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**Ordinary vibratory angioedema is not generally associated with
ADGRE2-mutation**

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CONFLICTS OF INTEREST

Prof. Zuotao Zhao: none; Dr. Sascha Reimann: none; Dr. Shan Wang:
none; Dr. Yuhan Wang: none; Prof. Torsten Zuberbier: none

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4 **Capsule summary**

5 Mild forms of vibratory angioedema/pruritus are more common than
6 expected. As the ADGRE2-mutation causing familial vibratory
7 angioedema was not seen in the population investigated, at least two
8 subtypes must exist.

9

10 **Keywords:** Histamine; mast cell; pruritus; vibratory angioedema

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13 To the Editor: We report on the prevalence and pathogenesis of vibratory
14 angioedema, an underinvestigated subtype of inducible urticaria first
15 described as occupational disease in patients working with a pneumatic
16 hammer with severe swelling of the whole arm but later also as sporadic
17 cases in occupations where only mild vibrations occur e.g. in a saxophonist
18 and trumpet player (1, 2) or following everyday vibratory stimuli like riding a
19 bicycle over cobblestone pavement. Regarding the prevalence and
20 pathogenesis little is known but recently a mutation with missense
21 substitution in *ADGRE2* was described in an affected family (3). To better
22 understand the condition we have studied a representative group of 91

1 medical students in China and 81 in Germany (all undergoing a lecture on
2 dermatology in a compulsory course at the university). They received a
3 3-minutes-introduction about the disease and a questionnaire asking, if
4 pruritus or swelling occurred during every day vibrations (such as riding by
5 bicycle or motorcycle on cobblestone pavement). All study subjects
6 responding positively in the questionnaire (7 in China, 18 in Germany) were
7 asked to participate in a provocation test using a vortex. In China five and in
8 Germany nine of those asked agreed. In addition six healthy controls in
9 Germany and seven healthy controls in China were included.

10 For provocation one palm was put on the vortex for five minutes as
11 described in (4, 5).

12 The differential diagnosis symptomatic dermographism was excluded by
13 using sheering forces according to the guideline (5).

14 A blood sample was taken for the measurement of serum-histamine
15 content from the draining vein before (0) and at 5, 15 and 30 minutes
16 after the vortex provocation. Palm thickness was measured with vernier
17 caliper at the thickest part of the palm before and after provocation. Three
18 of the five Chinese patients who showed positive symptoms on
19 provocation test in addition were checked for a mutation in *ADGRE2*
20 (Method see online repository).

21 81 participants in Germany with the mean age of 24 years (range: 22 - 37
22 years) were evaluated. 22.2% of the participants of the questionnaire

1 stated to have symptoms in the palms after vibratory stimuli. The main
2 symptoms were pruritus (100%), wheals (16.7%) and angioedema (5.6%).
3 Women were more frequently (2:1) having a positive anamnesis of
4 vibratory angioedema/ pruritus than men .

5 Of the 91 participants in China (mean age: 27.2 years), 7 study
6 participants (7.7%) reported symptoms of vibratory angioedema,
7 including erythema and pruritus (100%). Further clinical reactions were
8 angioedema of the hand (33.3%) and wheals (22.2%). In China the
9 male/female ratio was 1:6. In all subjects (Germany: 6 male, 12 female;
10 China: 1 male, 6 female) with a positive anamnesis, symptoms could be
11 reproduced in objective testing with a vortex.

12 Dermographism was only red but not urticarial after applying a sheering
13 force in all. Fig. E1 (see online repository) shows the swelling of hands
14 after the provocation test and the VAS (visual analogue scale) in the
15 Chinese group.

16 Study participants (n=3) with vibratory angioedema showed a significant
17 ($P=0.001$) increase of serum-histamine content after provocation in
18 contrast to the control group without anamnestic vibratory angioedema
19 both in China and in Germany (Fig. E2, see online repository) with a
20 rapid time course (Fig 1b,) indicating clearly a mast cell involvement.

21

22 Fig. 1 shows the time course of increased levels of histamine after

1 provocation. The testing with the vortex showed a positive result in all
2 participants who had mentioned a history of vibratory
3 angioedema/pruritus. Those exhibiting worst symptoms (total 5 persons)
4 were checked for the mutation in *ADGRE2*, however, the mutation in
5 *ADGRE2* described recently could not be detected.

6 The study was conducted to better understand the frequency also of mild
7 forms which may not necessarily lead to a visit at the dermatologist's
8 office as the eliciting stimulus can be easily avoided and to understand if
9 the recently detected *ADGRE2*-mutation causing familial vibratory
10 angioedema was also relevant for non familial forms.

11 With an overall prevalence of more than 14.4% in the group of young
12 adults tested in this study it is clear that vibratory angioedema/pruritus is
13 an underdiagnosed entity.

14 Like in other subtypes of inducible urticaria e.g. cholinergic urticaria,
15 different forms of severity appear to occur (6, 7).

16 While in some patients only pruritus and mild erythema occurred, in
17 others wheals and/or angioedema are signs of a more pronounced mast
18 cell degranulation and vibratory urticaria can have a high impact on
19 Quality of Life in general and be an impairment in work.

20 For diagnosis, patient history is of highest importance. In all subjects
21 claiming to have symptoms in the questionnaire, symptoms could be
22 reproduced in objective testing proving the guideline recommended

provocation test with a vortex is reliable. Measurement of histamine over time in the venous blood flow showed that the swelling is clearly mast cell- and histamine-dependent, but also explained a finding, often reported in patient history of symptoms worsening for several minutes after the stimulus had stopped. In this study all patients reacting with vibratory angioedema/pruritus did not react with a positive urticarial dermatographism to sheering forces. Also did the patients not report any signs of pressure urticaria. The distinct reaction to one stimulus only is typical in physical urticaria in general, possibly at least in a subgroup of patients with non-familial form, based on activation of different nerves leading to mast cell histamine release. Further research is needed in this area to better understand the neuronal interaction with mast cells. However it appears to be clear that this change in mast cell activation is not based on a genetic alteration in the non-familial form as the recently detected ADGRE2-mutation, which is independent of any neuronal mechanisms, was not seen in the population investigated.

The good news for the patient is that this subtype of urticaria is also histamine mediated and can be well treated following the algorithm of the guidelines (8, 9).

In conclusion our results demonstrate that vibratory angioedema is 1. more frequent than thought; 2. Abortive forms presenting mainly with pruritus and erythema exist; 3. a questionnaire provides a rapid and

1 reliable option for diagnosis; 4. provocation of by vortex is a simple way
2 for diagnosis and 5. the ADGRE2-mutation causing familiar vibratory
3 angioedema is not responsible for the frequent non familial form reported
4 here.

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2 This work was supported in part by Joint Sino-Germany Research Project
3 by National Natural Science Foundation of China and Deutsche
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FIGURE LEGENDS

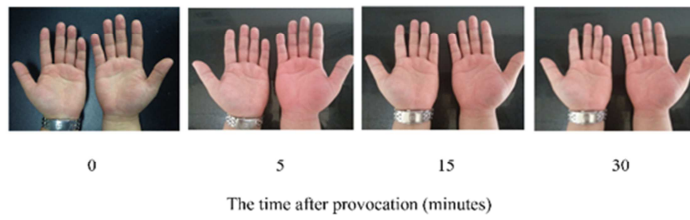
Fig. 1:

Fig. 1A: Picture showing the clinical changes with swelling and erythema of one representative patient in three before and after provocation test at different time point.

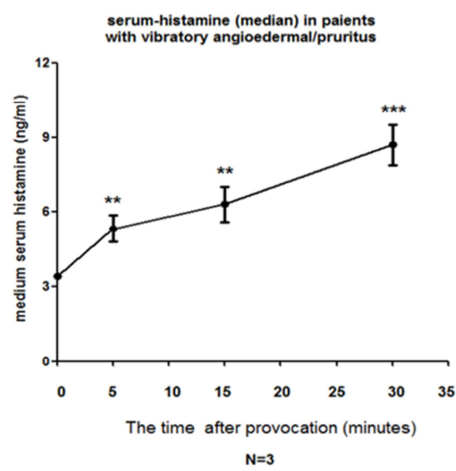
Fig. 1B: The palms and serum-histamine (median) content changes in patients with vibratory angioedema/pruritus before and after provocation at different time interval (n=3).

**** $P < 0.01$, *** $P < 0.001$, time interval: 5min, 15min, 30min vs. 0min**

A



B



Online repository

Checking for a mutation in *ADGRE2*

We designed a pair of primers to sequence the region flanked c.1475 of ADGRE2-F by sanger sequencing to detect site variation according to the reference [3]. A DNA fragment contained c.1475 of ADGRE2-F was amplified from three vibratory urticaria patient's genome DNA extracted from blood, wherein the primer sequence of the upstream primer was 5'-TGATCCCGAGACAGAAGGTG-3', and the downstream primer sequence was 5'CAACCAGGGAGCTTGGAGAA-3', the amplification length was 374bp. The sequence of ADGRE2-F fragment contained c.1475 was aligned with the reference sequences to confirm the site mutation. The aligning results showed that there is no variations occurred in the three vibratory urticaria patients' ADGRE2-F genes.

Sequence

```
GCTCTGTGACTGGCGATGGATGTGGTCACTGGGCCACCACAGGCTGCAG
CACAATAGGCACCAGAGACACCAGCACCATCTGCCGTTGCACCCACCTG
AGCAGCTTTGCCGTCCTCATGGCCCACTACGATGTGCAGGTGAGACCCT
TAGGAGGGGGATGCACTCTGCATTTATTGCCGTGTAACAAATCCCCAGAG
ACATAGCAGCCTTTTAAAAAAAATTTGGCTTATCCCCCGGTCCGGGGC
CACCAGCTGGGATAACAAGAAGGGTTTTCCGGTCCGGGGCTTAACAAAA
TGGAATCCTTCTGGCCCCCCCCCCCCCGGGGTGGCCTTTCCTTCGAAAAT
TGAAGGCCTTCCCCCAGCTTCCTGGTTGG
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Additional figures

Fig. E1:

Fig. E1A: Picture before and after provocation test showing the clinical changes with swelling and erythema of one representative patient in three.

Fig. E1B: Mean palm thickness of control subjects (n=3) and patients (n=3) before and after provocation, respectively. * $P < 0.05$, patient: before provocation vs. after provocation.

Fig. E1C: Mean VAS (visual analogue scale from 0-10) pruritus score of control subjects (n=3) and patients (n=3), respectively. * $P < 0.05$, control subjects vs. patients.

Fig. E2: Serum-histamine content (mean $\pm$ SEM) before and after provocation. * $P < 0.05$ (paired t-test), patient: before provocation vs. after provocation (n=3).

Vibratory Angioedema and Pruritus Questionnaire

Peking University First Hospital Dermatology Department

Vibratory angioedema (VA) is a rare physical urticaria which was first reported in workers using air-hammers with symptoms of as itching and swelling of the hands when exposed to vibration. When such patients ride a bicycle on a bumpy road, the symptoms may also occur. A research from Germany indicates that one out of every nine medical students may have vibratory angioedema (VA). This questionnaire is designed to investigate the incidence and characteristics of the disease among Chinese medical students

Hope you can help to take a few minutes to complete this short questionnaire, and your answers will provide us with valuable information !

Name : _____ Gender : ____ Age : ____ Phone number : _____

(Information for confidentiality)

1、 Do you represent the following symptoms after riding a bicycle/motorbike for a long time (especially on bumpy roads) or other causes of high-frequency vibration of your hands ?

Please tick the most accurate option.

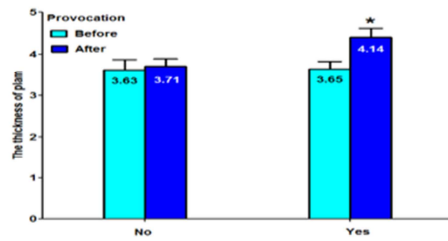
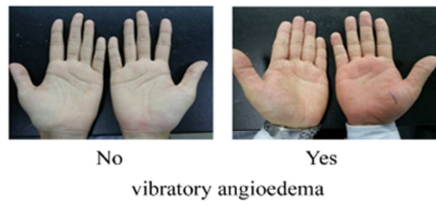
	Never	Seldom	Often	Almost every time
A. Pruritus				
B. Erythema				
C. Wheals				
D. Edema				

2、 Have you ever had any allergic disease?

3、 Do you have any other skin disease ?

-----THANKS-----

A



B

