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**Tmem79/Matt** is the matted mouse gene and is a predisposing gene for atopic dermatitis in human subjects

Sean P. Saunders, PhD,a,b,c,d,e Christabelle S. M. Goh, BSc,d,e,f Sara J. Brown, MD,g bet al.

**Background:** Atopic dermatitis (AD) is a major inflammatory condition of the skin caused by inherited skin barrier deficiency, with mutations in the filaggrin gene predisposing to development of AD. Support for barrier deficiency initiating AD came from flaky tail mice, which have a frameshift mutation in Flg and also carry an unknown gene, matted, causing a matted hair phenotype.

**Objective:** We sought to identify the matted mutant gene in mice and further define whether mutations in the human gene were associated with AD.

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Methods: A mouse genetics approach was used to separate the matted and Flg mutations to produce congenic single-mutant strains for genetic and immunologic analysis. Next-generation sequencing was used to identify the matted gene. Five independently recruited AD case collections were analyzed to define associations between single nucleotide polymorphisms (SNPs) in the human gene and AD.

Results: The matted phenotype in flaky tail mice is due to a mutation in the Tmem79/Matt gene, with no expression of the encoded protein mattrin in the skin of mutant mice. Matt8 mice spontaneously have dermatitis and atopy caused by a defective skin barrier, with mutant mice having systemic sensitization after cutaneous challenge with house dust mite allergens. Meta-analysis of 4,245 AD cases and 10,558 population-matched control subjects showed that a missense SNP, rs6694514, in the human MATT gene has a small but significant association with AD.

Conclusion: In mice mutations in Matt cause a defective skin barrier and spontaneous dermatitis and atopy. A common SNP in MATT has an association with AD in human subjects.

Key words: Allergy, association, atopic dermatitis, atopy, eczema, filaggrin, flaky tail, Matt, mattrin, mouse, mutation, Tmem79

Atopic dermatitis (AD) is the most common diagnosis in dermatology, affecting approximately 1 in 5 children in the developed world,1 and is frequently associated with atopic asthma and a wide range of allergies.2 AD is a highly heritable complex trait; however, environmental influences also play a role in triggering the atopic diathesis.3 Genome-wide association studies in AD have identified several susceptibility loci4-7; however, the major and only functionally characterized genetic factor is the filaggrin gene (FLG), which encodes the skin barrier protein filaggrin.8 Prevalent loss-of-function variants in FLG were identified as the cause of the single-gene disorder ichthyosis vulgaris (dry flaky skin).9 Soon thereafter, these variants were shown to be strongly associated with AD,1 with heterozygous odds ratios (ORs) of greater than 7 and homozygous ORs of greater than 150 in case-control studies in which both prevalent and rare variants were analyzed.10

The hypothesis that skin barrier deficiency in the context of FLG mutations is an initiator of AD was confirmed experimentally by using the flaky tail mouse mutant,11 which was shown to carry a frameshift mutation in the murine Flg gene.12 Flaky tail mice have a defective skin barrier, with increased percutaneous transfer of antigens and chemical haptens.12-15 The ft mutation arose spontaneously in 1958 in the progeny of crosses between heterogeneous stocks of mice with the recessive mutation matted (ma), and these mutations are maintained as a double-mutant (DM) strain known as matted.16 The matted hair phenotype was used for many years as a surrogate marker for the ft mutation because, remarkably, the ft and ma mutations are closely linked on chromosome 3 in the mouse.17 The DM maize mice have been routinely used for studies of skin barrier–deficient AD in recent years.14-15,17 In mice and human subjects the FLG gene resides in the epidermal differentiation complex, a cluster of more than 70 genes encoding proteins involved in skin barrier formation and differentiation of stratified epithelia,18 including those within the hair follicle.18-21 We suspected the nearby ma gene might also be involved in epithelial barrier function, and in this study we set out to separate this allele from Flg8 and identify the causative defect.

Abbreviations used
AD: Atopic dermatitis
DM: Double mutant
FLG: Filaggrin
HDM: House dust mite
hpf: High-power field
MAPEG: Membrane-associated proteins in eicosanoid and glutathione metabolism
OR: Odds ratio
SNP: Single nucleotide polymorphism
TEWL: Transepidermal water loss
WT: Wild-type

METHODS

Isolation of the matted mouse strain

DM Mattma/mattflgft/ft mice were provided by Dr John P. Sundberg (Jackson Laboratory, Bar Harbor, Me.).12 DM mice were crossed with C57BL/6j mice to generate Mattma/mattflgft/ft mice. The Flg and Mattma mutations were separated and backcrossed to congenic C57BL/6j background in accordance with the breeding strategy outlined (see Fig E1 in this article’s Online Repository at www.jacionline.org). C57BL/6j mice were used as wild-type (WT) control animals. B6.CBAKt/m-ma/J (JAX Mattma/ma) mice were obtained from the Jackson Laboratory. Mice were housed in specific pathogen-free conditions, with irradiated diet and bedding and water ad libitum. All animal experiments were performed in compliance with Irish Department of Health and Children regulations and approved by Trinity College Dublin’s BioResources Ethical Review Board.

Gene mapping

Skin samples were obtained from neonatal mice, and DNA was extracted by using the DNA Purification Kit (Promega, Madison, Wis). Genomic DNA extracted from murine neonatal blood was amplified with the GoTaq Flexi DNA Polymerase kit (Promega). All samples were sequenced by using the ABI 3730 DNA Systems (Applied Biosystems, Foster City, Calif). Mapping primers were used to amplify and sequence murine chromosome 3 (see Table E1, A, in this article’s Online Repository at www.jacionline.org). Matted genomic sequences were compared with C57BL/6j for regions of congenicity.

Next-generation sequencing and bioinformatics

Three replicates from each sample (WT and Mattma/matt) were submitted for next-generation sequencing. The replicates were run multiplexed on an Illumina GAIIx and HiSeq 2000 (Illumina, San Diego, Calif) by using v3 sequencing chemistry and the Roche 454 Titanium workflow (Roche, Mannheim, Germany). For further details on sequencing, bioinformatics, and single nucleotide polymorphism (SNP) and InDel methodologies, see the Methods section in this article’s Online Repository at www.jacionline.org.

Analysis and identification of murine Tmem79/Matt gene

Each of the 4 exons was amplified individually by using PCR with the following conditions for all exons: 1 cycle of 94°C for 5 minutes; 35 cycles of 94°C for 30 seconds, 54°C for 30 seconds, and 72°C for 1 minute; and a final extension at 72°C for 5 minutes.

Semi quantitative RT-PCR

Mouse tissue samples were lysed with TissueLyser LT (Qiagen, Hilden, Germany), and RNA was extracted with the RNeasy kit (Qiagen). RNA was reverse transcribed with the ImProm-II Reverse Transcription System (Promega). An intron-spanning amplification was carried out on Tmem79/Matt across exons 3 and 4. Krt14 was used as a loading control. RT-PCR primers used are shown in Table E1, B, in this article’s Online Repository.
Mouse genotyping
The 644-bp PCR product of the third *Tmem79/Matt* exon was digested with the restriction enzyme CviQI (New England Biolabs, Ipswich, Mass), and di-gested fragments were separated on agarose gel by using electrophoresis. Primers used are shown in Table E1, A. The *Fib* mutation was genotyped, as previously described.12

Immunoblotting
The *Fib* project was separated from the dermis of neonatal mice after immersion in 5 mol/L EDTA at 50°C for 5 minutes, followed by cooling in ice-cold PBS. The separated epidermis was extracted in urea/Tris buffer containing protease inhibitor cocktail (Halt; Thermo Scientific, Erembodegem, Belgium) by means of homogenization. Protein samples were separated on SDS-polyacrylamide gels and transferred to polyvinylidene difluoride membranes (Millipore, Temecula, Calif), which were probed with rabbit polyclonal antibodies specific for human matrix (TMEM79; Novus Biologicals, Littleton, Colo). Primary antibodies were detected by means of incubation with a horseradish peroxidase–conjugated goat anti-rabbit secondary antibody (Dako, Stockport, United Kingdom). Immunolabeled proteins were visualized by using chemiluminescence with the ECL detection system (Millipore).

Immunofluorescence and Nile Red staining
Dorsal murine sections were obtained from 4-day-old neonatal mice and snap-frozen immediately. All frozen samples were then cryosectioned at 4 to 5 μm and stored at 80°C until use. After drying, sections were fixed in 50% methanol acetone, washed in PBS, and incubated with primary antibodies. Nuclei were stained with 4′,6-diamidino-2-phenylindole (Sigma-Aldrich, St Louis, Mo), and slides were fixed in Hydromount (National Diagnostics, Atlanta, Ga). Primary antibodies used in whole mounts were as follows: polyclonal TMEM79 (TMEM79; Novus Biologicals) and monoclonal CK-13 (Millipore, San Jose, Calif). Primary antibodies were detected by means of direct ELISA. Total serum IgE levels were measured with a sandwich ELISA, according to the manufacturer’s instructions (BD Pharmingen, San Jose, Calif).

ELISA
Serum levels of HDM-specific IgE, IgG1, and IgG2a were detected by means of direct ELISA. Total serum IgE levels were measured with a sandwich ELISA, according to the manufacturer’s instructions (BD Pharmingen, San Jose, Calif).

Histology
Dorsal skin sections were removed and fixed in 10% formal saline. Paraffin-embedded sections were stained with hematoxylin and eosin and examined in blinded fashion by 2 observers independently. To quantify dermal cell numbers, we used a previously described scoring system.12 The total number of cells per high-power field (hpf) of view were counted on 20 hfps per mouse. For skin sections, an arbitrary histologic scoring system was used to quantify acanthosis and hyperkeratosis. Acanthosis scoring was based on the magnitude of epidermal hyperplasia, and hyperkeratosis scoring was based on the magnitude of stratum corneum thickening, with scores (0, basal; 1, mild; 2, moderate; 3, marked; 4, very marked; and 5, extreme pathology) for each parameter based on measurements per hpf in sections.

Measurement of transepidermal water loss
A Courage and Khazaka Tewameter TM210 (Enviroderm, Evesham, United Kingdom) was used for measurement of transepidermal water loss (TEWL), which was measured on the dorsal flank of mice 24 hours after hair clipping. TEWL was recorded at an ambient temperature of 19°C to 21°C and humidity of 50% ± 5%. In mice sensitized to HDM, TEWL was measured in PBS- and HDM-treated mice before and after the HDM challenge regimen.

Electron microscopy
For scanning electron microscopy, hair fibers were removed from mice and fixed in cacodylate-buffered glutaraldehyde. Samples were prepared for scanning electron microscopy by using established procedures11 and examined in a Zeiss Supra scanning electron microscope.

Statistical analysis of mouse studies
GraphPad Prism software (GraphPad Software, La Jolla, Calif) was used for data analysis. Differences between groups were determined by using the Student *t* test and 2-way ANOVA. Results are presented as means ± SEMs. Differences, indicated as 2-tailed *P* values, were considered significant at a *P* value of less than .05.

SNP identification in human subjects
Human samples from England, Scotland, and Ireland were obtained with consent from patients and Institutional Ethics Committee approval complying with the principles of the Declaration of Helsinki. Human *MATT* was sequenced by using primers listed in Table E1, C, in this article’s Online Repository at www.jacionline.org. Conditions for all exons except exon 2 were as follows: 1 cycle of 94°C for 5 minutes; 35 cycles of 94°C for 30 seconds, 54°C for 30 seconds, and 72°C for 1 minute; and a final extension at 72°C for 5 minutes. An annealing temperature of 58°C was used for exon 2. SNP rs6684514 (see Table E2 in this article’s Online Repository at www.jacionline.org) was genotyped across the case-control study populations by using the TaqMan allelic discrimination genotyping assay (C_25986870_10, Life Technologies Corporation).

Case-control studies
Five independently recruited AD case collections were compared with ethnically matched population control subjects (see the Methods section in this article’s Online Repository). Case definitions are described in the Methods section in this article’s Online Repository, and demographic data relating to these AD case collections and control subjects are summarized in Table E3 in this article’s Online Repository at www.jacionline.org.

Genotype imputation
For *in silico* replication, we used the 2 German AD case-control selections (see Table E3), which had been genotyped on Illumina 300k and Affymetrix
Matten is expressed in mouse and human skin

**Matt** is a compact 5-exon gene on mouse 3qF1 spanning 5781 bp of genomic DNA, encoding a 391-amino-acid protein with a calculated molecular weight of 43.5 kDa. The human ortholog, **MATT**, which is syntenic on 1q23.1, has an identical organization. Mattrin is a transmembrane domain protein with no previously ascribed function (Fig 1, E). Bioinformatics analysis predicts a long internal N-terminal domain, 5 transmembrane domains, and a short C-terminus (Fig 1, E, and see Fig E3 in this article’s Online Repository at www.jacionline.org). The mutation p.Y280* occurs before the third transmembrane domain (Fig 1, E). Immunohistochemistry revealed that mattrin was present in epidermal granular layer keratinocytes in WT mice (Fig 2, A) but was absent from Matt
tna/ma animals (Fig 2, B). Similarly, the protein was observed in granular layer cells in human epidermis (see Fig E4, A and B, in this article’s Online Repository at www.jacionline.org) and was also found in the hair follicles of mice (Fig 2, A) and human subjects (see Fig E4, C and D). In addition, the mRNA is widely expressed in human tissues and, consistent with immunohistochemistry, is strongly expressed in skin (see Fig E4, E).

Expression quantitative trait locus analysis23 showed that **Matt** is in a network of proteins expressed late in epidermal differentiation, with an expression quantitative trait locus profile closely matching that of **Rhbg** (transporter protein) and **Rab25** (membrane trafficking, data not shown). Mattrin shows distant sequence homology to the Membrane-Associated Proteins in Eicosanoid and Glutathione metabolism (MAPEG) protein family (see Fig E3),24 members of which have roles in lipid catalysis.25 Immunohistochemistry with the lipophilic dye Nile Red revealed highly organized stacks of cornified cell envelopes in the stratum corneum of WT animals (Fig 2, C) that were highly disorganized in Mattntna/ma mice, with discontinuous, uneven, and highly disorganized cornified cell envelopes (Fig 2, D).

**Mattntna/ma mice have spontaneous dermatitis**

Gross examination of adult Flg
bop and Mattntna/ma mice demonstrates that the 2 strains differ considerably from each other (Fig 3, A). Macroscopic clinical scoring22 demonstrated Mattntna/ma and DM mice spontaneously having progressive dermatitis-like skin inflammation, which did not occur in adult Flg
bop animals (see Fig E5, A, in this article’s Online Repository at www.jacionline.org). Although all Mattntma/ma and DM mice had marked skin inflammation, there was a broad spectrum of pathology, with some animals exhibiting profound lesions and excoriation and occasional blepharitis and eyelid dermatitis (see Fig E6, B, in this article’s Online Repository at www.jacionline.org). Interestingly, both neonatal Flg
bop and DM mice have significant ichthyosis (P < .001) compared with WT mice, but Mattntna/ma mice did not, indicating the postnatal importance of filaggrin (see Fig E5, A, and E6, A).

With respect to the matted hair phenotype,11,16 both Mattntma/ma and DM animals had the keratinization defect, with hairs forming clumps11,16 and hair breakage and occasional alopecia evident at 32 weeks (Fig 3, A, and see Fig E6, B). Scanning electron microscopy confirmed Mattntma/ma and DM mice had fragile hairs prone to longitudinal splitting and breakage with defective cuticle morphology (see Fig E7, A, in this article’s Online Repository at www.jacionline.org). Furthermore, Mattntma/ma mice had distorted hair follicle morphogenesis (see Fig E7, B).
Skin histology (Fig 3, B) showed that Mattma/ma and DM mice have marked acanthosis (P < .001) and prominent orthokeratosis (P < .001) with dermal inflammatory infiltrates (P < .001; see Fig E5, B). In contrast, Flgft/ft mice had occasional foci of acanthosis, mild diffuse orthokeratosis, and increased dermal cell infiltration relative to WT mice (P < .001). However, the phenotype in Flgft/ft mice was subclinical, with no overt dermatitis (Fig 3, A, and see Fig E5, A).

**Mattma/ma** mutant mice are atopic and have a defective skin barrier

All mutant strains spontaneously had increased IgE levels relative to WT mice, which was markedly more pronounced in Mattma/ma and DM animals relative to Flgft/ft mice (P < .001; see Fig E5, D). Because the severity of skin inflammation in AD parallels barrier permeability, 27,28 TEWL was analyzed to quantify skin barrier dysregulation in mouse strains. TEWL was significantly increased in adult Mattma/ma mice (Fig 4, A-C). Crucially, HDM allergen was applied to the intact skin of Mattma/ma and WT mice to address whether the altered skin barrier in Mattma/ma mice influences allergen sensitization. Percutaneous sensitization with allergen led to enhanced skin inflammation in Mattma/ma mice (Fig 4, A-C). Consistent with the defective barrier, TEWL was significantly upregulated (P < .001) in HDM-treated Mattma/ma mice after allergen application (Fig 4, D). Crucially,
controlling for the strong and significant population-matched control subjects (see Table 1). Notably, when controlling for the strong and significant FLG null mutations, it was shown that the association of rs6684514 with AD is independent of FLG null mutations, it was shown that the association of rs6684514 with AD is independent of FLG null mutations. Several noncoding SNPs and 1 known missense SNP, rs6684514, were identified (see Table E2 in this article’s Online Repository at www.jacionline.org). Case-control analyses conducted on 2 independent AD case collections, English adult AD and United Kingdom pediatric AD, with separate population-matched control subjects (see Table E3) showed a significant association between rs6684514 and AD (Table 1). The minor allele (A) is protective for disease in both the English adult AD (OR, approximately 0.79; \( P = .0038 \)) and UK pediatric AD (OR, approximately 0.77; \( P = .0143 \)) populations (Table 1). Notably, when controlling for the strong and significant FLG null mutations, it was shown that the association of rs6684514 with AD is independent of FLG (Table 1 and see Table E4 in this article’s Online Repository at www.jacionline.org). The association of rs6684514 with AD was further replicated in a German AD case-control analysis in which the OR after controlling for FLG mutations was 0.86 (95% CI, 0.76-0.97; \( P = .0161 \); Table 1). However, this association was not replicated in Irish or Scottish case-control analyses (Table 1). A meta-analysis using a fixed-effects model of all 4,245 AD cases from England, Scotland, Ireland, and Germany with 10,558 population-matched control subjects did not show significant heterogeneity between the study groups (\( P = .078 \)). A small but significant effect of rs6684514 on AD risk was confirmed in the meta-analysis (OR, 0.91; 95% CI, 0.86-0.96; \( P = .001 \); see Fig 5; Table E4). A random-effects meta-analysis also produced similar results (OR, 0.90; 95% CI, 0.82-0.98; \( P = .015 \); see Fig E8 in this article’s Online Repository at www.jacionline.org).

**DISCUSSION**

Previously, we demonstrated that FLG loss-of-function mutations have a very strong relevance for the common inflammatory skin disease AD and associated atopic phenotypes and identified an analogous mutation in the murine homolog Flg in the spontaneously occurring flaky tail DM (matt) mouse. Subsequently, these DM mice have been widely used as a model of heritable skin barrier deficiency and spontaneous dermatitis and as a model of filaggrin deficiency–associated AD pathogenesis in patients. In this study we have identified the matted phenotype in the DM mouse as arising from a second mutation in Mattrin (Tmem79). The Mattrin mutation results in defective expression of the transmembrane protein mattrin, which is highly expressed in the upper granular layer of epidermal keratinocytes, with a predicted role in lipid homeostasis. These studies have elucidated the relative contributions of the Flg and Mattrin mutations in the DM mouse. The Mattrin mutation led to the striking development of spontaneous AD-like skin pathology and atopy in adult mice. These data indicate that the DM mouse is not a true model of filaggrin deficiency–associated AD-like skin...
inflammation. It is notable that the Flg<sup>−/−</sup> mutation has a neonatal influence, whereas the Matt<sup>−/−</sup> mutation has a progressive influence with age. This indicates the polygenic nature of the DM mouse as an AD model and indicates the differential influence of both the Flg<sup>−/−</sup> and Matt<sup>−/−</sup> mutations. Recently, Flg<sup>−/−</sup> mice were shown to have no overt dermatitis with age, with the authors unable to sensitize Flg<sup>−/−</sup> mice by means of application of OVA, an allergen commonly used in models of skin inflammation, to the intact skin barrier, results similar to our data.

Notably, Flg<sup>−/−</sup> mice were not sensitized to HDM (data not shown), indicating an impermissibility of the Flg<sup>−/−</sup> skin barrier to protein antigen ingress. These data indicate that the DM mouse is not a true model of filaggrin deficiency–associated AD-like skin inflammation.

In this study we adopted a translational approach and also addressed whether mattrin was implicated in human AD. A missense SNP in MATT was shown to have a small but significant effect on the risk for human AD.
distant sequence homology to MAPEG family members, which are known to catalyze glutathione-dependent transformations of lipophilic substrates at the lipid bilayer, sequence homology suggests a possible role for mattrin in the biology of lipids or lipid-like molecules. Epidermal transcriptomic analysis of WT versus Mattma/ma mice has revealed changes in several transcripts involved in fatty acid and lipid biology (data not shown). However, 1-dimensional and 2-dimensional thin-layer chromatography of epidermal lipid extracts did not reveal any differences in the migration or abundance of ceramides, phospholipids, or polar or nonpolar lipids between WT and Mattma/ma mice (data not shown). Future work will require analysis of the glutathione binding of mattrin, elucidation of lipophilic substrates of mattrin, and an investigation of the downstream signaling pathways and local immunologic milieu in Mattma mice.

In summary, using a translational mouse-patient strategy, we have identified a new gene mutation that leads to dermatitis in mice and have further demonstrated that a variant in the human gene is associated with AD.

We thank the patients affected by eczema and their families for their interest and participation. We also thank Masa Amagai and his research group from Keio University, Tokyo, Japan, for their open and enthusiastic collaboration, discussion, and sharing of data.

### Table I. Results of case-control analyses to investigate the association of rs6684514 and AD in 5 populations

<table>
<thead>
<tr>
<th>Case-control comparison</th>
<th>Cases (n)</th>
<th>Control subjects (n)</th>
<th>$P$ value for rs6684514 OR 95% CI</th>
<th>$P$ value for rs6684514 association after controlling for FLG null mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>English adult severe AD vs English population control subjects from the 1958 Birth Cohort</td>
<td>505</td>
<td>1919</td>
<td>0.0038</td>
<td>0.791 0.674-0.929</td>
</tr>
<tr>
<td>UK mild-moderate pediatric AD vs English pediatric control subjects without AD</td>
<td>338</td>
<td>538</td>
<td>0.0153</td>
<td>0.770 0.622-0.953</td>
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<tr>
<td>Irish pediatric AD vs Irish adult population control subjects</td>
<td>724</td>
<td>1905</td>
<td>0.1300</td>
<td>1.025 0.896-1.172</td>
</tr>
<tr>
<td>German AD cases vs German population control subjects</td>
<td>1543</td>
<td>2005</td>
<td>0.0794</td>
<td>0.912 0.822-1.011</td>
</tr>
<tr>
<td>Scottish asthma cases with AD vs Scottish population control subjects</td>
<td>1135</td>
<td>4189</td>
<td>0.1365</td>
<td>0.922 0.831-1.023</td>
</tr>
</tbody>
</table>

English adult severe AD is defined as early-onset, persistent, and severe disease. UK mild-moderate pediatric AD includes cases collected from an English population birth cohort ($n = 177$) and a Scottish General Practice collection ($n = 161$); the English pediatric control subjects were ascertained not to have AD at the age of 7 to 9 years. Irish pediatric AD cases were collected in secondary and tertiary care clinics in Ireland; Irish population control subjects are healthy adult blood donors. Scottish asthma cases with AD are subjects with physician-diagnosed asthma and parent-reported AD. The German case and control rs6684514 genotypes were ascertained by imputation from genome-wide SNP analysis data; all other SNP genotypes and FLG null mutations were analyzed by using TaqMan allelic discrimination assays. In the English, United Kingdom, and Irish collections, 4 prevalent FLG null mutations were analyzed (R501X, 2282del4, R2447X, and S3247X), whereas in the German population 2 FLG null mutations were analyzed (R501X and 2282del4). Statistical analysis was performed through logistic regression in Stata 10.0 software (StataCorp). NA, FLG genotype data not available.

### Figure 5. Forrest plot showing results of a fixed-effects meta-analysis of 5 case-control studies to investigate the association of rs6684514 and AD. Study populations used were as follows: English, English adult severe AD versus English population control subjects from the 1958 Birth Cohort; UK, UK mild-moderate pediatric AD versus English pediatric control subjects without AD; Irish, Irish pediatric AD versus Irish adult population controls; German, German AD cases versus German population control subjects; Scottish, Scottish asthma cases with AD versus Scottish population control subjects. ES, Estimated odds ratio. Meta-analysis was carried out with the “metan” function in Stata software (StataCorp).
**Clinical implications:** The role of MATT mutations in susceptibility to AD and related allergic conditions should be further investigated.

**REFERENCES**