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Novel mutations identified by whole-exome sequencing in acral melanoma

To the Editor: There have been few studies examining mutational backgrounds for acral melanoma (AM) and different aspects of genetic alterations between nail apparatus melanoma (NAM) and non-nail acral melanoma (NNAM).[1-3] The aim of this study was to uncover previously unidentified novel mutations in patients with AM and compare genetic mutational profiles between NAM and NNAM.

We carried out paired whole-exome sequencing (WES) of saliva and affected tissue samples, collected from Korean patients with AM pathologically confirmed at Samsung Medical Center (Seoul, Korea) from September 2016 to March 2019, as described in our previous study.[4] Detailed methods are presented in Supplemental Appendix 1 (available via Mendeley at https://doi.org/10.17632/9kbh6p3cft.2).

The clinical details of patients included in this study are shown in Supplemental Appendix 2 (available via Mendeley at https://doi.org/10.17632/9kbh6p3cft.2). Among the 31 AMs tested, 6 were melanoma in situ; 24 patients had NNAM, and 7 patients had NAM. Through WES, single nucleotide variations (SNVs) and small insertions/deletions were identified (Supplemental Appendix 3; available via Mendeley at https://doi.org/10.17632/9kbh6p3cft.2). In NNAM, mutations were identified in *BRAF* (16.67%), *NRAS* (12.50%), and *KIT* (8.33%). In NAM, only 1 patient (14.29%) showed an alteration in *BRAF*, and no patients showed *NRAS* or *KIT* mutations. Fifty-three genes were repeatedly detected (≥2 times) as having somatic mutations in AMs (Fig 1). Of them, 11 genes have been previously reported to be associated with melanoma (Supplemental Appendix 4; available via Mendeley at https://doi.org/10.17632/9kbh6p3cft.2). Among SNVs, mutations in 25 genes were predicted to be significantly deleterious[5] in developing melanomas. Fisher's exact test showed that *CES1*, *CSMD3*, *EHMT1*, and *MAGI1* did not appear in NNAM but were distinct mutations in NAM ($P = .045$). We also identified genomic regions affected by copy number alterations (CNAs) (Fig 2). The CNA analysis was based on WES data. CNAs were relatively infrequent in NAMs but common in NNAMs.

In the present study, the frequencies of *BRAF* and *NRAS* mutations in patients with AM, especially in NAM, were lower than those in a previous study on cutaneous melanoma patients.[3] This suggests that NAM might require genetic alterations other than *BRAF* and *NRAS*. Hayward et al[2] reported, based on whole genome sequencing, that the frequencies of SNVs and insertions/deletions were lower but the frequency of structural variants was higher in AM and mucosal melanoma than in cutaneous melanoma. The present study is limited by the small number of cases and by using WES rather than whole genome sequencing.

Based on the results of analysis of significantly deleterious mutations, *CSMD3* and *EHMT1* might have an important role in the pathogenesis of NAM but not in NNAM. Previously, there have been several reports on the association of these genes with malignancies (Supplemental Appendix 5; available via Mendeley at https://doi.org/10.17632/9kbh6p3cft.2). Because our study used only WES, it is currently difficult to know the potential roles of these genes. Therefore, protein work or interaction analysis through transcript analysis may be helpful in the future.

In conclusion, we found possible pathogenic mutations previously unidentified in AM and identified differences between NAM and NNAM. Also, mutations in *CSMD3* and *EHMT1* could play a distinct oncogenic role in NAM. Further studies are needed to validate this result.

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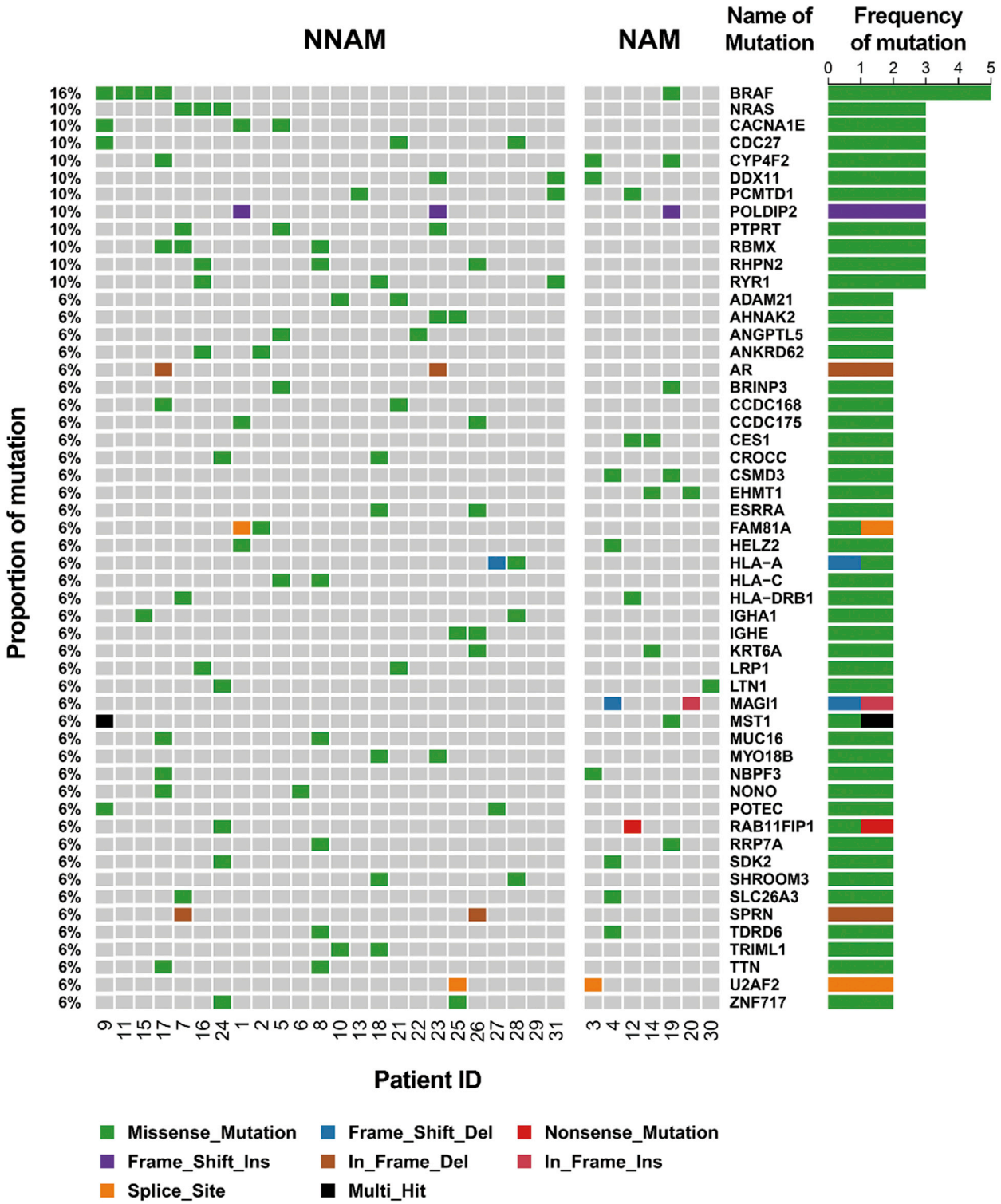

Fig 1. Heat map of somatic mutations detected in acral melanoma samples. There were 53 genes whose somatic mutations were repeatedly detected in AM, with frequencies shown from top to bottom. The horizontal axis of this figure shows patient ID number. The left side of the figure shows the mutational profiles of patients with NNAM, and the right side of the figure shows the mutational profiles of patients with NAM. The perpendicular axis of this figure shows the names of mutations repeatedly detected with frequencies. *AM*, Acral melanoma; *ID*, identification; *NAM*, nail apparatus melanoma; *NNAM*, nonnail acral melanoma.

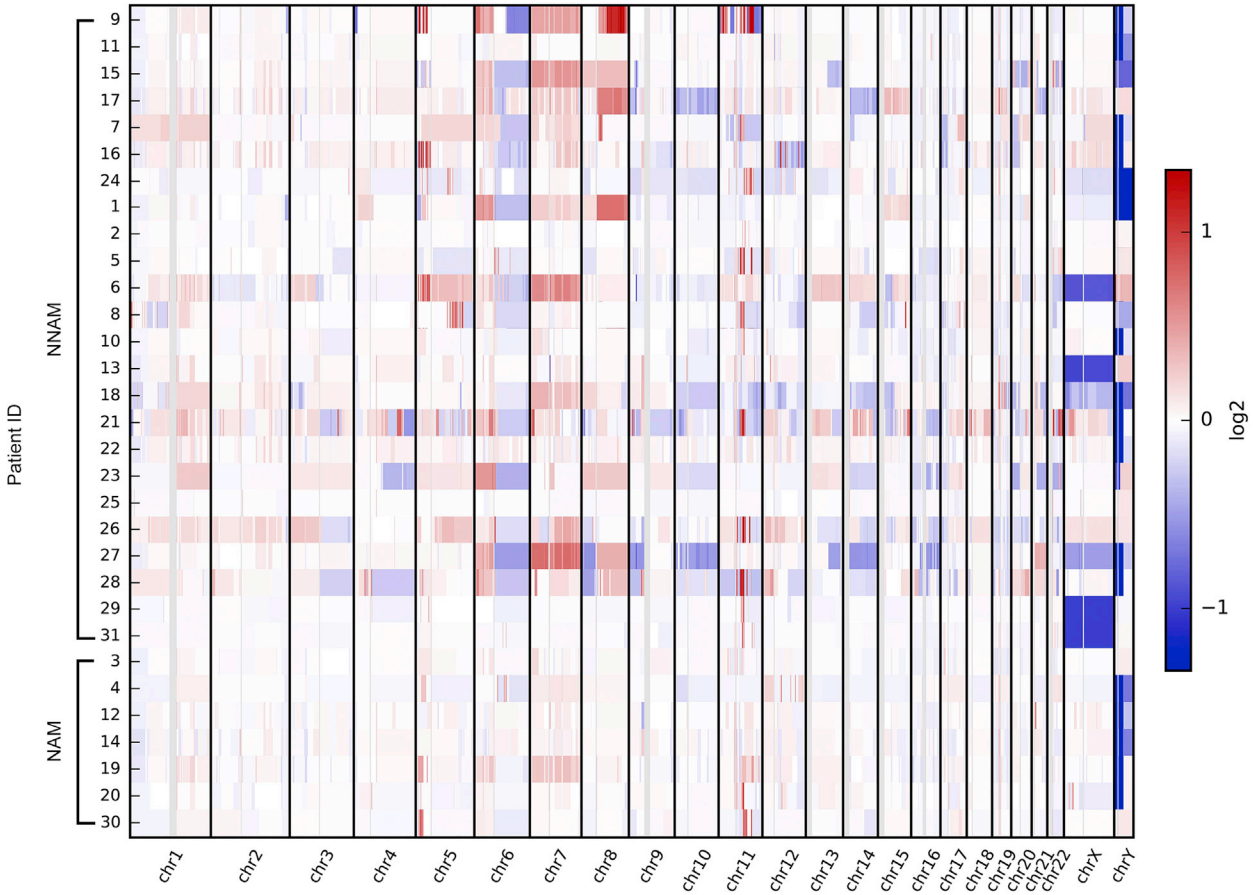

Fig 2. Heat map of copy number alterations detected in NNAM and nail apparatus melanoma NAM samples of patients. *ID*, Identification; *NAM*, nail apparatus melanoma; *NNAM*, nonnail acral melanoma.

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Clinical and pathological dermatological features of deficiency of adenosine deaminase 2: A multicenter, retrospective, observational study

To the Editor: Adenosine deaminase 2 deficiency (DADA2) is a monogenic autoinflammatory disease associated with *ADA2* mutations.[1]

Diagnosis of DADA2 remains difficult given its variable clinical presentation.[2] Although no tests are commercially available, serum ADA2 activity measurement can help secure the diagnosis, which is confirmed by *ADA2* sequencing. Recently, Rama et al[2] proposed a decision tree for the genetic diagnosis of DADA2 based on prerequisites including, among others, cutaneous manifestations. However, to our knowledge, no study has specifically described DADA2's dermatologic spectrum. Furthermore, pathologic findings on skin biopsy samples have rarely been reported,[1,3] and specific histologic features remain to be determined. We conducted a multicenter, retrospective study with