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ORIGINAL RESEARCH

Invasive Growth of *Ailanthus altissima* Trees is Associated with a High Rate of Sensitization in Atopic Patients

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Purpose: *Ailanthus altissima* is one of the world's most invasive species with a globally problematic spread. Pollen is dispersed locally and partially airborne. We aimed at investigating if (i) *A. altissima* pollen can be detected in relevant quantity in the air and if (ii) sensitization to *A. altissima* can be detected in patients with seasonal exacerbation of atopic diseases.

Patients and Methods: We recorded distribution of *A. altissima* in Leipzig, Germany. In 2019 and 2020, pollen was collected with a Hirst-type pollen trap placed on the roof of the University Hospital. Specific IgE investigations were performed in children and adults with history of atopic diseases with deterioration between May and July. We analysed specific IgE for *A. altissima, Alternaria* sp., birch, grasses, profilins, polcalcins and crossreacting carbohydrates.

Results: We found abundant growth of *A. altissima* and pollen was detected from early June to mid-July with a maximum pollen concentration of 31 pollen/m^3. Out of 138 patients (63 female, 69 children/adolescents), 95 (69%) had seasonal allergic rhinitis, 84 (61%) asthma, and 43 (31%) atopic dermatitis. Sensitization to *A. altissima* was shown in 59 (42%). There were no significant differences between age groups. In 59% of patients sensitized (35/59), there was no sensitization to possibly cross-reacting structures.

Conclusion: Sensitization to *A. altissima* pollen could be detected in 42% of our patients with atopic diseases, suggesting allergenic potential of this neophyte. In the context of further spread with climate change, eradication strategies and population-based sensitization studies are needed.

Keywords: allergy, invasive species, neophyte, pollinosis, pollen count

Introduction

Climate change and changing environmental conditions are altering habitats, mainly in urban areas, leading to the spread of invasive alien plant species. In parallel, atopic diseases have increased tremendously in the last decades and have become a global challenge imposing significant socioeconomic burden.[1–8] Indeed, allergy has been suggested as a sentinel measure of planetary health and biodiversity loss.[9,10] While multiple factors of climate change lead to higher

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allergenicity of pollen, invasive alien plant species may result in new sensitizations and more severe clinical signs and symptoms.[11,12]

A globally spreading and in many countries highly invasive species of concern is *A. altissima*,[13,14] an undemanding deciduous tree of the Simaroubaceae family, native to northeastern and central China, benefiting from the mild urban climate. The name is thought to derive from the Moluccan term "Aylanto", meaning "tree of heaven", referring to its rapid growth and height, which can reach 15 m in 25 years.[15] The spread of the tree is mainly limited to urban heat islands, as the seedlings are sensitive to low temperatures.[15,16] The flowering period of *A. altissima* is predominantly in June and lasts around 27 days after the gradual opening of the male flowers.[15,17]

Its success in Europe since its first introduction as an ornamental tree in 1751 is likely due to several factors.[13,16,18] *A. altissima* contains allelopathic chemicals such as ailanthone, which suppresses the growth of other plant species through phytotoxic effects.[15,19] Once the tree is established, it spreads aggressively vegetatively and by seeds; its pollen is mainly dispersed locally but also airborne. Control of the tree requires an extremely high level of effort, as it resprouts vigorously after pruning. It also grows in nutrient-poor soils and is resistant to drought, salt, and herbicides, which are major reasons why it is planted as an urban ornamental tree.[15,16]

In China, where the tree is native, 30% of patients tested for suspected allergic rhinitis had positive skin prick tests for *A. altissima*.[20] In Europe, there is one investigation among 54 allergic adult patients in Italy, as well as in some case reports dating back as far as 80 years.[21–26] However, there is a lack of comprehensive studies on sensitization to *A. altissima* in regions where the tree is spreading invasively. High exposure is particularly expected in cities, where population density is high and warmer temperatures provide optimal growing conditions for the tree. In our study, we aimed at investigating if (i) *A. altissima* pollen can be detected in relevant quantity and if (ii) sensitization to *A. altissima* can be detected in patients with seasonal signs and symptoms of their atopic diseases during its pollen season in Leipzig, Germany.

Materials and Methods

Distribution of *Ailanthus altissima* and Pollen Concentration

The tree registry of the City of Leipzig is publicly accessible online (https://www.leipzig.de/umwelt-und-verkehr/umwelt-und-naturschutz/baeume-und-baumschutz/stadtbaeume/) and was used to determine planting dates and location of planted trees of *A. altissima* in Leipzig (Supplemental Figure 1). We inspected fifteen 600×600 m grids along an east-west transect including city center and suburbs of approx. 10 km distance where the number of *A. altissima* plants had already been counted in 1982[27] and documented the current number of trees. When making counts, it is important to note that *A. altissima* trees form root runners. This means that around a big tree many small sprouts can emerge from the roots. As in 1982,[27] these shoots are counted as one plant with the tree from which they originate from. Also, groups of young trees in which the individual stems are located within a few square meters, are counted as one tree due to root fruiting. A seven-day recording volumetric Hirst-type pollen and spore trap (Burkhard Manufacturing Ltd., Hertfordshire, UK) (Supplemental Figure 2A) was placed at the roof of the University hospital in Leipzig (51.330847N 12.387845E, height 17.3 m asl) starting in April 2019. The power of the pump was set to a volumetric flow rate of approximately 10 L/min and the drum was replaced once a week. An analysis of the daily mean pollen concentration including all identifiable pollen types was achieved by a defined movement of the vaseline-covered strip on the drum. Based on a defined volumetric flow rate, pollen counts can be related to m^3 of air per day. The analysis followed the European regulation DIN EN 16868 for pollen and fungal spore sampling.

In addition, vaseline-covered slides (Supplemental Figure 2B and 2C) were exposed to individual trees at specific intervals along a transect for one week, and exposure was repeated for one and two additional weeks, respectively. The adhering *A. altissima* and grass pollen were analyzed with 200x magnification on an area of 2.6 mm x 60 mm in the middle of the cover glass (Counted pollen on slide stripe) according to recommendations of R. Wachter (http://www.dr-wachter.de/Messstellen/Messmethode%20f.htm). For an old tree (location: 51.35233482599263, 12.429702588848789, Breast height diameter (BHD) 1.02m, count data from two consecutive weeks (16.-30.06.2020) were averaged and measured in −50, −20, −10, 0, 10, 20, 50, 100 m distance to the tree, while for a younger tree (location:

51.328712546333406, 12.333695635475502, BHD 0.13m), three consecutive weeks (16.06.-07.07.2020) were used as the mean and measured in −100, −50, −20, −10, 0, 10, 20, 50, 100 m distance to the tree.

Study Population and IgE Measurement

In 2019 and 2020, pediatric and adult residents from Leipzig and neighboring communities who presented to our Comprehensive Allergy Center were enrolled if they had seasonal (May-July) allergic rhinitis (AR) and/or asthma and/or worsening of their atopic dermatitis. We recorded history of atopic diseases as well as known IgE sensitizations. The study was approved by the Medical Ethics Committee of the Medical Faculty of the University of Leipzig (reference number 082–10-19042, 10). All patients gave informed consent. The patients' data were processed in compliance with the Hospital Law of the Federal State of Saxony (§ 34 Abs.1 SächsKHG). Blood samples were collected and sera were stored at −20°C for a maximum of 3 months until further use. Specific IgE measurements for *A. altissima* (research allergen SAS 535 tree of heaven, same batch for all), *Betula verrucosa* 2/4 (Bet v 2/4, t221), and cross-reactive carbohydrate determinants (CCD; o214) were performed using ImmunoCAP® (Thermo Fisher, Freiburg, Germany). Values >/= 0.35kU/l (CAP1) were classified as positive. Intra- and interday coefficient of correlation was determined for research allergen SAS 535. Proportions of sensitization were plotted against place of residence (city center/suburbs).

Results

Ailanthus altissima in Leipzig

In Leipzig, Germany, there are significant populations of *A. altissima* and evidence of plantings dates back to 1817.[27,28] In the tree cadastre of the city of Leipzig, targeted plantings have been documented since 1920 (Figure S1). Thus, *A. altissima* has been present in Leipzig for at least 100 years. From 1950 to 1990, new trees were increasingly planted in the city center (Figures 1 and 2). While 67 planted trees were counted until 1980, a detailed vegetation mapping in 1983 showed about 2000 feral trees, resulting in *A. altissima* being called the "character tree" of the city center.[27] An inventory of a subset of records revealed another massive increase from 123 trees in one transect in 1982 to 2715 trees in 2019/2020, representing a 22-fold increase in 37 years (Figure 2B). Abundant numbers of plants were found mainly within the city center.

Pollen Concentrations

In 2019 and 2020, *A. altissima* pollen was recorded from early June to mid-July with a maximum pollen concentration of 31 pollen/m^3 on June 15th, 2019 and 21 pollen/m^3 on June 30th, 2020. During the flowering period of *A. altissima*, the following other bioaerosols were enumerated in similar or higher quantities: fungal spores (*Alternaria* and *Epicoccum*), as well as pollen of pine (*Pinus)*, plantains (*Plantago)*, grasses (*Poaceae)*, dock (*Rumex)*, lime (*Tilia)*, and stinging nettle (*Urtica)*. Potentially allergenic Poaceae pollen could be detected from mid-May to the end of July and co-occurred in the sample with the peaks of *A. altissima* (Figure 3). The assessment of local pollen concentrations showed that they were highest near the trees (0–20 m) and decreased at a distance of 10–50 m (Figure 4).

Patients and IgE Values

In 59/138 (42%) of patient's sera we detected specific IgE against *A. altissima* (Table 1). Proportions of sensitization was similar in children and adults (46% and 39%, respectively; n.s.). The mean specific IgE concentration against *A. altissima* was 4.14 kU (± 8.32 kU/L) with ImmunoCAP classes ranging from 1 to 4. Within the group of the *A. altissima*-sensitized patients, 59% had neither IgE antibodies against the combination of the profilin Bet v 2 and the polcalcin Bet v 4 nor against the cross-reactive carbohydrate determinants (CCD). The coefficients of variation of the determination of specific IgE against the research allergen SAS 535 tree of heaven were intra-day and inter-day 1.9 and 5.1, respectively. Sensitization to other aeroallergens was very common in both children and adults (Table 2). Geomapping showed that individuals from the city and neighboring communities were sensitized to *A. altissima* at about the same proportion (data not shown).

Figure 1 *Ailanthus altissima* in front of the Institute of Laboratory Medicine of the University Hospital Leipzig, young feral tree in the city center, and details of the leaves and flower of the tree.

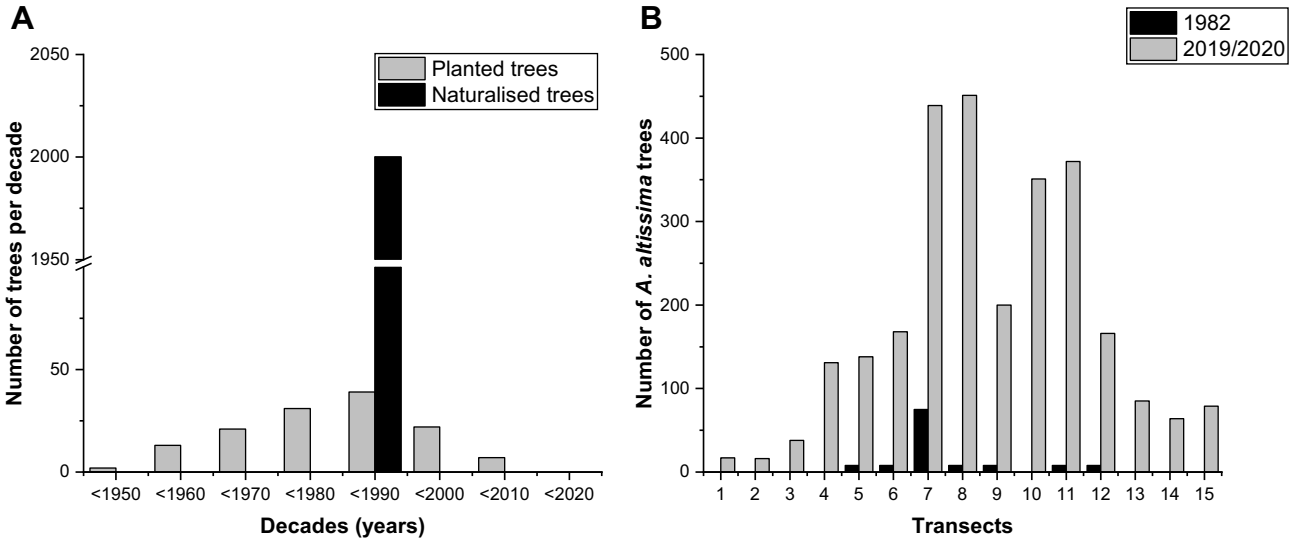

Figure 2 (**A**) Number of *Ailanthus altissima* trees planted in Leipzig per decade (gray) and feral trees identified in a detailed mapping by Gutte et al (1987).[27] (**B**) Numbers of *A. altissima* plants in 1982[27] and in 2019/2020, counted along an east-west transect with grid sizes of 600×600 m in Leipzig. Sites 6–10 were located at the city center.

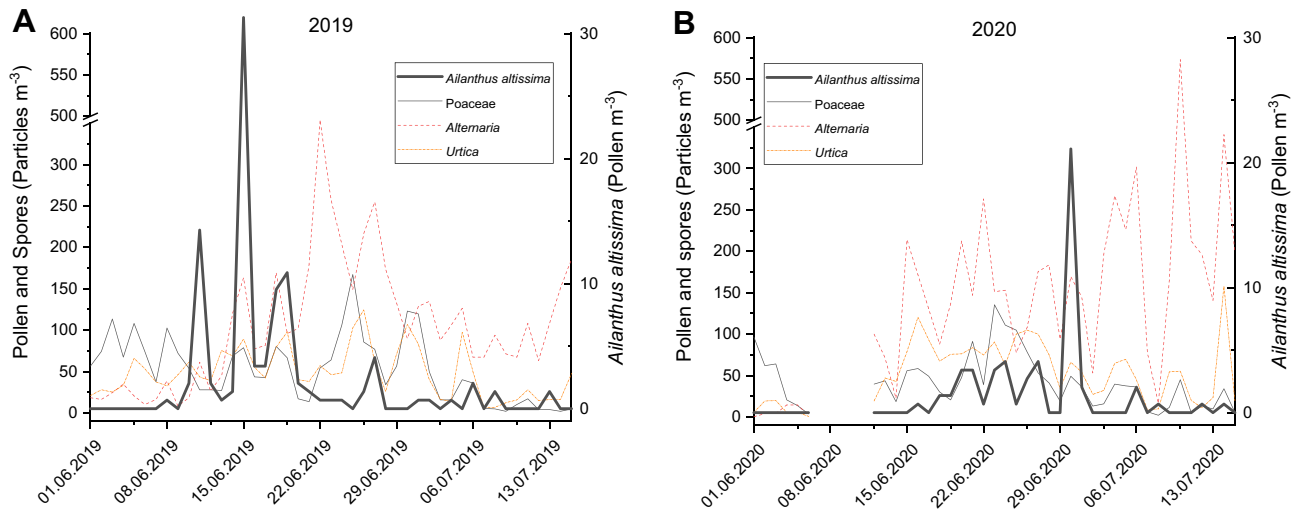

Figure 3 *Ailanthus altissima* (black line, right y-axis), grasses (Poaceae) (gray line), *Alternaria* (red dashed line), *Urtica* (orange dashed line) (all on left y-axis) pollen and spore concentrations (pollen m^{-3}) in 2019 (**A**) and 2020 (**B**).

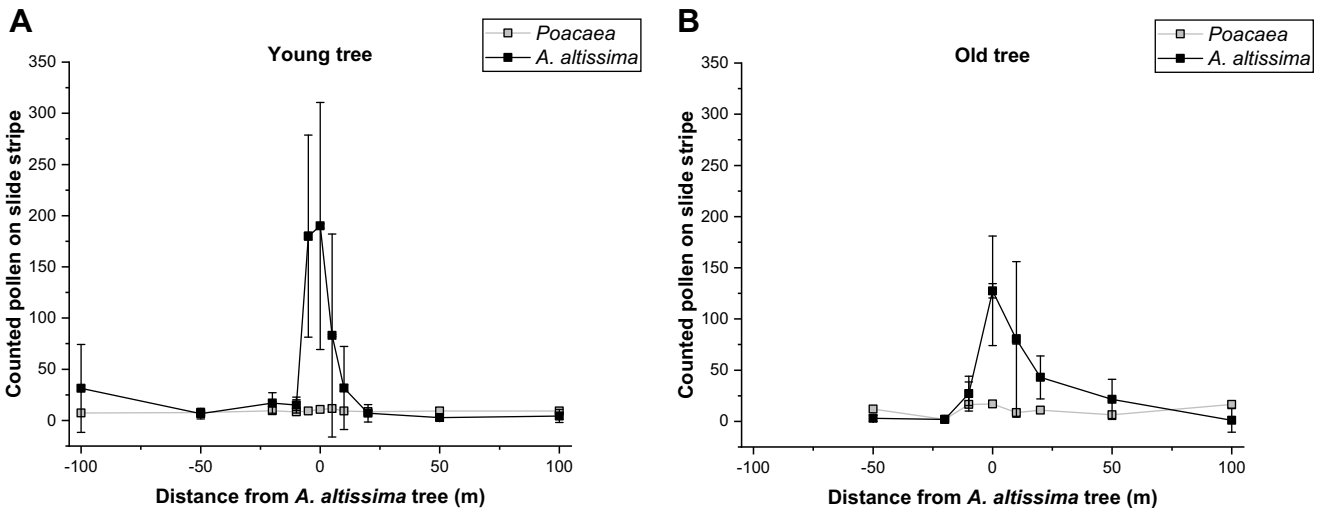

Figure 4 Local pollen counts for grass (Poaceae) and *Alternaria altissima* pollen near a young (**A**) and an old (**B**) solitary tree collected for one week (two/ three consecutive weeks) on a Vaseline-covered object slide (Supplemental Figure 2B and 2C).

Discussion

After several decades of active tree planting, a remarkable population of planted and feral *A. altissima* trees has developed in Leipzig. As we were able to detect *A. altissima* pollen in air samples, airborne allergic sensitization is possible. Accordingly, we found sensitization to *A. altissima* in 42% of pediatric and adult patients with seasonal exacerbations of their atopic diseases.

So far, there are no population-based studies evaluating sensitization to *A. altissima*. However, allergies to *Ailanthus* have been described repeatedly and as far back as 80 years ago.[23–25] Sensitizations may have been overlooked so far since the allergen is not included in European standards and flowering coincides with other aeroallergens such as grass pollen or *Alternaria* spores.[29,30] It is also possible that sensitization is only detectable in certain local regions with high tree abundance, because – as shown in our investigation - *A. altissima* pollen are distributed mainly locally.

However, the annual pollen load across the northern hemisphere has increased in recent decades.[31] *A. altissima* has already spread as an invasive neophyte in many parts of the world. Climate change and urban conditions promote further rapid spread and may lead to increased sensitization rates and ultimately enhanced healthcare utilization due to climate change-induced disruption of antigen-specific tolerance.[32–37] While 20 years ago the main pollen season for *A. altissima*

Table 1 Demographics and Proportions of Sensitization Against *Ailanthus altissmia* (*A. altissima*) and Crossreactive Panallergens

Baseline Data	
Total number of patients, n (female)	138 (63)
Number of children, n (%)	69 (50)
Age, mean±SD (range), years	25.3±19.7 (2.3–84.1)
Seasonal allergic rhinitis, n (%)	95 (68.8)
Asthma, n (%)	84 (60.9)
Atopic dermatitis, n (%)	43 (31.2)
Specific IgE against *A. altissima* >/=0.35 kU/l, total, n (%)	59 (42)
IgE values	
Total IgE mean (median), kU/L	704 (309)
Specific IgE *A. altissima*, mean±SD (median; range)	4.14 ± 8.32 (0.84; 0.35–42.20)
>/= 0.35–0.7 kU/L - CAP 1, n (%)	29 (49.2)
>/= 0.7–3.5 kU/L - CAP 2, n (%)	15 (25.4)
>/= 3.5–17.5 kU/L - CAP 3, n (%)	11 (18.6)
>/= 17.5–50 kU/L - CAP 4, n (%)	4 (6.8)
Concomitant sensitization in 59 patients with specific IgE against *A. altissima*	
Bet v2/4, CCD negative, n (%)	35 (59.3)
CCD positive only, n (%)	17 (28.9)
Bet v2/4 positive only, n (%)	18 (30.5)
CCD and Bet v2/4 positive, n (%)	11 (18.6)

Table 2 Concomitant Sensitization to Aeroallergens in Patients with Specific IgE to *A. Altissima*

Allergen	**Patients Examined, n (Children)**	**Proportion Sensitized, % (Children)**
Birch (*Betula*)	128 (63)	55.5 (46.0)
Grass (Poaceae)	120 (58)	63.3 (51.7)
Mugwort (*Artemisia*)	88 (32)	30.7 (9.4)
Ragweed (*Ambrosia*)	61 (17)	14.8 (11.8)
Dust mite *(Dermatophagoides)*	103 (49)	48.5 (55.1)
Molds (Fungal spores)	62 (26)	21.0 (19.2)
Animal dander	64 (29)	50.0 (55.2)
Other	76 (9)	73.7 (66.7)

was reported in July,[15,38] we now detected the highest pollen concentrations in June. This may be a result of very high temperature in early summertime in the years 2019 and 2020. In line, the importance of changing climate conditions for a change in pollination periods along with changes in sensitization rates has been previously documented.[39] Simultaneously with the *Ailanthus* pollen count, we also detected other pollen and spores so that inhalative symptoms at this time might falsely be attributed to these allergens and a relevant sensitization to *A. altissima* might be missed.

The allergen content of birch pollen was reported to be higher at sites with air pollution.[40] As *A. altissima* mainly spreads in urban areas, any impact of traffic pollution on its allergenicity should be an issue in further investigations. In our study, individuals from the city and neighboring communities were sensitized to *A. altissima* at about the same proportion. This can be explained by similar exposure due to visits to the workplace, school, daycare center, or city center, as well as a high degree of tree distribution throughout the city.

While the proportion of sensitization among the patients in our study is comparable to that in northeastern Iran, it is much higher than proportions previously reported from European and Chinese patient cohort without considering possible cross-sensitization.[20–22,41] At the same time, there is evidence that *A. altissima* has been present in the landscape of Leipzig city center for at least a hundred years. Sensitization may have occurred during this period. In the trajectories of atopic diseases, allergic sensitization can develop in early childhood and increases with age.[42] Therefore, due to the high, increasing and long-lasting population of *A. altissima* in Leipzig, the high proportion of sensitization appears reasonable. This also corresponds to the assessment that the tree has a high allergenic potential.[43] Sensitization in the aforementioned smaller cohorts from Italy was reported almost 20 years ago and may have increased in the meantime. Prediction models show a further spread of *A. altissima* in the future along with an increasing risk of allergic sensitization worldwide.[14] Our pilot study in Leipzig could therefore be a blueprint for many cities and regions worldwide with increasing risk of allergic sensitization worldwide.

While in our study the proportion of sensitization was approximately the same in the different age groups, Werchan et al reported higher proportions in patients younger than 20 years of age.[20] The exposure in Leipzig has obviously existed for many decades, explaining sensitizations in all age groups. In China, industrialization and habitat changes have taken a different course in time, which could explain the age dependency.[44] Differences may also result from the limited agreement between prick tests in the Chinese cohort and the IgE measurement used in our investigation.[45]

We included patients with worsening of their atopic diseases during the flowering period of *A. altissima*. Therefore, the *A. altissima* pollen may suspected to be a triggering allergen. Of course, other factors, including temperature, and other allergens may as well have contributed to the clinical symptoms. In particular, this includes grass and *Urtica* pollen or *Alternaria* spores, which appeared at the same time and were also detected in our pollen trap.[11,46]

We measured specific IgE directed against *A. altissima* using the established ImmunoCAP system with a research allergen that has been extracted from pollen in the manufacturer's standard procedure. Variation coefficients indicate high precision.[47,48] In half of the group, mean specific IgE levels against *A. altissima* reached levels above CAP class 1. Some of the patients have a rather low specific IgE value. These subjects may still be at the beginning of sensitization, as pollen is spread more locally. It is also possible that allergenic structures are underrepresented in the assay. However, since all our patients had seasonal exacerbations of their atopic diseases, IgE sensitization to *A. altissima* pollen could be clinically relevant.[49]

In the search for allergenic structures in *A. altissima* pollen, a number of proteins of 20–55 kDa and <10 kDa were found and identified as enolases, calreticulin, pectate lyases, conserved hypothetical protein, and ras-related protein RHN1-like.[23,50–52] It has been shown that *A. altissima* pollen contains cross-reactive calcium binding proteins and cross-reactive CCDs,[23,53,54] but 59% of our patients had no sensitization to CCDs, profilins, or polcalcins which suggests primary sensitization to specific allergens of *A. altissima.*

Limitations of our clinical study are the ongoing allergen identification of both the pollen itself and the CAP allergen used, and the non-inclusion of other possible panallergens, ie cyclophilin. Therefore, we cannot exclude a certain overestimation of the proportion of sensitization. No commercial and approved diagnostic allergen was available for skin prick tests. Therefore, sensitization could not be confirmed by this in vivo method.

Conclusions

A. altissima plantings in the city of Leipzig led to an expansive spread of this invasive species. The pollen could be detected both locally and remotely from trees in the flowering months of June and July. In a hospital-based, high-risk

group of patients with atopic diseases, we found sensitization to *A. altissima* in 42% with no significant differences between age groups and in the majority without cross-sensitization to panallergens.

Future international population-based cross-sectional and prospective studies including mapping of tree populations are needed to clarify epidemiology of *A. altissima* pollen allergy. Standardized testing procedures (IgE, skin prick test, provocation tests) need to be developed and validated. Our data suggest that planting of *A. altissima* should be avoided. Development of control strategies seems mandatory, due to the invasive growth and the allergenic potential of this alien species.

Data Sharing Statement

The pollen data relevant for the study will be available from Dr. Susanne Dunker (susanne.dunker@ufz.de) on reasonable request.

Ethics Approval and Informed Consent

The study was approved by the Medical Ethics Committee of the Medical Faculty of the University of Leipzig (reference number 082-10-19042010). All patients gave informed consent. For the patients under 18 years of age, parents or legal guardians of provided informed consent. The patients' data were processed in compliance with the Hospital Law of the Federal State of Saxony (§ 34 Abs.1 SächsKHG).

Consent for Publication

The authors give consent to publish the details of any images, videos, recordings, etc and that the person(s) providing consent have been shown the article contents to be published.

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Authors` Contributions

SD, FP, JS, JG, MH and RT designed the study. SD performed the pollen distribution assessments. FP, MH, TL, JZ, MB, VZ, PK and RT were involved in clinical investigations, SK and TK performed IgE diagnostics, TH conducted the plotting of Figure S1 and was involved in managing the pollen traps, MB counted the pollen of the Burkard (Hirst-type) pollen traps. SK provided local knowledge of *A. altissima*. FP, SD, RT, and JS prepared the draft.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Freerk Prenzel and Regina Treudler should be considered joint first author.

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Disclosure

Dr Freerk Prenzel reports personal fees from Sanofi Genzyme, personal fees from Novartis, personal fees from Takeda, personal fees from Nutricia Milupa, outside the submitted work. Dr Tobias Lipek reports personal fees from Novartis, personal

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