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著者 Author(s)	Yoshida, Yuichi; Ehara, Yuko; Noma, Hiroshi; Yamamoto, Osamu
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**Title: Simple method for estimating cutaneous neurofibromas in patients with neurofibromatosis 1.**

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Yuichi YOSHIDA<sup>1</sup>, Yuko EHARA<sup>1</sup>, Hiroshi NOMA<sup>2</sup>, Osamu YAMAMOTO<sup>1</sup>

<sup>1</sup>Division of Dermatology, Department of Medicine of Sensory and Motor Organs, Faculty of Medicine, Tottori University, Yonago

<sup>2</sup>Department of Data Science, The Institute of Statistical Mathematics, Tokyo, Japan

Correspondence to: Yuichi Yoshida, M.D.

Division of Dermatology, Department of Medicine of Sensory and Motor Organs, Faculty of Medicine, Tottori University, 86 Nishi-cho, Yonago-shi, Tottori 683-8503, Japan

Email: [yxyhifu1@med.tottori-u.ac.jp](mailto:yxyhifu1@med.tottori-u.ac.jp)

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Neurofibromatosis 1 (NF1) is an autosomal genetic disease caused by mutations in the *NF1* gene.<sup>1</sup> Although clinical manifestations of NF1 are variable between individuals, most of the patients develop cutaneous neurofibromas. We have already shown that the number of cutaneous neurofibromas significantly increases with age.<sup>2</sup> It is desirable to treat cutaneous lesions before a serious condition develops. However, patients are often reluctant to show the lesion on the trunk and it is arduous to evaluate the severity of cutaneous manifestations. Therefore, we conducted a case series study to establish a method for estimating the number of cutaneous neurofibromas.

We investigated the number of cutaneous neurofibromas in 47 NF1 patients with more than 10 neurofibromas (16 men and 31 women; average age, 41.1 years; age range, 7-79 years) at the Dermatology Department of Tottori University Hospital from 2014 to 2017.

All of the patients fulfilled the criteria for a diagnosis of NF1 by National Institutes of Health in 1988.<sup>3</sup> The study protocol was approved by the Ethics Committee of Tottori University Hospital. We counted the number of cutaneous neurofibromas (> 5 mm in diameter) at the 4 divisions of the body surface area, the head & neck, trunk, and upper and lower extremities, by visual judgment. A fused tumor was counted as one tumor. Subcutaneous neurofibromas were not counted in this study.

As reported previously,<sup>2</sup> cutaneous neurofibromas occurred most frequently at the trunk

(56.8%), followed by the lower extremities (16.7%), upper extremities (15.7%), and head & neck (10.8%) (see Table S1). To construct a simple method for estimating total number of cutaneous neurofibromas, we conducted regression and correlation analyses. The estimated regression lines are presented in Fig. 1. The correlation coefficients between the number of cutaneous neurofibromas at each division and the total number of cutaneous neurofibromas were  $R = 0.84$  (95%CI: 0.73, 0.91;  $P < 0.001$ ) for the head & neck,  $R = 0.96$  (95%CI: 0.94, 0.98;  $P < 0.001$ ) for the trunk,  $R = 0.96$  (95%CI: 0.94, 0.98;  $P < 0.001$ ) for the upper extremities and  $R = 0.93$  (95%CI: 0.88, 0.96;  $P < 0.001$ ) for the lower extremities.

We proposed for the first time a simple method for estimating the total number of cutaneous neurofibromas in NF1 from any sites. At first, we considered that it would be possible to predict the total number of neurofibromas from the number at the head & neck. However, it was not easy to count the exact number on the scalp covered by hair. We consider the upper extremities to be the most appropriate sites for estimation without hesitation by the patient. Cunha et al. reported a technique using paper frames on the back, abdomen and thigh with a specific formula to quantify cutaneous neurofibromas.<sup>4</sup> However, their method is not simple compared to our method because they have to count the number on three different areas with special paper frames. Whole-body MRI is

another quantitative method to investigate the state of cutaneous neurofibromas,<sup>5</sup> but is not practical because of the cost effectiveness in daily medical examinations.

There is a limitation in our study. Our method may not be applicable if there is extremely large number of neurofibromas because it is difficult to count the number accurately due to numerous fused tumors. In addition, it is not possible to count subcutaneous neurofibromas from the surface. Nevertheless, our proposed method will be useful for physicians to estimate the severity of cutaneous neurofibromas. The appropriate assessment of dermatological manifestations of NF1 may result in better patient care.

## References

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### Figure legend

Figure 1 Scatter plot of the total number of cutaneous neurofibromas versus the number of those at the head & neck (a), trunk (b), upper extremities (c) and lower extremities (d).