metastatic tumor analysis, our findings suggest the need for further investigational studies to assess the outcomes of *PRKAR1A*-inactivated melanomas, including possible stratification of patients for personalized therapeutic options.

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Drugs associated with development of pityriasis rubra pilaris: A systematic review

To the Editor: Pityriasis rubra pilaris (PRP) is an idiopathic chronic disorder of keratinization characterized by follicular hyperkeratosis, orange-red plaques, islands of sparing, and waxy keratoderma. PRP-like eruptions have been reported with the use of various therapeutics and are important for health care providers to recognize and treat. This systematic review summarizes reports of PRP-like eruptions in association with various drugs.

An Embase and MEDLINE search was conducted on June 15, 2020, in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplemental Files 1 and 2, available via Mendeley at https://doi.org/10.17632/ndkcrb86k3.1). The 19 studies identified (Fig 1, Table I) included 25 patients (19 men) with a mean age of 59.4 years. The time period between initiation of drugs and PRP onset ranged from 3 days to 5 months, with a mean of 31.3 days. Reported drugs included tyrosine kinase inhibitors (n = 10), topical Toll-like receptor 7 agonists (n = 4), phosphoinositide 3-kinase inhibitors (n = 3), antiviral medications (n = 2), biologic (n = 1), programmed cell death protein 1 inhibitor (n = 1), vascular endothelial growth factor inhibitor (n = 1), statin (n = 1), insulin (n = 1), and an angiotensin-converting enzyme inhibitor (n = 1).

The location of PRP eruptions was generalized, with no predilection for anatomic sites. The suspect drug was discontinued in 10 patients, 8 continued on the drug, and continuation of