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## Three peanut-allergic/sensitized phenotypes with gender difference

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1 **Three peanut allergic/sensitized phenotypes with gender difference**

2 **7 words**

3 **Short title: peanut allergic/sensitized phenotypes**

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31 **Contributors**

32 Jocelyne JUST: involvement in the conception, hypotheses delineation, writing the article and  
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34 Chabi Fabrice ELEGBEDE: acquisition, analysis and interpretation of the data, and  
35 substantial involvement in its revision prior to submission

36 Antoine DESCHILDRE: involvement in the conception, hypotheses delineation, acquisition,  
37 analysis and interpretation of the data, and substantial involvement in its revision prior to  
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39 Denise Anne MONERET-VAUTRIN: involvement in the conception, hypotheses delineation,  
40 acquisition, analysis and interpretation of the data, and substantial involvement in its revision  
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51 **Abstract 293 (300)**

52 **Background:** Peanut allergic reactions are heterogeneous ranging from mild symptoms to  
53 anaphylaxis. **Objective:** Identify peanut allergic/sensitized phenotypes to personalize patient  
54 management. **Methods:** A combined factor and cluster analysis was used to study the  
55 phenotypes of 696 patients diagnosed with peanut sensitization and enrolled in the MIRABEL  
56 survey. The method was first applied to the 247 patients with an Oral Food Challenge (OFC).  
57 It was then applied to the 449 patients without OFC to confirm the findings in an independent  
58 population. **Results:** Three independent clusters emerged from the OFC subgroup. Cluster 1,  
59 “*Severe peanut allergy with little allergic multimorbidity*” (123 subjects), had the highest  
60 proportion of patients with positive OFC (92%), a medium level of peanut protein inducing a  
61 positive OFC (235 mg), lower percentage of allergic multimorbidity (2% asthma plus atopic  
62 dermatitis (A+AD), no cases of A+AD + multiple food allergies (MFA)). Cluster 2, “*Severe*  
63 *peanut allergy with frequent allergic multimorbidity*” (62 subjects), had a high proportion of  
64 patients with positive OFC (85%) with the lowest level of peanut protein inducing a positive  
65 OFC (112mg), 89% allergic subjects, 100% with allergic multimorbidity (A+AD) and 84%  
66 with A+AD+MFA. Cluster 3, “*Mild peanut allergic/sensitized phenotype*” (62 subjects), had  
67 the lowest mean age, the lowest proportion of patients with positive OFC (53%) with a high  
68 level of peanut protein inducing a positive OFC (770 mg), a low percentage of allergic  
69 multimorbidity (48% A+AD+MFA). The two severe peanut allergy phenotypes were more  
70 frequent in girls. The same clusters were found in the subgroup of patients without OFC.  
71 **Conclusion & Clinical Relevance:** Besides the classic markers associated with lower  
72 threshold doses of OFC (such as SPT and rAra h2), allergic multimorbidity and female gender  
73 should also be taken into account to better adapt the progressive dosage of provocation tests.

74

75 **Key words:** asthma, atopic dermatitis, cluster analysis, gender, peanut allergy,  
76 multimorbidity.

77 **Abbreviations**

78 Specific immunoglobulin E: sIgE

79 Skin prick test: SPT

80 Atopic dermatitis: AD

81 Asthma: A

82 Allergic rhinitis: AR

83 Multiple Food Allergies: MFA

84 Oral food challenge: OFC

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## 86 **Introduction**

87 Peanut allergy is a common food allergy affecting up to 1.3% of children in Europe<sup>1</sup>. Its  
88 prevalence is on the increase and this is reflected in an increased prevalence of hospitalization  
89 for peanut-induced anaphylaxis in the United States<sup>2</sup>. However, the severity of systemic  
90 allergic reactions to peanut is variable and fatal peanut-induced anaphylaxis is rare<sup>3</sup>.  
91 Moreover, a considerable number of children with positive specific immunoglobulin E (sIgE)  
92 and positive skin prick test (SPT) are asymptomatic or present a milder clinical picture<sup>4,5,6,7</sup>.  
93 Thus, it is crucial to better detect patients with a severe food allergy phenotype for appropriate  
94 follow-up care and management.

95 The diagnosis of peanut allergy in comparison to peanut sensitization is not always easy.  
96 The most relevant features to diagnose peanut allergy would appear to be clinical in real life  
97 or in provocation tests. Moreover, a small proportion of children with peanut allergy can  
98 outgrow their allergy<sup>8</sup>. On the other hand, the severity of the disease can also increase over  
99 time. This is illustrated by contradictory results in studies, some of which have previously  
100 suggested a relationship between a history of anaphylaxis or severe symptoms and the risk of  
101 anaphylaxis upon subsequent exposure and others the opposite<sup>9,10,11</sup>.

102 Nicolaou et al.<sup>12</sup> found a high rate of false-positive SPT and irrelevant sIgE results for peanut.  
103 The threshold level of peanut sIgE or SPT to predict a positive provocation test is unclear<sup>13,14</sup>.  
104 These discrepancies in the current approach to peanut allergy testing could be improved by  
105 component-resolved diagnosis which has been extensively explored in this area. In 2004,  
106 Koppelman et al.<sup>15</sup> first suggested the importance of the peanut component rAra h 2 in  
107 predicting reactivity or tolerance to peanut. More recently, other components of peanut such  
108 as rAra h 6, have been found to be associated with the risk of anaphylaxis<sup>16</sup>. However, to date,  
109 a provocation test remains necessary not only to confirm diagnosis but also to assess the  
110 severity of peanut allergy (related to the threshold reactive dose).

111 These features underline the necessity to perform provocation tests to distinguish between  
112 peanut sensitized and allergic patients, but this test is at risk of anaphylaxis and time  
113 consuming.

114 A novel approach to distinguish patients who present peanut allergic or sensitized phenotypes  
115 with different clinical and biological characteristics, is to identify different disease phenotypes  
116 by cluster analysis. This statistical approach has never been performed to identify  
117 allergic/sensitized phenotypes.

118 The MIRABEL survey is a multicentre survey based on the voluntary participation of peanut-  
119 allergic/sensitized patients from Metropolitan France, Belgium and Luxembourg to evaluate  
120 the allergic risk in patients with well-characterized peanut allergy or sensitization <sup>17</sup>. It is thus  
121 an ideal cohort in which to test the hypothesis that peanut allergic/sensitized phenotypes exist.

122 We set out to define allergic/sensitized phenotypes by unsupervised analysis in a subgroup of  
123 patients of the MIRABEL survey who had undergone oral food challenges (OFC) taking into  
124 account informative parameters such as clinical symptoms, SPT, sIgE to native and  
125 informative epitopes (rAra h 2). To generalize these phenotypes to the entire allergic  
126 population, the same analysis was performed in an independent population of patients without  
127 OFC.



## 128 **Material and Methods**

### 129 *MIRABEL design and inclusion of patients*

130 Between April 2012 and December 2013, allergists were asked to include consecutive  
131 patients with suspected peanut allergy. Patients were then classified as “sensitized” on the  
132 basis of positive SPT performed with commercial extracts (mean wheal diameter  $\geq 3$  mm) and  
133 sIgE to rAra h 2 ( $\geq 0.35$  kUA/L; ImmunoCAP, Thermofisher, Sweden)<sup>18</sup> without any clinical  
134 reaction, or “allergic” based on sensitization (as previously defined) with an allergic reaction  
135 to peanut exposure.

### 136 *Ethics*

137 The study was approved by the French Data Protection Authority (CNIL) (Authorization no.  
138 DE-2011-048). All patients or parents signed an informed consent.

### 139 *Medical questionnaire and oral food challenge*

140 Data were collected by a questionnaire filled in by the allergist after medical diagnosis of  
141 peanut allergy and included the following variables (as previously published<sup>19</sup>). Briefly:

142 The age at diagnosis of peanut allergy.

143 Symptom severity during real-life exposure was classified into two categories: *mild to*  
144 *moderate reactions* (urticaria or angioedema without respiratory symptoms, rash/dermatitis,  
145 isolated and mild to moderate gastro intestinal symptoms); or *severe reactions* (anaphylactic  
146 shock, laryngeal angioedema, acute asthma, systemic serious reaction (involving two or more  
147 organs)<sup>20</sup>.

148

149 Active allergic comorbidities over [the past year](#), including asthma (A), atopic dermatitis (AD),  
150 allergic rhinitis (AR) and multiple food allergies (MFA) [were diagnosed by an experienced](#)  
151 [allergist from the patient's medical records](#).

152 SPT were performed using different peanut and food extracts (mainly from Stallergènes,  
153 Antony, France). As the MIRABEL survey is observational, the patients were administered  
154 the OFC according to the physician's practice either by a single-blind or double-blind  
155 placebo-controlled challenge or as an open OFC. For positive OFCs, the reactive cumulated  
156 dose, based on objective symptoms only, was expressed in mg of peanut protein equivalent.  
157 The OFC was considered negative in the absence of an objective sign for a cumulative dose  $\geq$   
158 7 g of peanut.

159 Dietary advice provided by the allergist was recorded as: "strict eviction " if the patient was  
160 advised to avoid all products containing peanuts and products with PAL; compared with a  
161 combined category of "lax" if the patient was merely advised to avoid products containing  
162 peanuts but that PAL products were allowed; and "absent" if the patient was advised that no  
163 avoidance was necessary.

#### 164 ***Variable selection for cluster analysis***

165 The variables for statistical analysis were those that reflected physiologic parameters (age at  
166 diagnosis and age at time of OFC, gender) and those related to the clinical presentation of  
167 peanut allergy such as the allergic/sensitized status, route of exposure that induced reaction  
168 (ingestion and/or inhalation and/or contact), the test results (SPT, rAra h 2, OFC) and allergic  
169 comorbidities. In case of two highly correlated variables, only the one considered as the most  
170 relevant was retained in the analysis. The variables selected for analysis are marked in Table 1

171 by a ‡. Composite variables were used to distinguish patients with one, two or three  
172 multimorbidity symptoms: one variable for patients with both A and AD (A+AD), and one for  
173 patients with both A+AD and MFA (A+AD+MFA).

#### 174 *Variable reduction and cluster analysis*

175 Phenotype clusters were identified by coupling a factor analysis with a cluster analysis as  
176 previously reported by Just et al .<sup>19</sup>. A factor analysis for mixed data (categorical and  
177 continuous) was first applied to the selected variables to study their associations and identify  
178 which variables contributed the most to explaining the variability of the dataset<sup>21</sup>. Factor  
179 analysis also makes it possible to reduce the dimension of the dataset to a few principal  
180 components. A hierarchical cluster analysis was then applied to these principal components to  
181 classify the population into homogeneous groups of peanut allergy severity. The method is  
182 based on Ward's minimum variance criterion which minimizes the total within-cluster  
183 variance. The distance between individuals was calculated using the Euclidian distance. Thus,  
184 variables between the different groups were compared using the one-way ANOVA test for  
185 continuous variables and the Chi-squared test for categorical variables. The Kruskal-Wallis  
186 and the Fisher's exact tests were respectively used when the required conditions were not  
187 respected to perform the ANOVA and the Chi-squared tests. Statistical analyses were  
188 performed with the FactoMineR package of R version 3.1.1.

## 189 **Results**

### 190 *Description of the population*

191 785 patients were recruited by 70 allergists. Complete information was available for 696  
192 patients, and 247 of these had complete OFC results. The variables have been fully described  
193 in a previous article about the MIRABEL survey<sup>17</sup>.

### 194 *Variable associations*

195 Factor analysis applied to the OFC subgroup using all selected variables resulted in three  
196 principal components explaining 46% of the total variance. The first component was  
197 composed of allergic multimorbidity variables. The second component was composed of the  
198 age at which the OFC was conducted and the time between diagnosis and the OFC. The third  
199 component included SPT, sIgE to rAra h 2 and OFC results. A similar structure was obtained  
200 when applying factor analysis to the population without OFC, except that the  
201 allergic/sensitized status was also part of the second component and associated with age at  
202 diagnosis.

### 203 *Peanut allergic/sensitized phenotypes of the 247 patients with OFC*

204 Three independent clusters emerged from the application of a hierarchical classification on  
205 the three principal components selected from the previous factor analysis.

206 Cluster 1, “*Severe peanut allergy with little allergic multimorbidity*” (123 subjects), had the  
207 highest proportion of patients with positive OFC (92%), the highest proportion of severe  
208 reactions upon exposure via ingestion (84%), a medium level of peanut protein equivalent  
209 inducing a positive OFC (235 mg) associated with a high mean level of rAra h 2 (34kUA/l),  
210 and finally a lower percentage of allergic multimorbidity (2% asthma plus atopic dermatitis  
211 (A+AD), no cases of A+AD + MFA) (Table 1).

212 Cluster 2, “*Severe peanut allergy with frequent allergic multimorbidity*” (62 subjects), had a

213 high proportion of patients with positive OFC (85%) with the lowest level of peanut protein  
214 inducing a positive OFC (112mg) associated with the highest mean level of SPT wheal size  
215 (13mm), the highest mean level of rAra h 2 (43 kUA/l) and the highest proportion of severe  
216 reactions upon exposure via inhalation. This cluster was characterized by the highest  
217 percentage of allergic multimorbidity compared to the two other clusters, 100% (A+AD) and  
218 84% A+AD+MFA (Table 1).

219 Cluster 3, “*Mild peanut allergic/sensitized phenotype*” (62 subjects), had the lowest mean  
220 disease duration (3.5 years), the lowest proportion of patients with positive OFC (53%) with  
221 the highest level of peanut protein inducing a positive OFC (770 mg), a low percentage of  
222 allergic multimorbidity (48% A+AD+MFA) and AD only found in a high percentage of cases  
223 (95%) (Table 1).

#### 224 ***Peanut allergic/sensitized phenotypes in subgroup of patients without OFC***

225 Clusters of the subgroup without OFC (n=449) are similar to those of the OFC subgroup  
226 (n=247), for most parameters and especially for allergic comorbidities (Table 2). The results  
227 were consistent even though the statistical significance of some variables decreased slightly.

#### 228 ***Analysis based on gender***

229 Separate cluster analyses were carried out for boys and girls with OFC. These analyses  
230 identified the same three clusters as the previous analysis for the boys (Table 3) but only two  
231 clusters for the girls (Table 4) i.e. the severe peanut allergic phenotypes called the “*Severe*  
232 *peanut allergy with frequent allergic multimorbidity*” and the “*Severe peanut allergy with*  
233 *little allergic multimorbidity*”.

234

## 235 **Discussion**

236 Cluster analysis of the MIRABEL data showed that peanut allergy is a heterogeneous disease.  
237 The clustering approach divided the population into two subgroups of severe peanut  
238 phenotypes “*Severe peanut allergy with little allergic multimorbidity*” and “*Severe peanut*  
239 *allergy with frequent allergic multimorbidity*” and one non-severe subgroup “*Mild peanut*  
240 *allergic/sensitized phenotype*”. The severe peanut allergy phenotypes were more frequently  
241 encountered in girls.

## 242 ***Strengths and weaknesses***

243 One strength of this study is that it is a multicenter study performed in large population of 696  
244 peanut allergic/sensitized patients recruited by allergists. Moreover, for a large part of this  
245 population (almost 250), peanut allergy was diagnosed by OFC, although the reasons for  
246 undergoing an OFC or not are not known in this real-life survey. Another strength is that the  
247 statistical analyses to identify different phenotypes were conducted by an unsupervised  
248 approach with a large range of variables and in a large cohort of patients with severe allergy.  
249 The factor analysis was conducted in several steps. A first analysis was performed including  
250 all available variables; a second analysis was then conducted excluding variables that were  
251 too highly correlated, variables that did not play a large role in explaining the variance, and in  
252 combining some variables frequently encountered in patients with multiple food  
253 allergies/sensitization. The phenotypes described here remain stable in all the analyses.  
254 Moreover, this concordance of three phenotypes (established in patients with and without  
255 OFC) highlights the one message of our article, i.e. the importance of multiple comorbidities  
256 (especially A+AD or A+AD+MFA) to define a particular phenotype of severe peanut-allergy.  
257 One limitation of the study is the different ways in which the OFC was carried out. However,  
258 this actually reflects physicians’ daily practices and the OFCs selected for analysis were  
259 supported by objective symptoms (for positive OFC) and a high dosage of peanut ingested

260 during OFC (> 7 g of peanut) for the negative test. Similarly, SPTs were not standardized.  
261 Another limitation of our study is the heterogeneity of the population, in which patients were  
262 probably at different disease stage (for instance, initial diagnosis vs. resolution of peanut  
263 allergy). This explains cluster 3 which has the lowest mean disease duration (3.5 years) with  
264 the highest proportion of sensitized children. This result is in accordance with the natural  
265 history of the disease in which sensitization (more than allergy) is associated with a smaller  
266 diameter of the SPT and lower levels of rAra h 2<sup>8</sup>. The clustering algorithms are different  
267 when working on the group with OFC and the group without. We consequently analyzed the  
268 group with OFC as follows: first using the variables related to the OFC (as presented), and  
269 then without the variables related to OFC. Three similar phenotypes were obtained with both  
270 methods (data not shown). Therefore, we can conclude that we do not need to have  
271 information about OFC to correctly classify a patient into the right cluster. Finally, by our  
272 analysis, it was not possible to distinguish at individual level, sensitized or allergic patient,  
273 but parameters associated to severe allergic phenotypes (in our cluster analysis) will be taking  
274 into account to adapt the schedule of provocation tests.

275

### 276 ***“Severe peanut allergy with frequent allergic multimorbidity”***

277 This result underlines that allergic multimorbidity (asthma with AD and/or MFA) is  
278 associated with a higher reported severity of peanut-induced allergic reactions. Colver et al.  
279 showed that asthma was a strongly significant risk factor for severe allergic reactions to food,  
280 specifically with peanut<sup>22</sup>. Bock et al. reported similar findings among 32 fatal cases; all of  
281 those for whom medical records were available had a history of asthma<sup>23</sup>. Summers et al.<sup>24</sup>, in  
282 a study of 1,094 patients with tree nut and peanut allergies demonstrated that, as well as  
283 severe asthma being associated with life-threatening bronchospasm, severe pharyngeal edema  
284 was more common in patients with severe AR. They also found that having severe AD was

285 associated with a 3-fold increased risk of becoming unconscious during an acute allergic  
286 reaction, thus further highlighting the link between the severity of acute allergic reactions and  
287 the severity of co-existing atopic disease. We recently described<sup>25</sup>, a “*Multiple Allergies and*  
288 *Severe Asthma phenotype*” in which 100% of the children had AD and multiple sensitizations.  
289 This is very close to the “*Severe peanut allergy with frequent allergic multimorbidity*”  
290 phenotype we present here. This phenotype could correspond to the previously described  
291 phenotype of AD associated with filaggrin loss-of-function mutations associated to a greater  
292 risk of severe asthma<sup>26</sup>.

293 ***“Severe peanut allergy with little allergic multimorbidity” or the high proportion of patients***  
294 ***with severe reaction during OFC had a high level of rAra h 2***

295 This severe phenotype underlines the axis of recombinant rAra h 2 in predicting clinical  
296 severity of peanut allergy. rAra h 2 is a heat-stable seed-storage protein and is considered to  
297 be the major peanut allergen contributing to peanut sensitization. Peeters et al. looked at  
298 whether sensitization to rAra h 1, 2, 3, or 6 can predict the severity of allergic reactions to  
299 peanut in a group of 30 patients. They found that patients with severe reactions had a greater  
300 SPT response to rAra h 2 and rAra h 6 at low concentrations and to rAra h 1 and rAra h 3 at  
301 higher concentrations. They also found that patients with more severe symptoms recognized a  
302 greater number of allergens. Sensitization to rAra h 2 plus sensitization to rAra h 1 and/or  
303 rAra h 3 was associated with greater severity of reactions<sup>27</sup>. Peptide microarray  
304 immunoassays in a group of 77 patients similarly showed that those with wide epitope  
305 diversity were associated with a history of more severe allergic reactions<sup>28</sup>.

306 ***“Mild peanut allergic/sensitized phenotype” or mild severity of peanut allergy was***  
307 ***explained by a high proportion of sensitized patients compared to the other clusters***



308 The subjects in this phenotype were younger at diagnosis, more likely to be sensitized  
309 (41.9%), had the lowest positive allergic reaction during OFC, the smallest SPT wheal size,  
310 the lowest mean levels of rAra h 2 and a higher percentage of AD (95% of cases). This  
311 phenotype could correspond to the current hypothesis that allergic sensitization to food occurs  
312 through low-dose cutaneous sensitization<sup>29</sup>. Many studies suggest<sup>30,31,32</sup> that late introduction  
313 of potential food allergens and cutaneous exposure<sup>33</sup> might be associated with allergy while  
314 early oral exposure might contribute to tolerance. It is thus possible that the young children in  
315 our mild peanut phenotype could be in the process of developing real peanut allergy in the  
316 case of delayed oral exposure.

### 317 *More females have the severe phenotypes of peanut allergy: a possible gender effect*

318 The food allergy register has already shown an age-dependent gender distribution, with a M/F  
319 sex ratio of 0.67 from early adulthood, in contrast to children where the ratio is 1.50<sup>34</sup>. Similar  
320 differences in gender have emerged from several questionnaire-based studies in other  
321 countries<sup>35,36</sup>. This observed age-related gender difference is similar to that reported for  
322 asthma, hay fever and atopic disease, suggesting that puberty and the influence of sex  
323 hormones may have an important impact on the prevalence of atopic diseases in general<sup>37</sup>. In  
324 the same vein, a survey reporting on severe allergic reactions defined by the necessity of  
325 medical care, showed a higher incidence of food allergy in females. Finally, an Australian  
326 study has also reported that females outnumbered males in both acute allergic reactions and  
327 anaphylaxis<sup>38</sup>.

### 328 *Conclusions*

329 Our results underline that, beside the classic markers associated with lower **threshold doses of**  
330 **OFC** (such as SPT or rAra h2), allergic multimorbidity and female gender should also be  
331 taken into account to better adapt the progressive dosage of provocation tests.



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362 **Conflicts of interest**

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368 work.

369 The rest of the authors declared that they have no relevant conflicts of interest.



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