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Contact dermatitis in the construction industry: the role of filaggrin loss-of-function mutations

running head

FLG mutations and contact dermatitis in construction workers

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Conflict of interest

The authors have no competing interests to declare.

What is already known about this topic?

- Prevalence of self-reported skin symptoms and contact dermatitis is high in construction workers
- Filaggrin loss-of-function mutations have been related to atopic dermatitis and respiratory symptoms.

What does this study add?

- Dermatological evaluations confirm high prevalences of occupational contact dermatitis in construction workers.
- Filaggrin loss-of-function mutations were strongly related to contact dermatitis in construction workers.
- Filaggrin loss-of-function mutations were not associated with respiratory symptoms or atopy in construction workers.

Abstract

background

A high prevalence of contact dermatitis (CD) and respiratory symptoms has been observed in the construction industry, probably due to widespread exposure to irritants and allergens. It is unknown if carriers of loss-of-function mutations in the gene encoding filaggrin (*FLG*), a known risk gene for eczema and asthma, are at increased risk.

objectives

To investigate associations of *FLG* mutations with CD and respiratory symptoms in Dutch construction workers.

methods

A questionnaire including items on dermal and respiratory symptoms such as wheeze, shortness of breath and asthma was administered to construction workers. Total and specific serum IgE was analysed by enzyme immunoassays. Four *FLG* loss-of-function mutations were genotyped. CD was diagnosed by a team of a dermatologist and a clinical occupational medicine specialist using photographs of the subjects' hands and self-reported questionnaire data.

results

Of the 506 participating workers, 6.3% carried at least one *FLG* mutation. Mild CD was diagnosed by the specialists in 34.0%, severe CD in an additional 24.3%. CD was considered work-related in 282 subjects (95.6%). Carriers of *FLG* variants had an increased risk of CD compared to subjects carrying wild-type alleles (odds ratio (OR) mild CD: 5.71, 95% confidence interval (95% CI): 1.63-20.06; OR severe CD: 8.26, 95% CI: 2.32-29.39). *FLG* variants and the presence of CD were not associated with respiratory symptoms and atopy.

conclusions

CD prevalence in construction workers is high. *FLG* loss-of function mutations increase the risk of CD even further. *FLG* mutations were not associated with respiratory symptoms or atopy.

Introduction:

Contact dermatitis (CD) is an inflammation of the skin, caused or worsened by contact with an exogenous substance. This substance can be either irritant, causing irritant contact dermatitis (ICD), or allergenic, causing allergic contact dermatitis (ACD). When the contact occurs in the workplace setting, the CD is considered to be occupational contact dermatitis (OCD).¹

In the general population, the one-year prevalence of CD is estimated to be around 5% for men and 11% for women.² In a routine occupational health survey among more than 152,000 Dutch construction workers, we recently found higher prevalences of self-reported skin symptoms (25%).³ An even higher prevalence of self-reported CD was found using a validated questionnaire during visits to construction sites (47%).⁴

Construction workers have a considerable risk of developing CD as they may come into contact with various allergenic and/or irritant substances like cement, epoxy products, solvents and abrasive materials.⁵⁻¹⁰ In addition to these external risk factors, a number of intrinsic risk factors may increase susceptibility to CD, such as female gender and atopic predisposition.² Moreover, well-known loss-of-function mutations in the filaggrin gene (*FLG*) were reported to increase the risk of atopic dermatitis,^{11,12} but also other atopic diseases like atopic rhinitis and asthma in co-occurrence with atopic dermatitis.^{13,14} *FLG*

encodes the protein profilaggrin, which is cleaved to filaggrin monomers.¹⁵ Their degradation products, so-called natural moisturizing factors (NMFs), play an important role in maintaining skin hydration.^{16,17} Disruption of filaggrin expression leads to a dry and more permeable skin,¹⁸⁻²¹ making it a strong risk factor for metal allergy and skin fissures.^{17,19,22} Loss-of-function mutations in *FLG* are carried by 8-10% of the European population.^{11,23,24} The interplay between *FLG* variants and dermatitis is complex. Some studies report no direct association with dermatitis but an association with earlier onset and longer duration of dermatitis^{25,26} but also direct associations with ICD and combined ACD and ICD are reported.^{27,28} However, most studies report that *FLG* variants are only associated with CD in the presence of atopic dermatitis.^{29,30} Many studies on *FLG* variants have been performed in children.³¹⁻³³ Only recently, an increased risk of both occupational ICD and ACD related to *FLG* mutations has been shown in several high risk occupational populations,^{27,30,34-36} mainly in nurses and cleaners.

We hypothesized that carriage of *FLG* mutations may predispose to CD in construction workers. Therefore we aimed to investigate the prevalence of four major *FLG* loss-of-function mutations^{11,23} and the associations between these mutations and CD, atopy and (allergic) airway symptoms in a sample of Dutch construction workers. Better understanding of these associations may help to improve strategies for prevention of skin disorders.

Methods

Study population and design

In this cross-sectional study, two approaches were used to recruit subjects. First, we collaborated with a large occupational health service where construction workers are seen for

their voluntary periodical medical checkup. For the purpose of this study, an additional ‘skin module’ was added to the regular checkup, consisting of a questionnaire, the drawing of 10ml extra blood (blood is routinely drawn at the checkup) and photographing of the skin of the hands of all subjects. The second approach was to visit a number of construction companies during an education session on skin protection and glove use in the construction industry. After this session, the participating companies facilitated the participation of their employees. In both approaches, only subjects who worked on the construction site were invited; office personnel was not included. Written informed consent was obtained from all study subjects. The study was approved by the Medical Ethical Committee of the University Medical Centre, Utrecht, The Netherlands.

Dermatological evaluations

Dermatological evaluations were performed by a team consisting of a dermatologist and an occupational physician specialized in dermatological problems (‘the expert panel’). Photographs of the subjects’ hands and questionnaire data were assessed. Photographs of both sides of the hands of the subjects were taken using a Nikon Coolpix S1100 pj, NIKKOR 5X WIDE OPTICAL ZOOM 5.0-25.0 mm 1:3.9-5.8 VR. A specially constructed lighting chamber was used to ensure standardized, sufficient and homogeneous lighting of the hands, see Online Supplement 1.

Using a standardized protocol and blinded for FLG status, the expert panel assessed the following possible symptoms of CD: erythema, papules, skin scales, crusts, pigment changes and atrophy (all mild symptoms); fissures, vesicles, bullae and ulceration (severe

Accepted Article

symptoms).³⁷ When at least two mild symptoms were present, the subjects were diagnosed with mild or beginning CD, when (also) one or more severe symptoms were present, severe CD was diagnosed. Example photos of these symptoms as seen in the study population are given in online supplement 2. Type of CD (e.g. ICD, ACD), atopic predisposition, and occupational relevance were assessed based on aetiological information in the questionnaire data: when skin allergy or allergen exposure were not reported in the questionnaire, subjects were diagnosed with irritant CD. Occupational relevance was mainly based on job title and hobbies. Relevant questions for assessing atopic predisposition are given in online supplement 3.

Questionnaire

Construction workers were asked to fill in a questionnaire including items on skin symptoms; respiratory symptoms, like wheezing, shortness-of-breath and asthma; hand hygiene and occupational activities and exposures. The questionnaire consisted of parts of other, validated, questionnaires^{4,38,39} and relevant questions can be found translated in Online Supplement 3. Self-reported CD was defined using questionnaire items, based on questions that were taken from the ‘Dutch Society of Occupational Medicine guideline: prevention of contact eczema’,⁴⁰ used by occupational physicians to screen workers for CD as we described before⁴ (Table 1).

Atopic sensitization

Serum samples were collected and analysed for IgE by enzyme immunoassays as described before.⁴¹ IgE sensitization was defined as specific serum IgE to one or more of the following

common allergens: house dust mite, cat, dog, and grass and birch pollen; high IgE was defined as serum total IgE levels >100kU/l. Atopy status was also calculated according to Jungbauer *et al.*,⁴⁰ who provided a guideline to signal an increased risk for dermatitis based on self-reported atopy symptoms. This method is based on self-reported itch and eczema (current and past), childhood eczema, asthma, hay fever and a dry skin.

Genotyping

DNA was extracted from EDTA anti-coagulated blood using the Qiagen Qiaamp® DNA blood mini kit. DNA extracts were analysed for the R501X, S3247X, 2282Del4 and R2447X^{11,23,24} loss-of-function mutations in the filaggrin gene using the Kompetitive Allele Specific Polymerase Chain Reaction (KASP) single nucleotide polymorphism genotyping system by LGC Genomics (Hoddesdon, UK) as was performed earlier.^{42,43} The call rates for the different *FLG* variants were 96.6% (R501X), 93.0% (2282del4), 95.9% (R2447X) and 97.1% (S3247X).

Data analysis

All statistical analyses were performed using SAS 9.4 (SAS System for Windows, SAS Institute, Cary, NC). Univariate associations of *FLG* variants with the various CD and respiratory outcomes were calculated using logistic regression analysis, and presented as odds ratios (OR) with 95% confidence intervals (95% CI). Carrying one or more *FLG* variants was the main explanatory variable. Method of recruitment, season and job title were also explored as independent variables, but not associated with *FLG* genotype and therefore not corrected for.

Results

A total of 1157 construction workers were invited in the study, of whom 860 participated (response 74.3%). A flow chart of the population is presented in Fig. 1. After exclusion of subjects with incomplete data (only blood received, n=14; no/poor quality photos of the hands, n=19; only part of the questionnaire filled in, n=8), age below 18 years (n=5), or who never worked on a construction site (n=63), 751 subjects had complete data on questionnaire and doctors' diagnosis, of whom 561 subjects had blood samples available (DNA and serum). Analyses for this paper were confined to subjects with successful genotyping of all four *FLG* variants (n=506).

Almost all subjects were male: 2 subjects (0.4%) were female and for 15 subjects gender data were missing. This is representative for the percentage of female construction site workers attending the occupational health services that were included in our study during the study period (0.3%). Mean age was 43.6 years (standard deviation 12.8 years, table 2). *FLG* variants were found in 32 subjects (6.3%). The most common variant was the 2282del4 variant (n=18, 3.6%), followed by R501X (n=10; 2.0%), R2447X (n=3; 0.6%) and S3247X (n=1; 0.2%). One subject was homozygous for the 2282del4 variant.

Prevalence of CD and respiratory symptoms and their associations with *FLG* variants are shown in Table 3. CD was diagnosed by the expert panel in 295 subjects (55.7%), of whom 123 (24.3%) subjects were considered severe cases. Carrying a *FLG* variant was significantly associated with both mild and severe CD (ORs: 5.71, 95% CI: 1.63-20.06 and 8.26 (2.32-29.39), respectively). A strong association was found between *FLG* variants and CD with an atopic predisposition according to the expert panel (OR: 17.15, 95% CI: 4.31-68.29). CD was considered work-related in 282 subjects (95.6%), 89% of CD was diagnosed as ICD, which was diagnosed in 263 subjects.

Self-reported CD was less prevalent than doctor-diagnosed CD, and associations with *FLG* variants were less pronounced for self-reported CD. A total of 25.9% of all subjects reported symptoms leading to a 'possible CD' classification (OR for *FLG* variants: 2.74, 95% CI: 1.27-5.91), an additional 8.1% were classified as 'CD' (OR: 2.47, 95% CI: 0.77-7.90). Prevalence of all symptoms and their association with *FLG* status are provided in online supplement 4. Workers who refused blood collection and those who provided a sample did not differ with regard to self-reported symptoms prevalence ($p>0.05$).

A total of 13.0% of the subjects reported to suffer from symptoms indicating atopy. Serum total IgE levels $>100\text{kU/l}$ were found in 31.6% of subjects, specific IgE against at least one of five common allergens was found in 28.3% of all subjects. No significant associations were found between *FLG* variants and self-reported atopy, IgE sensitization, total IgE, allergy or respiratory symptoms as listed in Table 3. The number of *FLG* mutation carriers was too small to conduct separate analyses within subjects with and without CD.

Discussion

This study amongst Dutch construction workers shows a high prevalence of self-reported CD and still higher prevalence of CD as diagnosed by an expert panel consisting of a dermatologist and an occupational physician specialized in dermatological problems. More than 95% of CD was of occupational origin. A strong positive association was found between loss-of-function *FLG* mutations and doctor-diagnosed presence of CD. Positive but less pronounced associations were observed between *FLG* variants and self-reported CD. No associations were found between *FLG* variants and respiratory symptoms or atopy.

This is the first study focussing on doctor-diagnosed CD amongst construction workers in The Netherlands in more than 25 years.⁴⁴ Recently, we reported high prevalences of self-reported skin symptoms³ and self-reported CD.⁴ However, the current study was not confined to self-reported data. Instead, we used doctors' diagnoses, providing a well-characterized disease endpoint. Prevalence of CD was high, both self-reported and doctor-diagnosed, although self-reported prevalence was not as high as in one of our earlier studies that was carried out at construction sites.⁴

The self-reported one-year prevalence is expected to be higher than the doctor-diagnosed point prevalence, although subjects may not recall symptoms that have disappeared some time ago.³ However, self-reported prevalences were much lower than doctor-diagnosed prevalences. This may be explained by the fact that the expert panel also reported the mild and beginning symptoms of CD (like redness, scaling), whereas construction workers tend to report only the more severe symptoms like fissures.

Another important strength of the current study was the high response of 74.3%. Moreover, we attempted to recruit a random sample of subjects, which increases generalizability of the study sample to the construction industry as a whole, and reduces the potential of selection bias. Distribution of job titles in our study sample was comparable to the Dutch construction industry as a whole.⁴⁵

In this study, we used two different recruitment approaches: at the occupational health service and at construction companies. Main advantage of subject recruitment at the occupational health service is the representative sample regarding different job titles. However, only ~50% of all construction workers visit the voluntary medical check-up.³ Construction workers visiting the check-up may be more aware of their health or may have symptoms, including skin symptoms. In the second approach, companies that signed in for the education session on

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skin health and glove use may be companies that are more aware of health and safety at work than the average construction company, resulting in better working circumstances and less skin problems in this population.. However, among subjects recruited at the occupational health services, CD was less frequently diagnosed than among subjects recruited at construction companies (52.6% vs. 67.1%, $p=0.001$), which might be due to the fact that the construction company visits were performed during the spring, when dermatitis symptoms are most frequently reported.³ In both recruitment approaches, subjects might have been more willing to participate if they experienced skin symptoms. Nevertheless, it is unlikely for selection bias to explain the strong associations between *FLG* variants and CD. Subjects are not aware of their genotype, and we found no evidence that subjects with *FLG* mutations were over-represented in our sample. In addition, genetic variants do not change over time, and confounding by variables such as age, recruitment method, job title or season is therefore unlikely to occur. As non-Caucasians form only a small part of the construction workers in The Netherlands, underrepresentation of *FLG* mutations in our study population is unlikely.

In our study sample, 6.3% (95% CI: 4.2%-8.4%) carried a *FLG* variant, a somewhat lower percentage than those reported in literature in the general population (8-10%).^{11,23,24} This might indicate a healthy worker effect: construction workers carrying a *FLG* variant might be more likely to develop skin problems and leave their job as a result. Moreover, Bandier *et al.*⁴⁶ reported that *FLG* mutation carriers who report having had hand eczema before 15 years of age avoid occupational exposure to irritants, indicating a so-called healthy worker hire effect. In our cross-sectional study, healthy worker selection bias would lead to underestimation of the risk of carrying a *FLG* variant. A longitudinal study investigating newly hired construction workers would be needed to estimate the impact of a possible

healthy worker survival effect on the association between *FLG* mutations and the development of skin and respiratory problems.

The positive association between *FLG* variants and CD corresponds with recent findings in various other high risk job sectors i.e. health care, metal and construction, hairdressing, food and catering, and cleaning.^{30,36} The weaker association of *FLG* variants with self-reported CD advocates the use of dermatological evaluations instead of self-reported questionnaires in construction workers.

No associations were found between *FLG* variants and respiratory symptoms, asthma, or IgE sensitization. None of the *FLG* variant carriers reported to have woken up due to shortness-of-breath or suffered from wheeze or an asthma attack in the past 12 months. In earlier studies in children, *FLG* null mutations were positively associated with wheeze, asthma and hay fever in the context of prior eczema^{11,14,32,33,42,47} but an extensive meta-analysis showed associations of *FLG* null mutations and asthma, independent of eczema.¹³ In a recent study in adults, asthma was not over-represented in subjects carrying *FLG* variants,⁴⁸ but in that study and in a number of studies in children, higher total serum IgE levels were found in *FLG* null mutation carriers.^{12,48,49} The low number of subjects with respiratory symptoms in our contact dermatitis group did not permit a stratified analysis in the dermatitis group only. Although our study is underpowered to exclude modest associations between *FLG* variants and respiratory symptoms and atopy, the ORs were all around 1.0. The lack of a trend towards an association between *FLG* variants and asthma and airway allergies might again point to a healthy worker effect. A healthy worker hire effect has been shown for subjects with pre-existing asthma⁵⁰, and it could be hypothesized that *FLG* variant carriers with early respiratory symptoms are more likely to choose a different occupation. Moreover, construction workers with (severe) respiratory symptoms might be forced to search other employment due to their symptoms.

Atopy prevalence based on self-reported data from the questionnaire was much lower than based on IgE serology (13.6% vs 42.7%), which can be explained by the fact that IgE sensitized subjects are not necessarily symptomatic. The expert panel in our study used the self-reported atopy data to assess whether subjects with CD had an atopic predisposition. The association of *FLG* variants with CD with an atopic predisposition was stronger than with CD without atopic predisposition (OR: 17.15, 95% CI: 4.31-68.29 vs. 5.61(1.65-19.07)) although 95% CIs overlap.

The question can be raised how the strong relation between *FLG* loss-of-function mutations and CD can be used to improve occupational health care in the construction industry. Several authors have mentioned the advantages but also the great ethical challenges of genetic screening in occupational health care.^{48,51} Workers who are more susceptible to occupational exposures than others could be protected by providing them with personalized education, prevention and (medical) supervision. This targeted, personalized care could help reduce the burden of CD in the construction industry. For this purpose, a genetic test should have a very high positive predictive value (PPV).⁵² In our study, the genetic test had a PPV of 91% for CD (i.e., 29 out of 32 subjects with *FLG* variants had mild or severe CD), which we consider to be high enough to be used in practice. However, the attributable fraction⁵³ for CD of the four *FLG* variants was only 8.5%, indicating that many other factors play a role than these *FLG* variants. Although the relationship between *FLG* loss-of-function mutations and skin problems is well established, and genotyping tests are useful, differences across populations (e.g. race) can occur⁵⁴ and should also be taken into account to avoid discrimination in (occupational) health care.

In conclusion, prevalence of CD in the construction industry is high and underreported. Although the self-reported prevalence is lower than prevalence of symptoms as diagnosed by a dermatological expert panel, it is still high compared to earlier studies among Dutch

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construction workers but in line with our earlier reports.^{3,4} A strong association of *FLG* loss-of-function mutations was found with doctor-diagnosed CD and to a lesser extent also with self-reported CD, but not with respiratory symptoms or atopy. Health care and prevention should be improved, especially in workers who are more susceptible. Testing for *FLG* variants as part of occupational health care in construction workers may help to target workers at increased risk of developing skin problems.

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Table 1. Scoring table for contact dermatitis (CD) according to Jungbauer *et al.*, 2006.⁴⁰

Question	Points for positive answer
Did you have one of the following symptoms on your hands or fingers in the past 12 months?	
Red and swollen hands or fingers	1
Scaly hands or fingers	1
Itchy hands or fingers	1
Hands or fingers with fissures	2
Vesicles on the hands or between the fingers	2
Red bumps on hands or fingers	2
Did one or more of these symptoms last for more than three weeks?	1
Did one or more of these symptoms occur more than once the past 12 months?	1

Scores

0-2 points:	no CD
3-5 points:	possible CD
>5 points:	CD

Table 2. Study sample demographics and prevalence of *FLG* variants

	Occupational Health					
	Services		Construction companies		Total	
	mean	SD	mean	SD	mean	SD
Age	46.2	11.5	40.0	13.6	43.6	12.8
	N	(%)	N	(%)	N	(%)
Female gender	0	0.0	2	1.0	2	0.4
Job title						
Carpenter	123	42.1	102	52.3	225	46.0
Bricklayer	34	11.6	10	5.1	44	9.0
Painter	34	11.6	28	14.4	62	12.7
Other	101	34.6	55	28.2	156	32.0
FLG variant	N	(%)	N	(%)	N	(%)
R501X	6	2.0	4	1.9	10	2.0
2282del4	10	3.4	8 ^(a)	3.8	18	3.6
R2447X	0	0.0	3	1.4	3	0.6
S3247X	0	0.0	1	0.5	1	0.2
Total	16	5.4	16	7.6	32	6.3

^(a) 1 subject was homozygous mutation carrier

Table 3. Prevalences of contact dermatitis (CD) and respiratory symptoms and associations with *FLG* loss-of-function mutations

	<i>FLG</i> variants		<i>FLG</i> wildtype		OR	
	(n=32)		(n=474)		OR	
	N	%	N	%	OR	95% CI
CD						
<i>Doctors' diagnosis</i>						
No CD	3	9.4	205	43.3	<i>Reference</i>	
Mild CD	15	46.9	157	33.1	5.71	1.63-20.06**
Severe CD	14	43.8	109	23.0	8.26	2.32-29.39**
No CD	3	9.4	205	43.3	<i>Reference</i>	
CD with no atopic predisposition	21	65.6	248	52.3	5.61	1.65-19.07**
CD with atopic predisposition	8	25.0	30	6.3	17.15	4.31-68.29***
<i>Self-reported symptoms of CD</i>						
No CD	14	43.8	320	67.5	<i>Reference</i>	
Possible CD	14	43.8	117	24.7	2.74	1.27-5.91*
CD	4	12.5	37	7.8	2.47	0.77-7.90
<i>Self-reported respiratory symptoms</i>						
Wheeze in past 12 months	0	0.0	61	12.9	-	-
Woken up due to shortness-of-breath in past 12m	0	0.0	28	5.9	-	-
Asthma (ever)	2	6.3	41	8.6	0.75	0.17-3.25
Doctor diagnosed asthma	2	6.3	41	8.6	0.75	0.17-3.25

Asthma attack in past 12m	0	0.0	5	1.1	-	-
Current asthma drug use	1	3.1	15	3.2	1.04	0.13-8.18
Current treatment (skin/respiratory disease)	2	6.3	22	4.6	1.36	0.31-6.06
Allergy	5	15.6	105	22.2	0.72	0.27-1.92
Airway allergy, including hay fever	5	15.6	80	16.9	1.01	0.37-2.73
Atopy/IgE sensitization						
Based on serology						
Total IgE >100 kU/L	8	25.0	152	32.1	0.70	0.31-1.59
Specific IgE ^(a)	9	28.1	134	28.3	0.99	0.45-2.19
Based on self-reported questionnaire ^(b)	4	12.5	62	13.1	1.02	0.34-3.02

* p<0.05, ** p<0.01, *** p<0.001

^(a) Against house dust mite, cat, dog, and grass or birch pollen

^(b) Based on Jungbauer *et al.*, 2006⁴⁰

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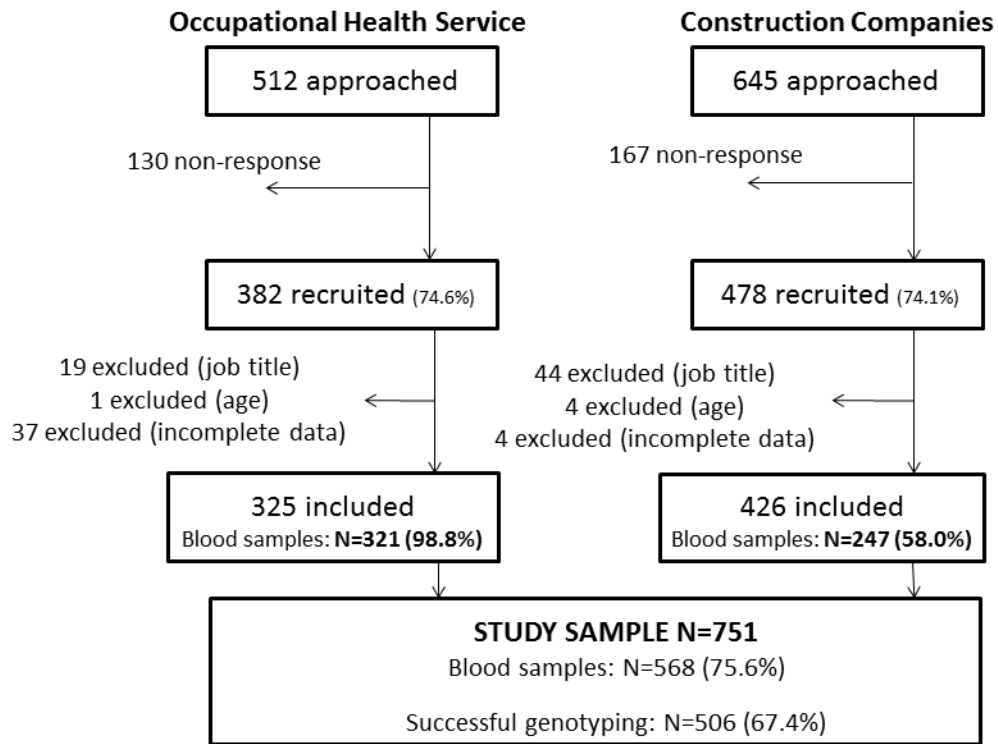
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CONTACT DERMATITIS AND RESPIRATORY SYMPTOMS IN THE CONSTRUCTION INDUSTRY: THE ROLE OF FILAGGRIN GENE VARIANTS LOSS-OF-FUNCTION MUTATIONS

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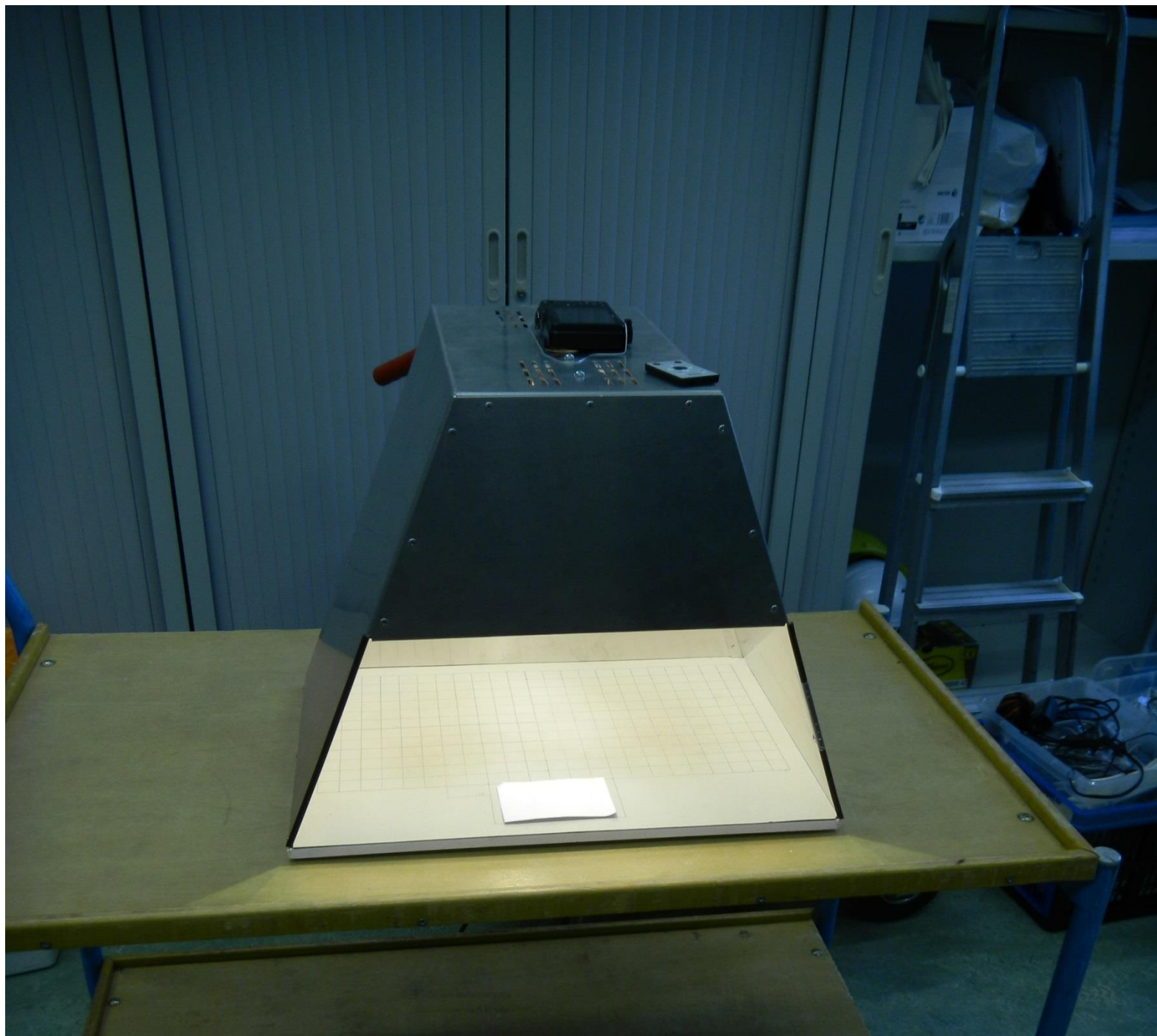
³ Arbo Unie Expert Centre for Chemical Risk Management, Haarlem, The Netherlands

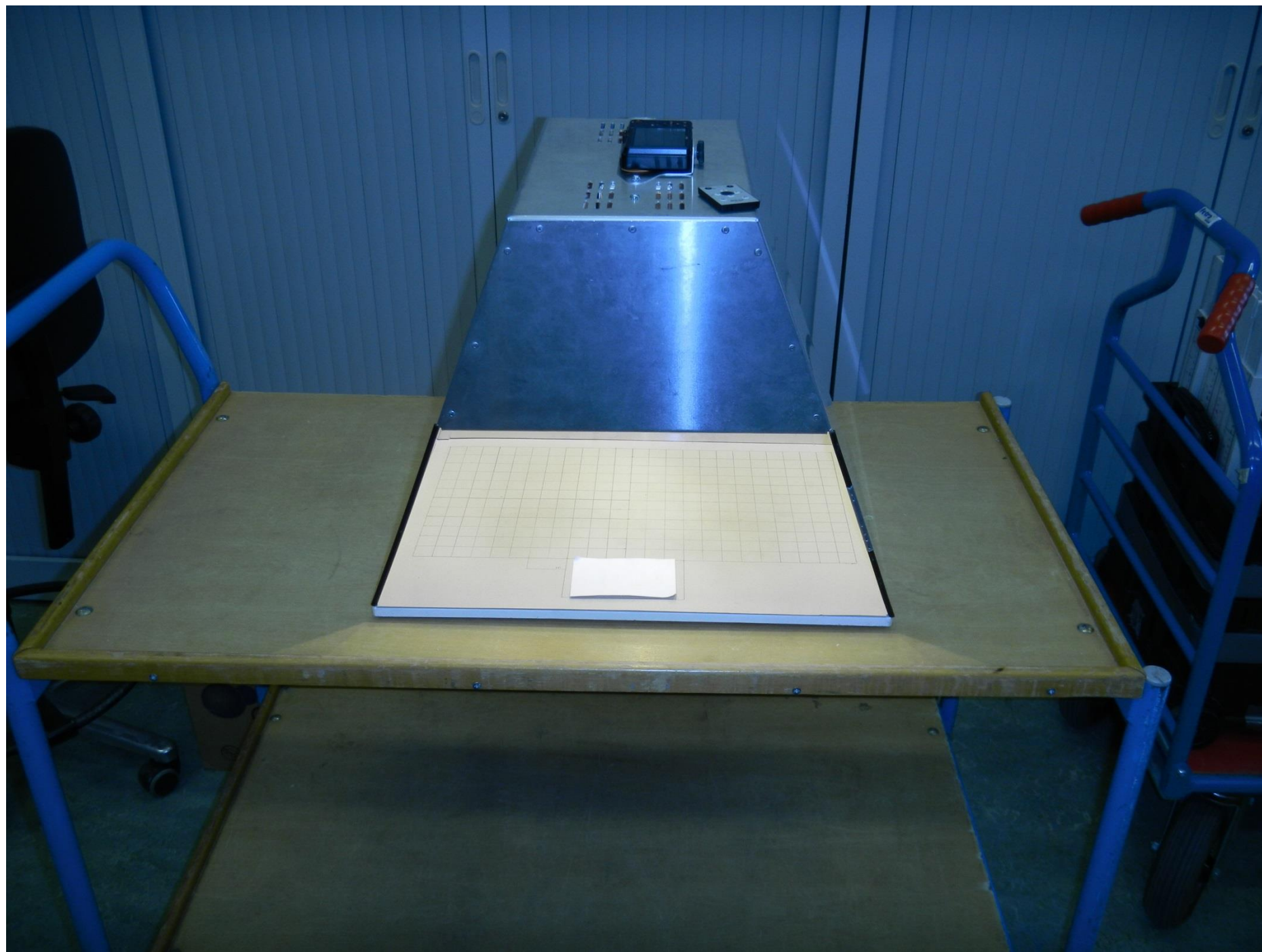
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Online Supplement 1:The lighting chamber





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Online Supplement 2: Examples of symptoms of contact dermatitis

Erythema (redness)



Figure 1a: Example of redness (erythema), also visible are: scaling (squamae) and fissures.



Figure 1b: High resolution example of redness (erythema), also visible are: scaling (squamae) and fissures.

Erythema (redness)

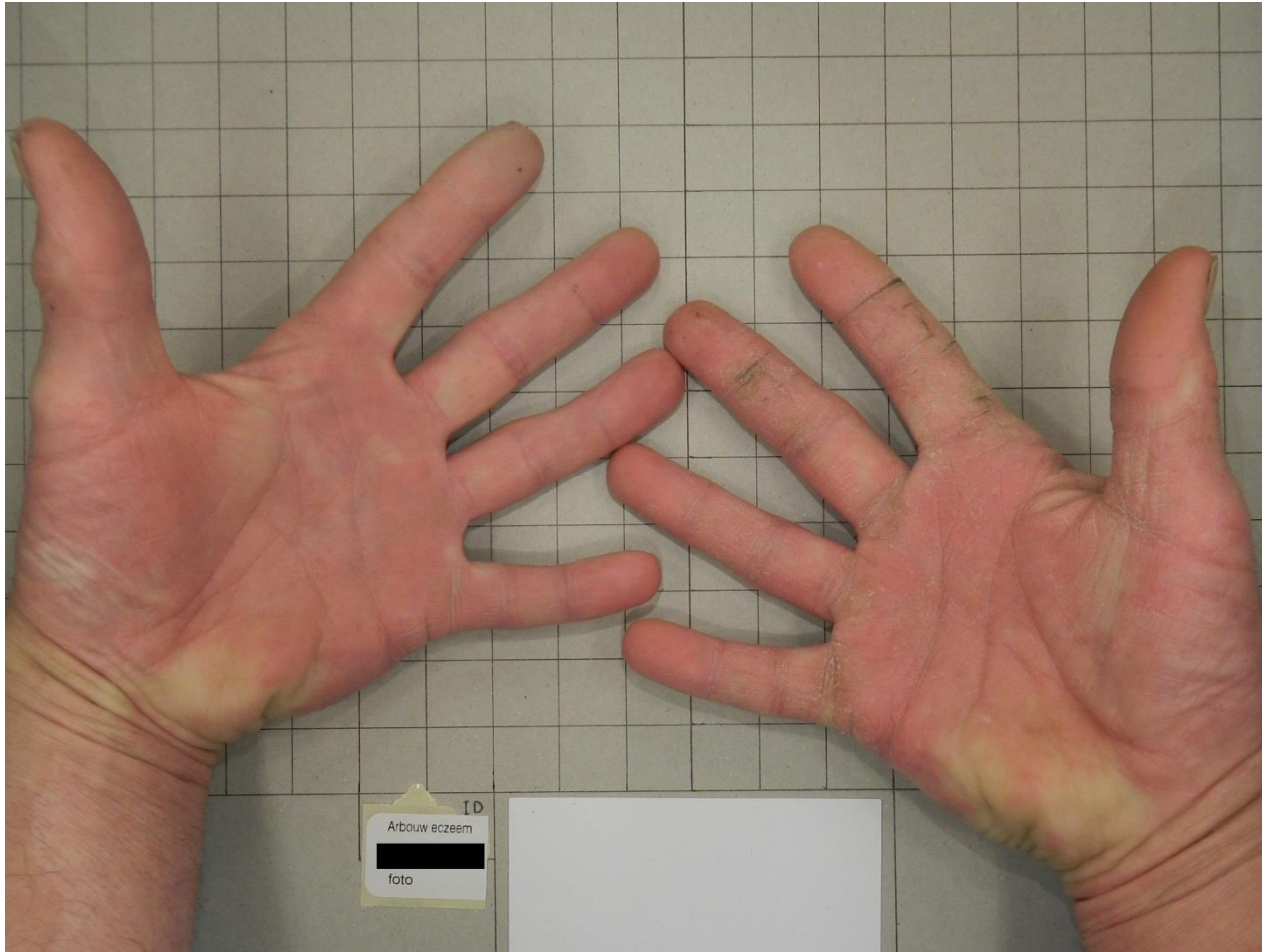


Figure 2: Example of redness (erythema), also visible are: scaling (squamae) and fissures.

Papulae (bumps)



Figure 3a: Example of bumps, also visible are: redness (erythema), scaling (squamae) and fissures



Figure 3b: High resolution example of bumps, also visible are: redness (erythema), scaling (squamae) and fissures.

Squamae (scalyness)

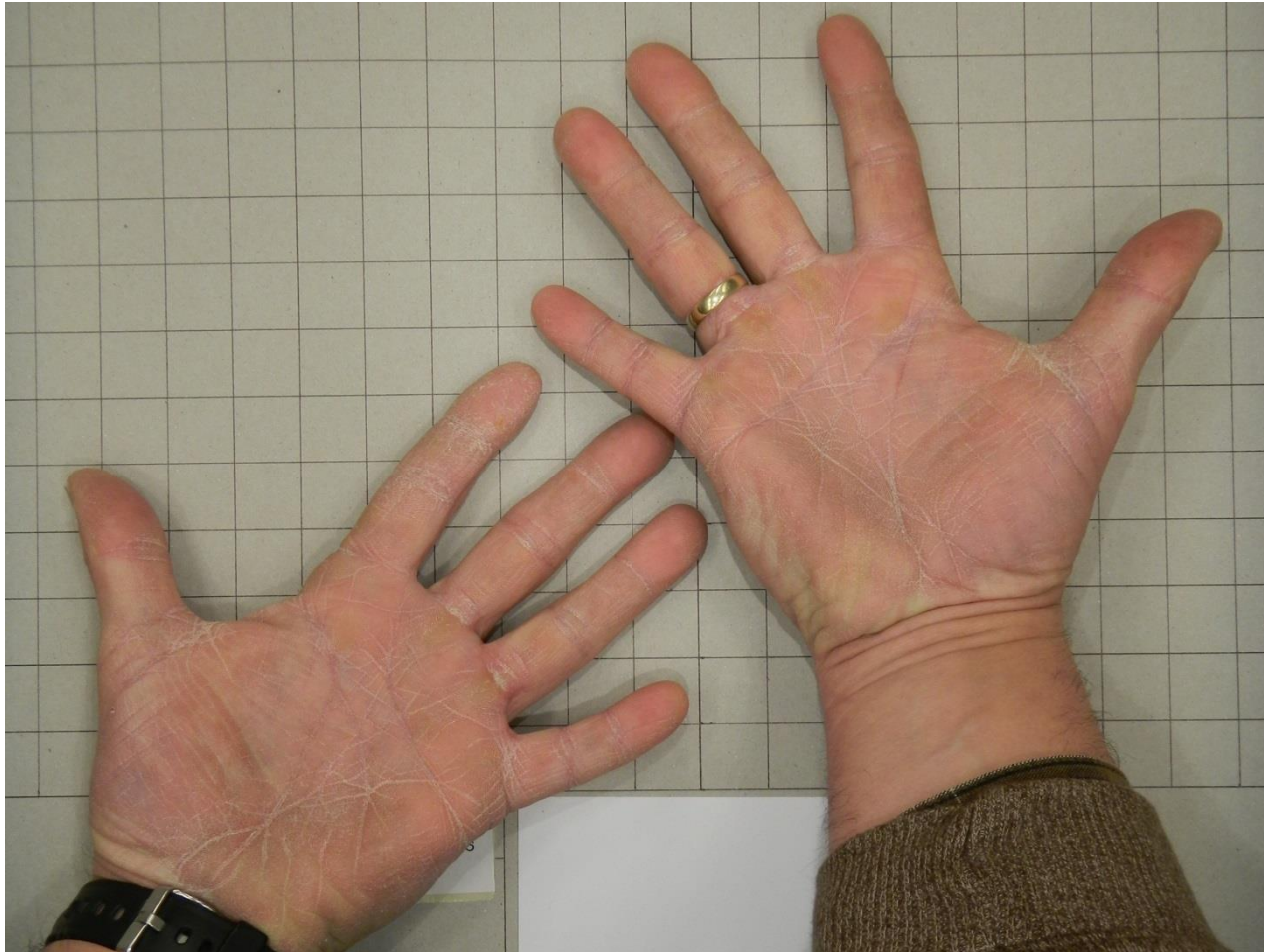


Figure 4a: Example of scaling (squamae), also visible is: redness (erythema).



Figure 4b: High resolution example of scaling (squamae).

Squamae (scalyness)

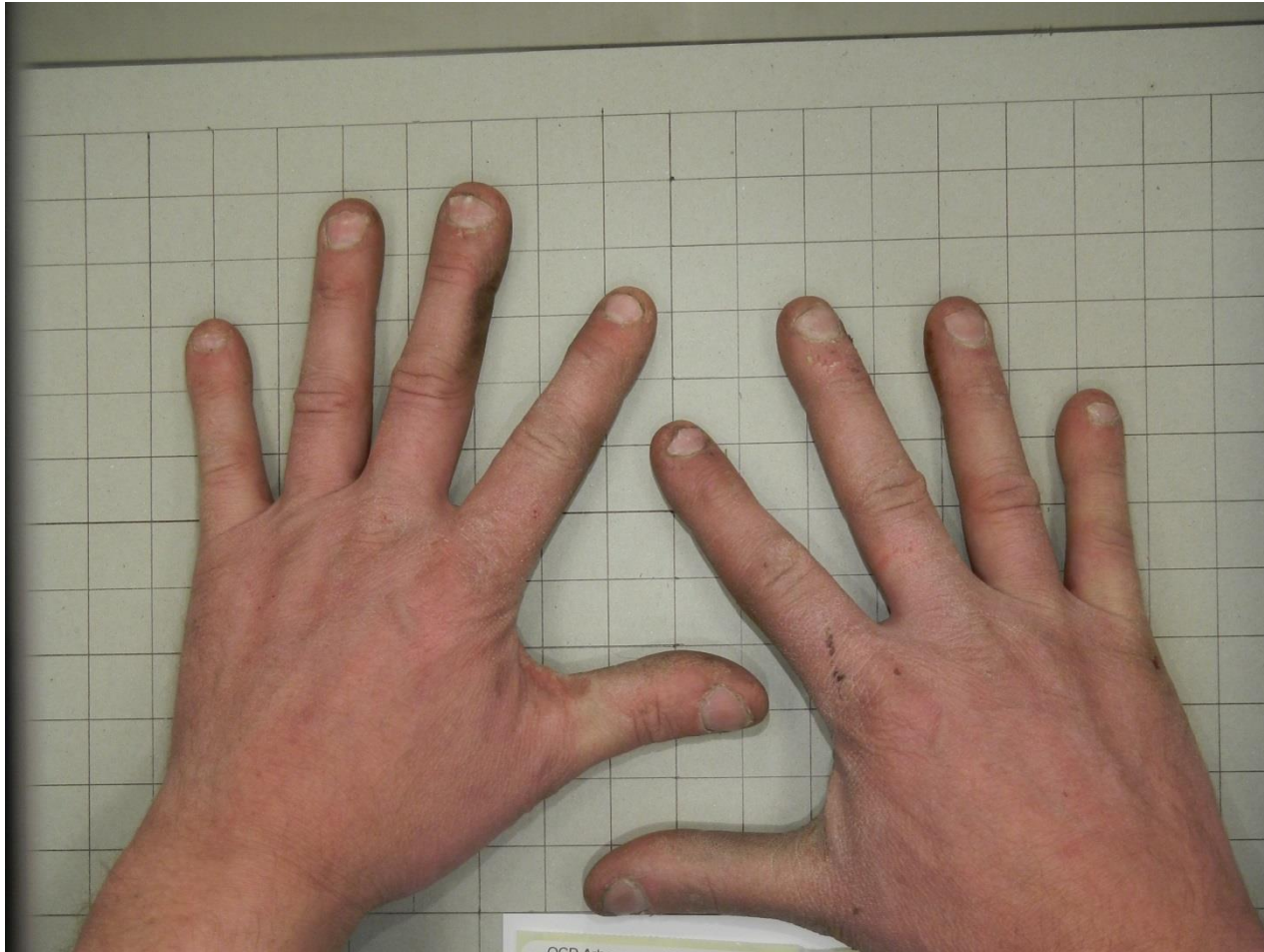


Figure 5a: Example of scaling (squamae), also visible is: redness (erythema).



Figure 5b: High resolution example of scaling (squamae), also visible is: redness (erythema).

Crusts

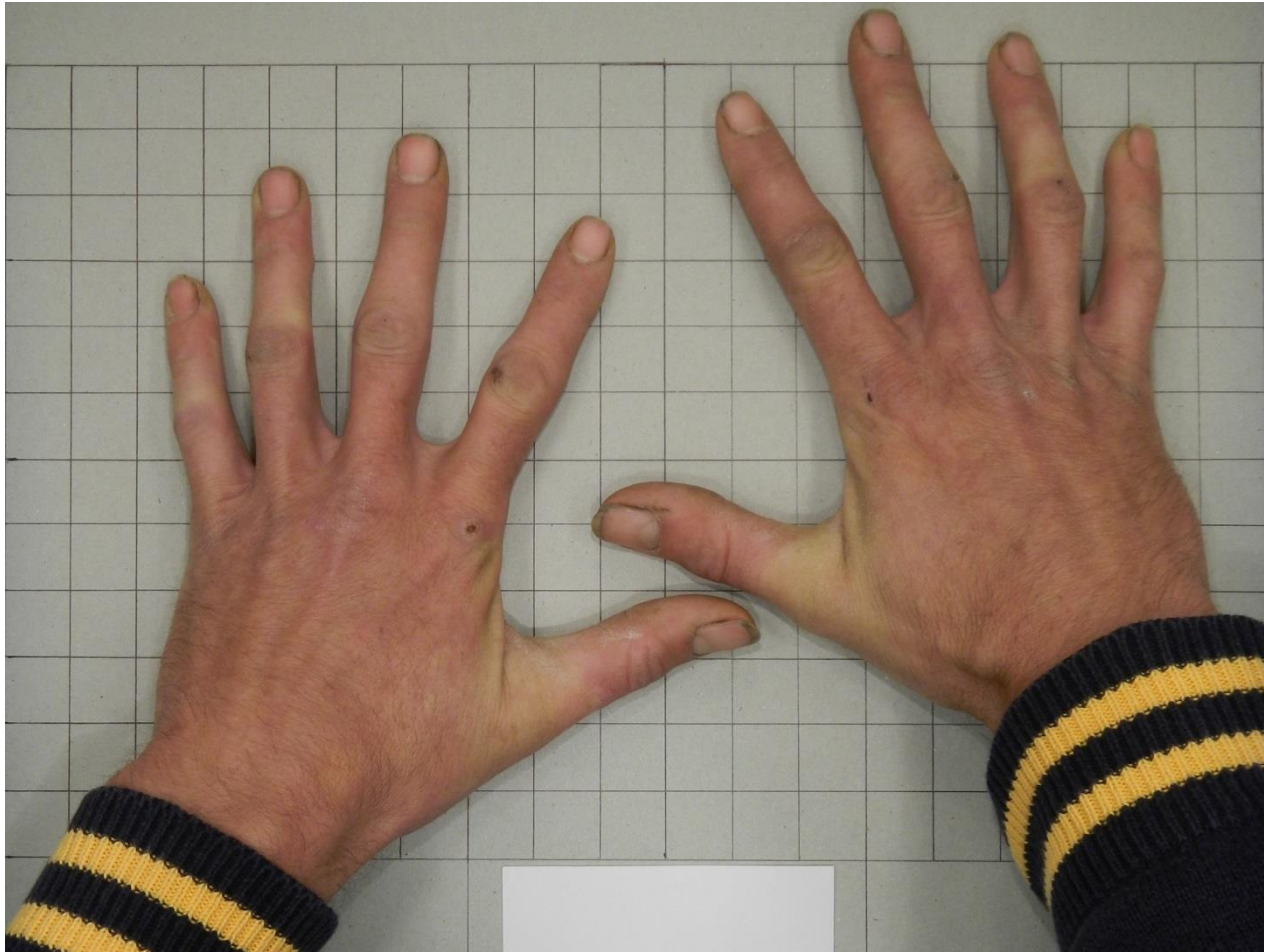


Figure 6a: Example of crusts, also visible is: redness (erythema), scaling (squamae) and fissures.

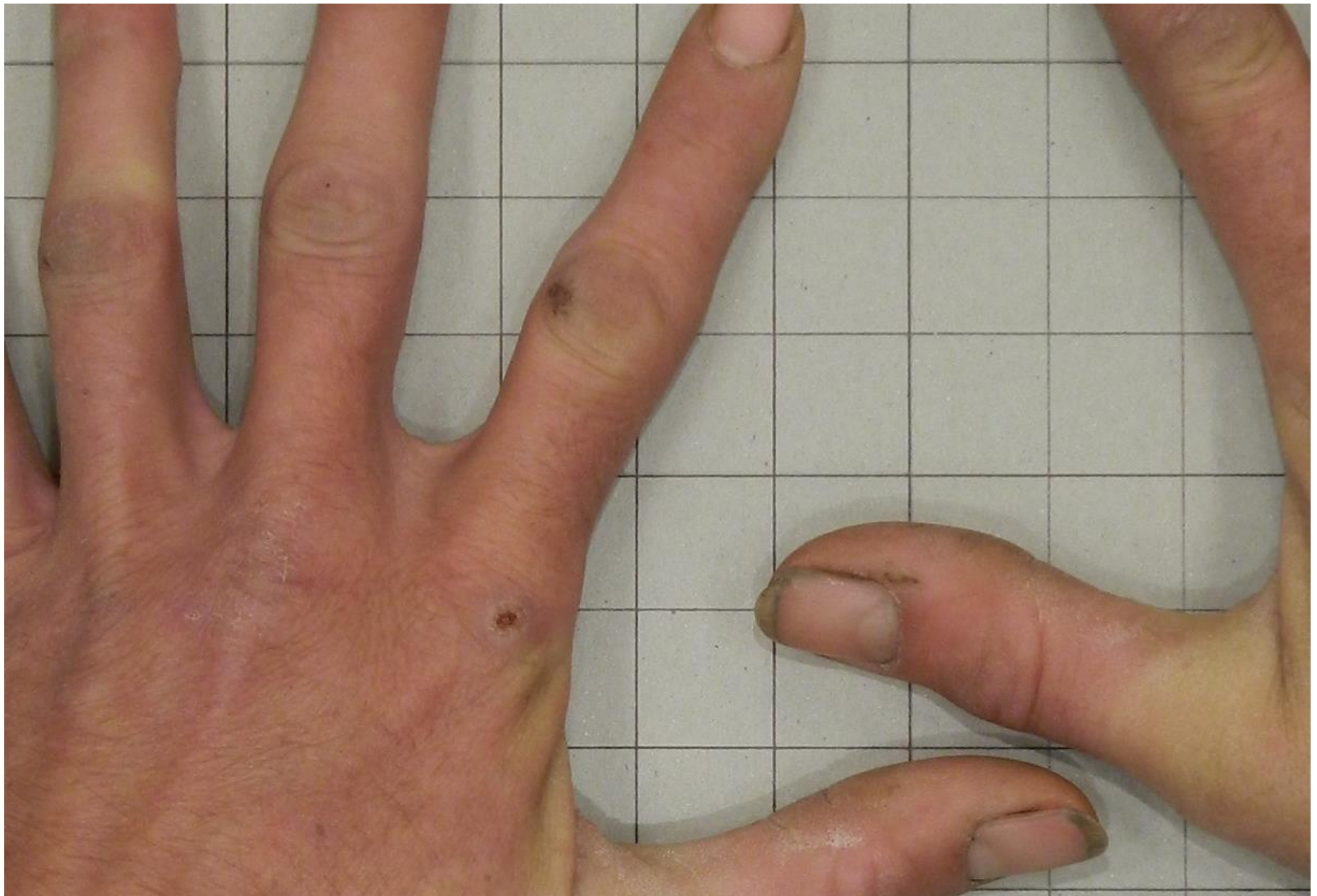


Figure 6b: High resolution example of crusts, also visible are: redness (erythema), scaling (squamae) and fissures.

Pigment

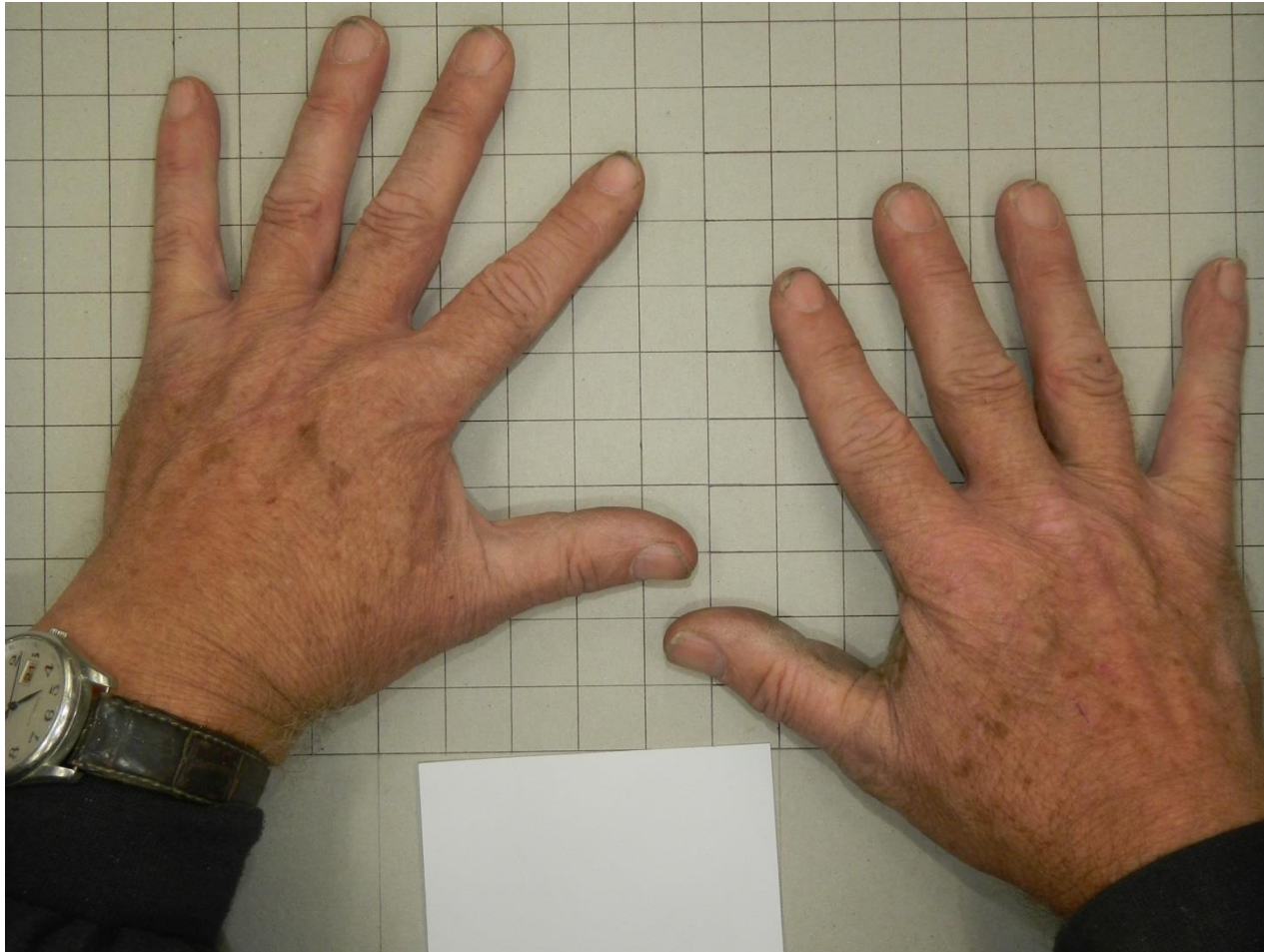


Figure 7a: Example of pigment changes, also visible is: scaling (squamae).

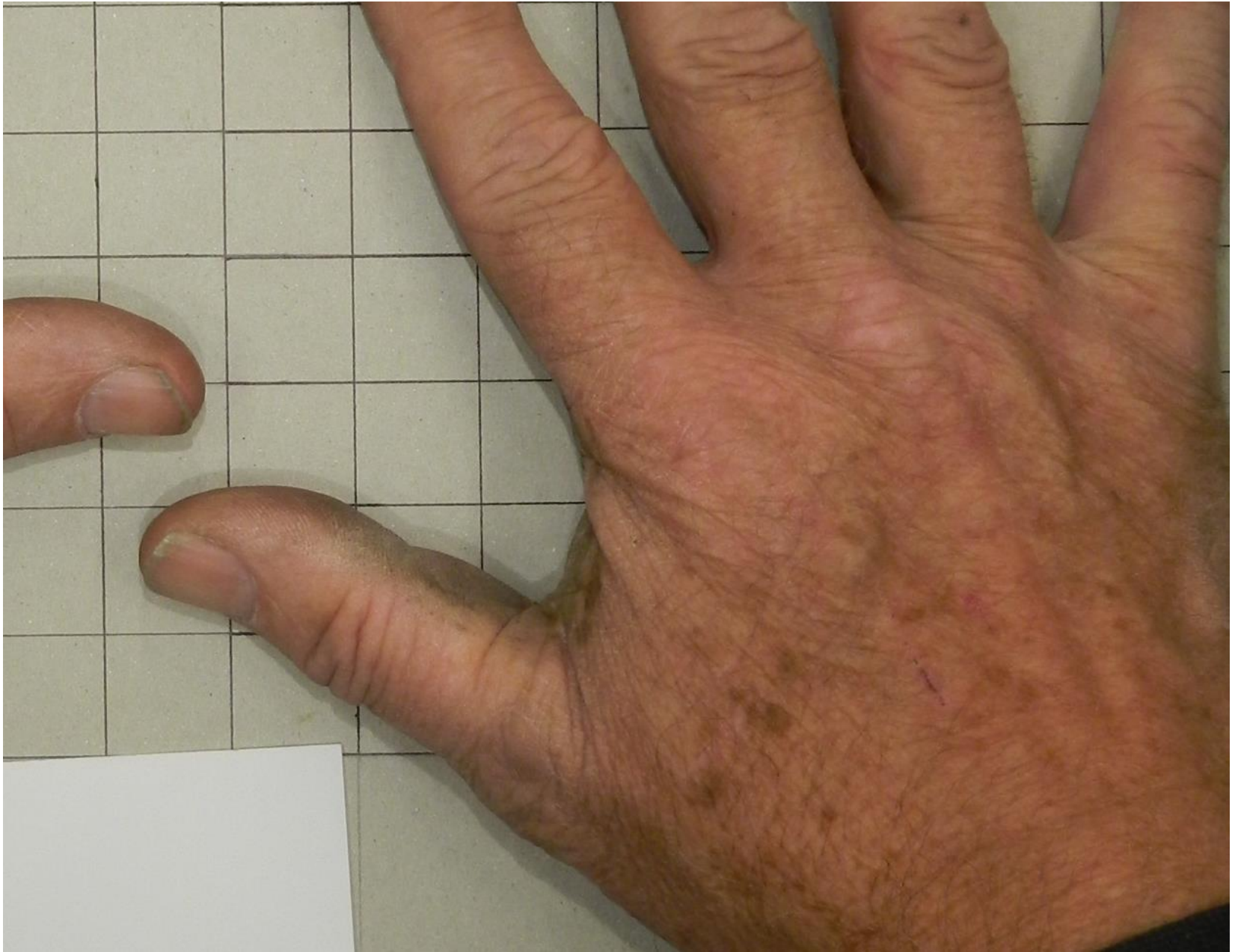


Figure 7b: High resolution example of pigment changes, also visible is: scaling (squamae).

Atrophy

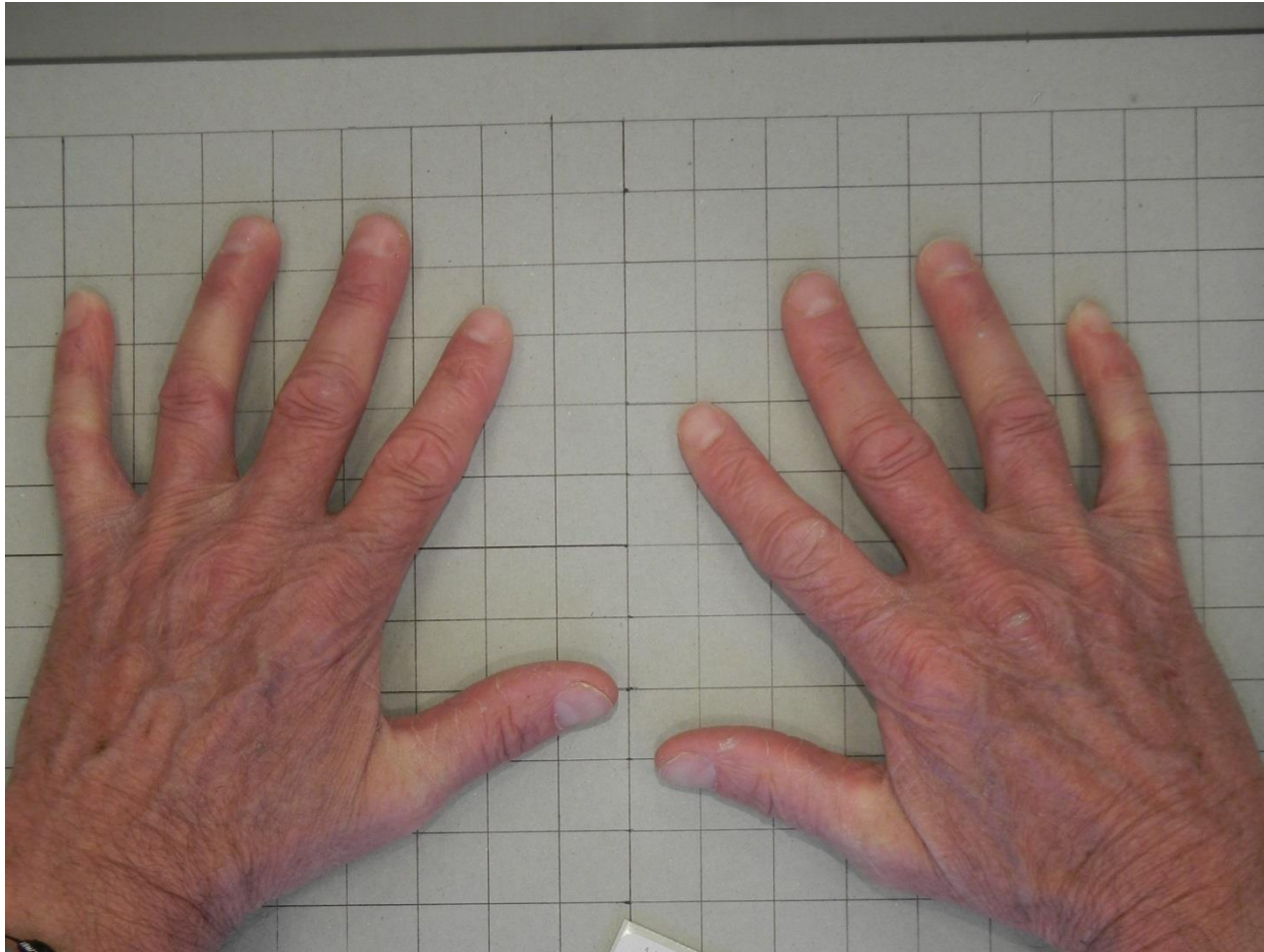


Figure 8a: Example of atrophy, also visible are: redness (erythema) and scaling (squamae)

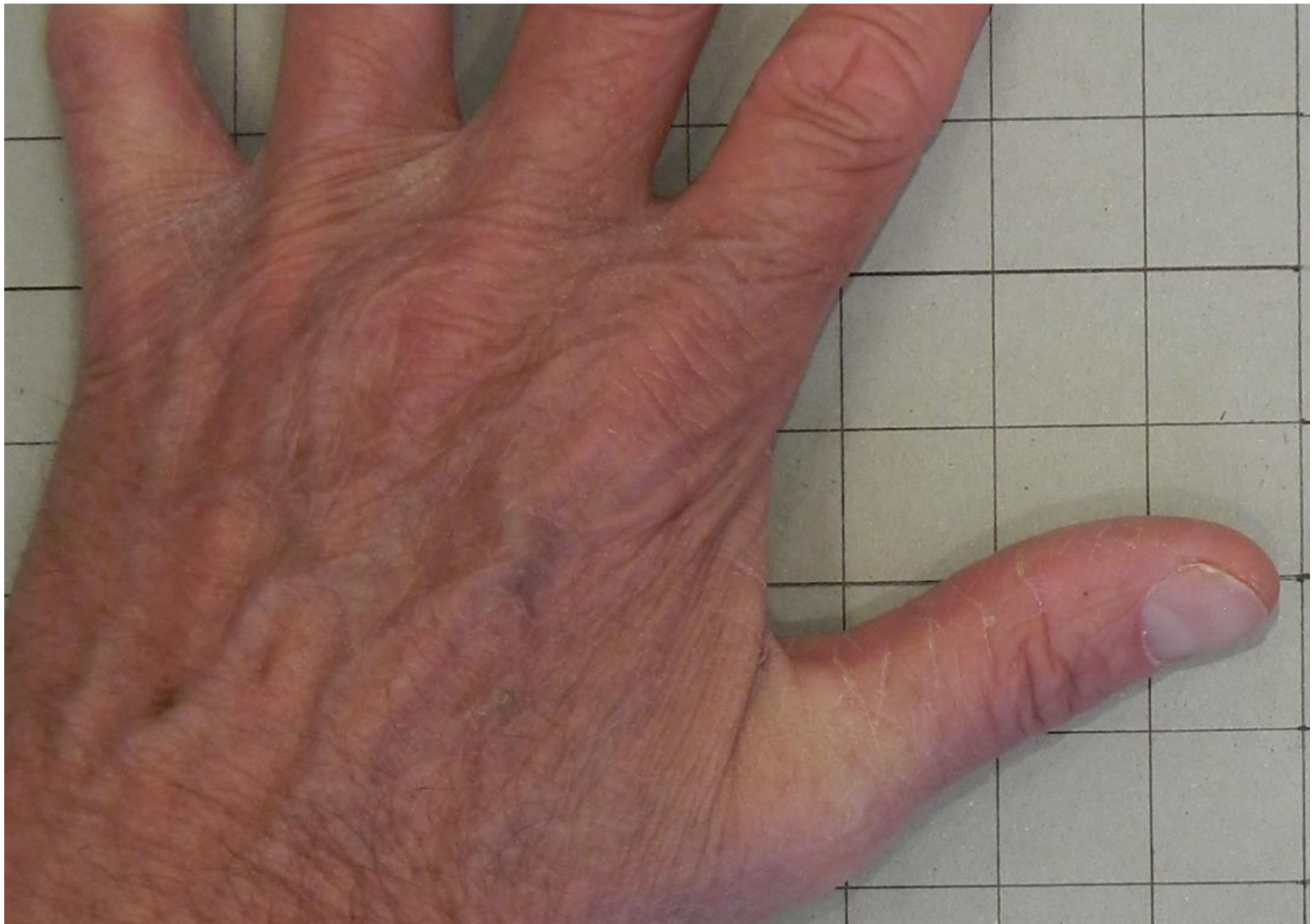


Figure 8b: High resolution example of atrophy, also visible are: redness (erythema) and scaling (squamae)

Fissures



Figure 9a: Example of fissures, also visible are: redness (erythema), scaling (squamae) and crusts



Figure 9b: High resolution example of fissures, also visible are: redness (erythema), scaling (squamae) and crusts

Fissures



Figure 10a: Example of fissures, also visible are: redness (erythema) and scaling (squamae)



Figure 10b: High resolution example of fissures, also visible are: redness (erythema) and scaling (squamae).

Ulcers

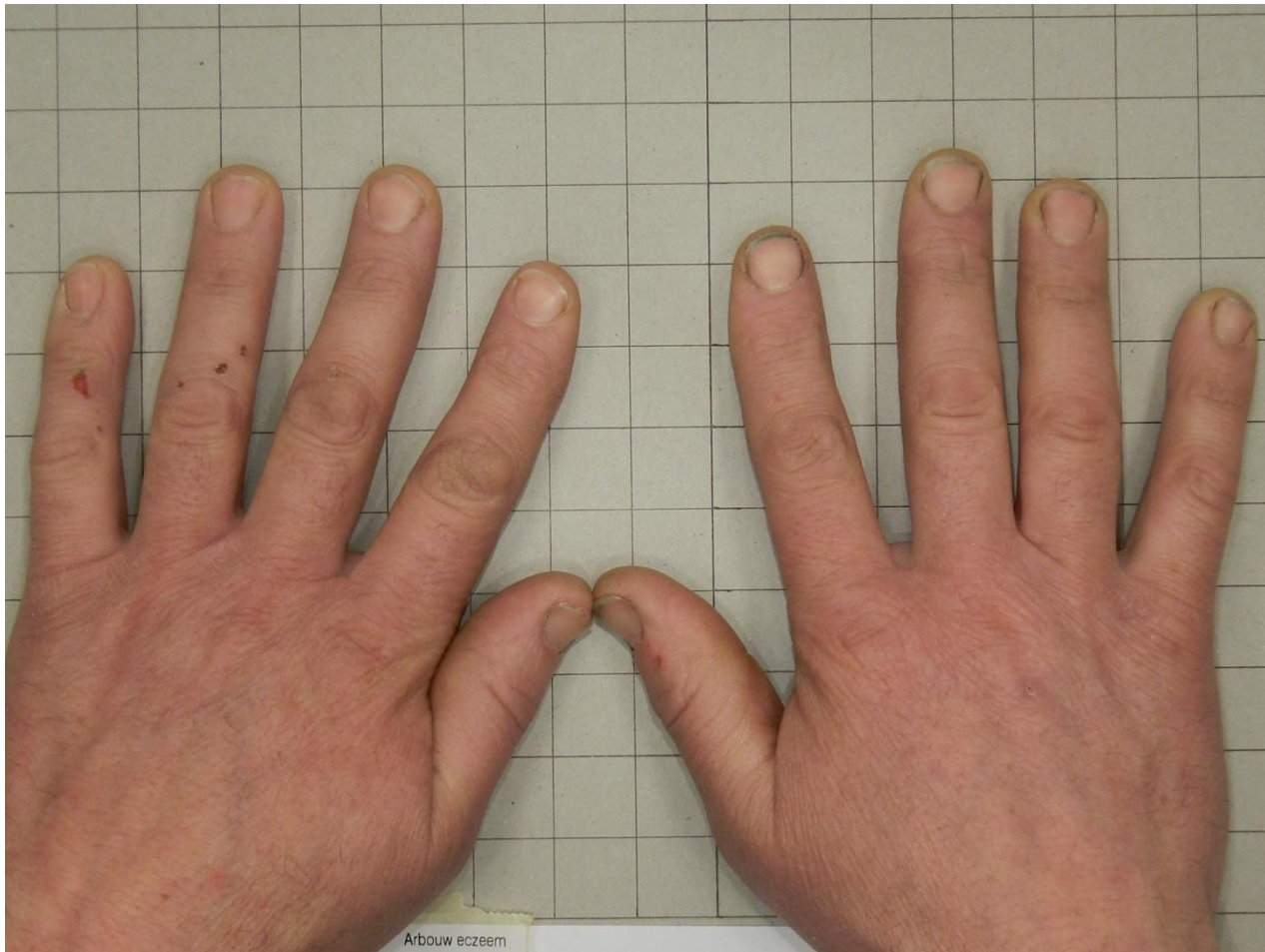


Figure 11a: Example of ulceration, also visible are: redness (erythema), scaling (squamae) and crusts (traumatic). NOTE: this is the only example of ulceration in our study population.



Figure 11b: High resolution example of ulcering, also visible is: redness (erythema), scaling (squamae), and crusts (traumatic).

Vesicles

(not seen in our study population)

Bullae

(not seen in our study population)

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Online supplement 3: relevant questionnaire items

questions used for assessing atopic predisposition are marked with an asterisk ()*

0.1 What is your gender?

(1) ☐ male

(2) ☐ female

0.2 What is your date of birth?

____ - ____ - ____
day month year

0.3 What is your main jobtitle?

.....

*** 1.1** Have you **ever** had an itchy rash?

(1) ☐ yes

(2) ☐ no

If yes, ...

*** 1.1.1** Has this rash begun before you were 2 years of age?

(1) ☐ yes

(2) ☐ no

*** 1.2** Have you ever had eczema in the folds of the elbows, knees, ankles or around the neck?

(1) ☐ yes

(2) ☐ no (**if no, continue with question 1.3**)

If yes, ...

* **1.2.1** Do you currently have eczema in skin folds or elsewhere on your body?

(1) ☐ yes (2) ☐ no

* **1.3** Did you suffer from a dry skin in the **last 12 months**?

(1) ☐ yes (2) ☐ no

1.4/1.5 Did you have one of the following symptoms on your hands or fingers **in the past 12 months**?

(multiple answers possible)

(1) ☐ red and swollen hands or fingers

(2) ☐ scaly hands or fingers

(3) ☐ itchy hands or fingers

(4) ☐ hands or fingers with fissures

(5) ☐ vesicles on the hands or between the fingers

(6) ☐ red bumps on hands or fingers

(7) ☐ none of the above mentioned symptoms (*continue to question 1.13*)

If you selected one ore more of the above mentioned symptoms, ...

1.6 Did one or more of these symptoms last for more than three weeks?

(1) ☐ yes (2) ☐ no

1.7 Did one or more of these symptoms occur more than once the past 12 months?

(1) ☐ ja (2) ☐ nee

1.8 Do the symptoms decrease during free days or sickness leave or increase when working?

(1) ☐ yes (2) ☐ no

1.9 Do you think your current or earlier symptoms are related to your work?

(1) ☐ yes (2) ☐ no (*if no, continue with question 1.10*)

If yes, ...

1.9.1 What do you think is the cause of your symptoms?

(1)

1.10 Do you have colleagues with comparable symptoms?

(1) ☐ yes (2) ☐ no

1.11 Are your symptoms known to your occupational physician?

(1) ☐ yes (2) ☐ no

* **1.12** Are you currently being treated for skin or airway symptoms?

(1) ☐ yes (2) ☐ no (*if no, continue to question 1.13*)

If yes, ...

* **1.12.1** Which medicines do you take for this?

(1)

1.13 Did any of your (grand)parents and/or siblings suffer from eczema?

(1) ☐ yes (2) ☐ no

3.1 Have you had whistling in your chest at any time **in the last 12 months?**

(1) ☐ yes (2) ☐ no

3.2 Have you been woken by an attack of shortness of breath at any time **in the last 12 months?**

(1) ☐ yes (2) ☐ no

3.3 Have you **ever** had asthma?

(1) ☐ yes (2) ☐ no (*if no, continue with question 3.4*)

If yes, ...

3.3.1 Was your asthma confirmed by a doctor?

(1) ☐ yes (2) ☐ no (*if no, continue with question 3.3.2*)

If yes, ...

3.3.1.1 In which year was your asthma confirmed?

_____ (year)

3.3.2 Have you had an attack of asthma **in the last 12 months?**

(1) ☐ yes (2) ☐ no

3.3.3 Are you currently taking any medicines for asthma?

(1) ☐ yes (2) ☐ no

3.4 Do you have any form of nasal allergy, including 'hay fever'?

(1) ☐ yes (2) ☐ no

*** 3.5** Are you hypersensitive ("allergic") to certain substances?

(1) ☐ yes (2) ☐ no (*if no, continue to question 4.1*)

If yes, ...

*** 3.5.1** Which substances are you hypersensitive to?

(*you can fill in more than one substance*)

(1)

(2)

(3)

6.6 What are your main hobbies?

(*You can give more than one answer.*)

(1)

(2)

(3)

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Online supplement 4: prevalences of the different skin changes and their associations with *FLG* status.

	<i>FLG</i>					
	<i>FLG</i> variants		wildtype		OR	
	(n=32)		(n=474)			
	N	%	N	%	OR	95% CI
<i>Doctor-diagnosed</i>						
Atrophy	2	6.3	2	0.4	15.73	2.14-115.61
Scaling skin	29	90.6	281	59.3	6.64	1.99-22.10
Bumps	2	6.3	5	1.1	6.26	1.17-33.60
Redness	29	90.6	309	65.2	5.16	1.55-17.20
Fissures	14	43.8	109	23.0	2.61	1.26-5.41
Crusts	2	6.3	15	3.2	2.04	0.45-9.34
Pigment	1	3.1	19	4.0	0.77	0.10-5.96
Ulcer	-	-	1	0.2	-	-
Vesicles	-	-	-	-	-	-
Bullae	-	-	-	-	-	-
<i>Self-reported</i>						
Fissures	18	56.3	143	30.2	2.98	1.44-6.15
Itchy skin	9	28.1	61	12.9	2.65	1.17-5.99
Scaly skin	5	15.6	51	10.8	1.54	0.57-4.17
Swellings	1	3.1	17	3.6	0.87	0.11-6.73
Vesicles	-	-	20	4.2	-	-
Red skin	-	-	21	4.4	-	-