**Supplementary material**

Christina Orsmark Pietras, PhD,[1] Anna James, PhD,[2] Jon R Konradsen, MD, PhD,[3,4] Björn Nordlund, RN,[3,4] Cilla Söderhäll, PhD,[1] Ville Pulkkinen, PhD,[2,5] Christophe Pedroletti, MD, PhD,[4] Kameran Daham, MD,[6,7] Maciek Kupczyk, MD, PhD,[2] Barbro Dahlén MD, PhD,[6,7] Juha Kere, MD, PhD,[1,8] Sven-Erik Dahlén, MD, PhD,[2] Gunilla Hedlin, MD, PhD,[3,4*] and Erik Melén, MD, PhD,[2,3*]

[1] Department of Biosciences and Nutrition at Novum, Karolinska Institutet (KI)
[2] Institute of Environmental Medicine, KI
[3] Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm
[4] Department of Women's and Children's Health, KI
[5] Department of Medical Genetics, Biomedicum Helsinki, University of Helsinki, and Folkhälsan Institute of Genetics, Helsinki, Finland,
[6] Lung/allergy clinic at Karolinska University Hospital Huddinge,
[7] Department of internal medicine at Huddinge University Hospital, KI
[8] Science for Life Laboratory, KI
All belonging to The Centre for Allergy Research at Karolinska Institutet, Stockholm, Sweden and being members of GA$^2$LEN, The Global Allergy and Asthma European Network.

[*]Shared last authorship.

Correspondence and reprint requests: Sven-Erik Dahlén, MD, PhD, The National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

E-mail: sven-erik.dahlen@ki.se

***Table E1.*** Criteria for inclusion of children suffering from problematic severe (PA) and controlled persistent (CA) asthma. The severe, therapy resistant asthmatics (SA) were selected from the PA group.

| **Problematic severe asthma (PA)** | **Controlled persistent asthma (CA)** |
|---|---|
| **Major criteria** (all required) | **Major criteria** (all required) |
| ▪ A diagnosis of asthma by a pediatric allergist | ▪ A diagnosis of asthma by a pediatric allergist |
| ▪ Daily high-dose administration of ICS (≥800 μg budesonide or ≥400 μg fluticasone/momethasone per day) in combination with LABA and/or LTRA* | ▪ Daily low- to medium-dose administration of ICS ( ≥100 - ≤400 μg budesonide or ≥50 - ≤200 μg fluticasone per day). Use of either LABA *or* LTRA was acceptable. |
| **Minor criteria** observed within the preceding 12-month period (minimum of at least one required) | **Minor criteria** observed within the preceding 12 month period (all required) |
| ▪ at least one emergency hospitalisation | ▪ no hospitalisation |
| ▪ at least two emergency out-patient visits | ▪ no emergency out-patient visits |
| ▪ at least one oral treatment with corticosteroid | ▪ no oral corticosteroid treatment |
| ▪ at least twelve exacerbations of asthmatic symptoms per year or symptoms present continuously for at least 3 months | ▪ less than five exacerbations of symptoms** |
| ▪ symptoms that limited daily activities (including sport or leisure activities) more than twice a week for at least three 3 consecutive months | ▪ occasional symptoms related to strenuous exercise only, otherwise no symptoms |
| ▪ nocturnal symptoms more than twice a week for at least three consecutive months | ▪ no nocturnal symptoms |

Abbreviations in order of appearence: ICS, Inhaled corticosteroid; LABA, long-acting β-2 agonist; LTRA, leukotriene receptor antagonist. *High-dose administration of ICS for at least 6 months during the preceding year; previous use of LABA or LTRA only was considered acceptable if this treatment was discontinued due to inefficacy or the occurrence of unacceptable side-effects. **An increase in the ICS dosage for a maximum of 2 weeks in connection with asthma exacerbations was considered acceptable. Children with vocal cord dysfunction, cystic fibrosis, immunodeficiencies, serious neurological disease or who had undergone major lung surgery or been born prematurely (at <36 wk of gestational age) were excluded.

***Table E2.*** Clinical data for the 12 adult asthmatic adults from whom blood was collected for the TAS2R expression and function analyses.

| | Adult asthmatics (n=12) |
|---|---|
| Age | 34 (10) |
| Sex (F/M) | 3/9 |
| ICS | 0 |
| $FEV_1$, % of predicted | 102 (8) |
| Methacholine $PD_{20}$* | 351 (74-561) |
| Total WBC ($10^9$ x $L^{-1}$) | 6.6 (1.4) |
| Eosinophils ($10^9$ x $L^{-1}$) | 0.2 (0.1) |
| Neutrophils ($10^9$ x $L^{-1}$) | 3.7 (0.9) |
| $FE_{NO}$, ppb* | 19.7 (15-39) |
| Total IgE, kUA/l | 155 (107) |

Abbreviations in order of appearance: F, female; M, male; ICS, inhaled corticosteroids; $FEV_1$, forced expiratory volume during 1 second; Methacholine $PD_{20,}$ accumulated dose of methacholine causing a 20% fall in $FEV_1$ (µg); WBC, white blood cells; $FE_{NO}$, fraction of nitric oxide in exhaled air (ppb, parts per billion); IgE, immunoglobin E (kUA/L, kilounits of antibody per liter). The values are presented as means (standard deviation), unless otherwise indicated. *Median (interquartile range).

***Table E3.*** 1378 significantly differentially expressed genes in asthmatic patients (see separate file, Supplementary material Table E3)

***Table E4.*** Enriched biological processes in controlled and severe asthma.

| GO TERM | Biological process | Contrast or cluster | Adj.P* |
|---|---|---|---|
| GO:0050909 | Sensory perception of taste | SA vs. ctrl | $3.4x10^{-5}$ |
| GO:0018212 | Peptidyl-tysosine modification | CA vs. ctrl | 0.007 |
| GO:0018108 | Peptdyl-tysosine phosphorylation | CA vs. ctrl | 0.040 |
| GO:0007166 | Cell surface receptor linked signal transduction | CA vs. ctrl | 0.040 |
| GO:0046649 | Lymphocyte activation | CA vs. ctrl | 0.044 |
| GO:0006497 | Protein amino acid lipidation | SA vs. CA | 0.007 |
| GO:0042158 | Lipoprotein biosynthetic process | SA vs. CA | 0.008 |
| GO:0006505 | GPI anchor metabolic process | SA vs. CA | 0.003 |
| GO:0006506 | GPI anchor biosynthetic process | SA vs. CA | 0.04 |
| GO:0042157 | Lipoprotein metabolic process | SA vs. CA | 0.049 |
| | | Dendogram row cluster† | |
| GO:0009057 | Macromolecule catabolic process | A | 0.02 |
| GO:0030163 | Protein catabolic process | A | 0.01 |
| GO:0015031 | Protein transport | A | 0.01 |
| GO:0051603 | Proteolysis involved in cellular protein catabolic process | A | 0.009 |
| GO:0044257 | Cellular protein catabolic process | A | 0.008 |
| GO:0045184 | Establishment of protein localization | A | 0.007 |
| GO:0006497 | Protein amino acid lipidation | A | 0.01 |
| GO:0044265 | Cellular macromolecule catabolic process | A | 0.02 |
| GO:0042158 | Lipoprotein biosynthetic process | A | 0.02 |
| GO:0008104 | Protein localization | A | 0.02 |
| GO:0009060 | Aerobic respiration | A | 0.03 |
| GO:0019941 | Modification-dependent protein catabolic process | A | 0.04 |
| GO:0043632 | Modification-dependent macromolecule catabolic process | A | 0.04 |
| GO:0006886 | Intracellular protein transport | A | 0.04 |
| | *NA* | B | *NA* |
| GO:0043067 | Regulation of programmed cell death | C | 0.046 |
| GO:0010941 | Regulation of cell death | C | 0.03 |
| GO:0050909 | Sensory perception of taste | D | $5.1x10^{-9}$ |

Abbreviations: GO, gene ontology; SA, severe asthma; CA, controlled asthma; Ctrl, healthy controls. *Benjamini and Hochberg's,correction for multiple testing, † See Figure 2 for dendogram row cluster classification. *NA* implies no significantly enriched biological processes after multiple testing.

***Figure E1.*** Expression of *TAS2Rs* in healthy and asthmatic children. qPCR analyses examining the expression of 11 *TAS2Rs* relative to that of the housekeeping gene *GAPDH* were performed using RNA from 18 healthy children and 19 children with severe therapy resistant asthma. Results are presented as mean+SEM. Normally distributed data were compared by Students' unpaired t-test and skewed data using the Mann Whitney test.