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Food Allergy Detection With Ml: Developing Machine Learning Algorithms To Detect And Prevent Allergens In Food Products

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Abstract: Synthetic biology and genome editing are two examples of cutting-edge technology that have opened the door to the production of new foods and functional proteins. It is important to appropriately assess their toxicity and allergenicity, nevertheless. Some proteins are known to cause allergies due to certain sequences of amino acids, however the identities of many of these sequences are yet unknown. Here, we present a data-driven strategy and a machine-learning technique for discovering previously unknown allergen-specific patterns (ASPs) in amino acid sequences. The proposed method allows for a thorough search for subsequences of amino acids that are statistically more common in proteins that cause allergies. For this proof-of-concept, we used the proposed technique on a database consisting of 21,154 proteins for which the allergy status is already known. This proof-of-concept investigation found ASPs that were in agreement with previous biological findings. Using these ASPs improved allergenicity prediction performance compared to existing methods, suggesting this approach could be valuable for assessing the practicality of synthetic meals and proteins.

1. Introduction

1.1 Food allergy

Some people are more likely to get an unfavorable immune response known as a food allergy if they are repeatedly exposed to specific foods. In many cases, proteins are the ones to blame for triggering these undesirable responses. Interactions between immunoglobulin E (IgE) antibodies and allergenic proteins are the main mechanism of food allergy. To be more precise, "epitopes" are sequences of amino acids (aa) that are associated with an allergenicity in an antigen protein (Figure 1). The immune system recognizes these epitopes as three-dimensional complexes, and they can be either (A) linear or sequential, defined by a certain aa sequence, or (B) conformational or discontinuous. Hydrogen bonds, electrostatic, van der Waals, and hydrophobic forces, as well as weak interactions like these, are what really hold antigens and antibodies together, rather than covalent bonds [1].

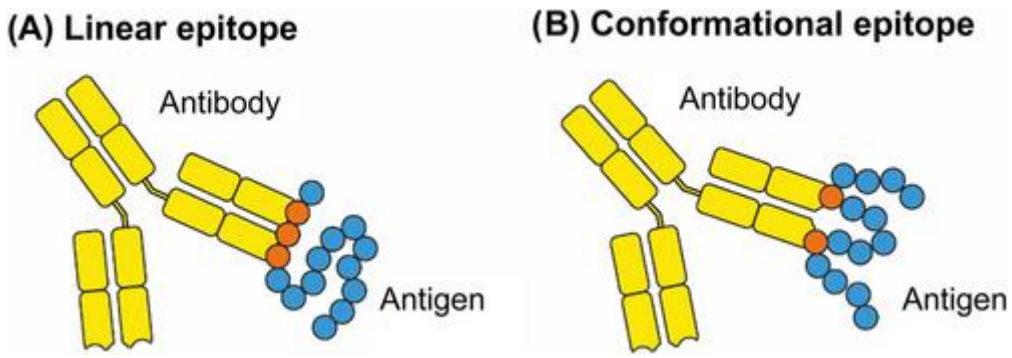


Figure 1 Antibody binding of linear and conformational epitopes.

There are two stages to the development of a food allergy, which follows a common disease mechanism [2]. The first step of sensitization is the repetitive, non-effectual interaction of the antigen with the intestinal mucosa. An allergic reaction can happen soon after consuming even little amounts of an allergen in the diet of someone who is already sensitive to it. Some routes of exposure, including food consumption, inhalation, and skin contact, might cause sensitization [3-5]. A variety of symptoms can be experienced by those with IgE-mediated food allergies. These include urticaria, angioedema, nausea, abdominal cramps, and cardiovascular issues like hypotension and arrhythmia. In extreme circumstances, anaphylaxis can manifest as an abrupt reaction [6, 7].

Skin prick tests (SPTs), oral food challenges (OFCs), and food-specific IgE determination are some of the methods used to detect food allergies that are mediated by IgE. Because of their affordability, reliability, speed, and ease of use, SPTs have surpassed all other diagnostic tools in terms of usage [8]. In a skin prick test (SPT), a little amount of allergen is introduced into the skin just under the surface by passing a prick device through a drop of each allergen extract that has been cleansed. In cases where the patient has developed an allergy to the allergen, a wheal may develop [8]. The patient's serum is left to incubate on a device that contains immobilized allergens in a food-specific IgE test. The antigens are recognized by a fluorescently tagged anti-IgE when specific serum IgE binds to them. Although the selectivity of these tests is above 85%, a cross-reaction with related proteins is still possible [9].

2. Literature Review

The oral food challenge (OFC) test is the most reliable method for identifying food allergies [10]. It involves a meticulous procedure where the quantity of the allergen in question is progressively raised. When the patient has side effects or the test comes out negative, it is given in a placebo-controlled or open-label fashion. The OFC test requires a regulated setting with qualified staff and access to suitable medical equipment because of the serious reactions that could occur [11, 12]. There is currently no known way to cure food allergies; the only option for people who suffer from them is to avoid foods that contain allergic substances [13]. As a result, safeguarding the health of individuals with food sensitivities requires the identification of both known and unknown allergenic proteins in complex and processed meals.

ELISA is also the standard operating procedure for the vast majority of commercial kits developed for the purpose of measuring trace amounts of food allergens in both raw and cooked meals, drinks, and ingredients [14]. The problem with traditional ELISA is that it is often done in a central lab using normal laboratory equipment and a microtiter plate spectrophotometer. This method is costly, takes a long time to get results, and requires payment for sample delivery and storage. This has led to a persistent need for analytical methods that may be applied in non-laboratory settings to evaluate the quality and safety of foods directly.

An integrated bioreceptor-transducer device, a biosensor can transform a biorecognition event into a concentration-dependent, quantifiable signal. The majority of research on optical biosensors for food allergy identification has focused on those that rely on absorption, fluorescence, or surface-plasmon resonance (SPR) [15]. Because of its high surface sensitivity, automation, and real-time findings, SPR is an effective method. By utilizing binding between the allergens in the sample and the specific antibodies mounted on the surface of a sensor chip, SPR biosensor technology is able to detect changes in the refractive index at the surface of the chip.

Due to their reliance on high-performance optical equipment and processors, most SPR biosensor systems are rather expensive, despite the fact that SPR biosensors offer a high degree of automation and reduce assay time [16]. Soon, food control authorities should be able to use simple, fast, cheap, and dependable biosensors that detect food allergies with a high degree of sensitivity.

The unique benefits of microfluidics—including shorter reaction times, reduced sample consumption, increased sensitivity, tiny dimensions, short diffusion distance, and high surface tension—have contributed to its meteoric rise in popularity and effectiveness as a tool in biochemistry applications [17, 18-25]. Despite the abundance of literature on immunoassays in microfluidic devices using a variety of detection methods—including SPR, colorimetric and fluorometric measurement—very few have addressed their application to the identification of food allergies. Nevertheless, the majority of approaches that solely rely on microfluidic chips necessitate cumbersome and costly hardware or employ intricate chip fabrication procedures, hence restricting their potential for use in the development of portable devices.

3. Methodology

In this research, we offer allerStat, a machine learning approach for finding ASPs, or amino acid subsequences, that are strongly linked to allergic reactions. We used allerStat on a protein dataset we built as a proof-of-concept, which includes both allergic and nonallergic proteins across several biological domains.

3.1 Allergen protein dataset

In Figure 2A, we can see the allerStat dataset input format. A protein is depicted in each row of the table. The three bits of data that make up a protein are its amino acid sequence, its biological category, and whether or not it has been labeled as having an allergic reaction. An allergenic protein is one that triggers an allergic response, while a nonallergenic protein is one that does not. Avoiding the mistake of labeling category-specific patterns as ASPs requires biological category knowledge. We extracted the data shown in Figure 2B, which classifies each biological category in the original dataset into three categories, from the dataset itself. The first kind is known as the paired category, and it includes both allergic and nonallergenic proteins. [26-31] The second kind is known as the positive-only category, while the third kind is known as the negative-only category. It is necessary to differentiate between these three kinds of categories because, for instance, it is impossible to tell if amino acid subsequences seen in a positive-only category are category-specific or indicative of an allergic reaction.

A

ID	Amino Acid Sequence	Category	Label
1	LLVAALCALVA…	Oribatida	Allergen
2	EIASQIAQED…	Carnivora	Allergen
3	WQTYVDDHLMC…	Carnivora	Allergen
4	NKLFLVSATLAL…	Bos taurus	Allergen
5	NCLFLVSATLAL…	Bos taurus	Allergen
6	PTSVAVDQGS…	Bos taurus	Allergen
7	LKVAAKCAKVA…	Gallus gallus	Non-Allergen
8	EICSQNAQED…	Oryza sativa	Non-Allergen
9	REKTGAGMQLMS…	Bos taurus	Non-Allergen
⋮	⋮	⋮	⋮

B

ID	Category	Category Type	# of Allergen	# of Non-Allergen	Total
1	Oribatida	Positive-Only	226	0	226
2	Gallus gallus	Paired	18	2262	2280
3	Actinidia deliciosa	Paired	21	11	32
4	Bos taurus	Paired	25	5953	5978
⋮	⋮	⋮	⋮	⋮	⋮

C

An Example: Patterns from Sequence "MKRRELEK"

Length	# of Patterns	Patterns (Subsequences)
1	5	M, K, R, E, L
2	7	MK, KR, RR, RE, EL, LE, EK
3	6	MKR, KRR, RRE, REL, ELE, LEK
4	5	MKRR, KRRE, RREL, RELE, ELEK
5	4	MKRRE, KRREL, RRELE, RELEK
6	3	MKRREL, KRRELE, RRELEK
7	2	MKRRELE, KRRELEK
8	1	MKRRELEK

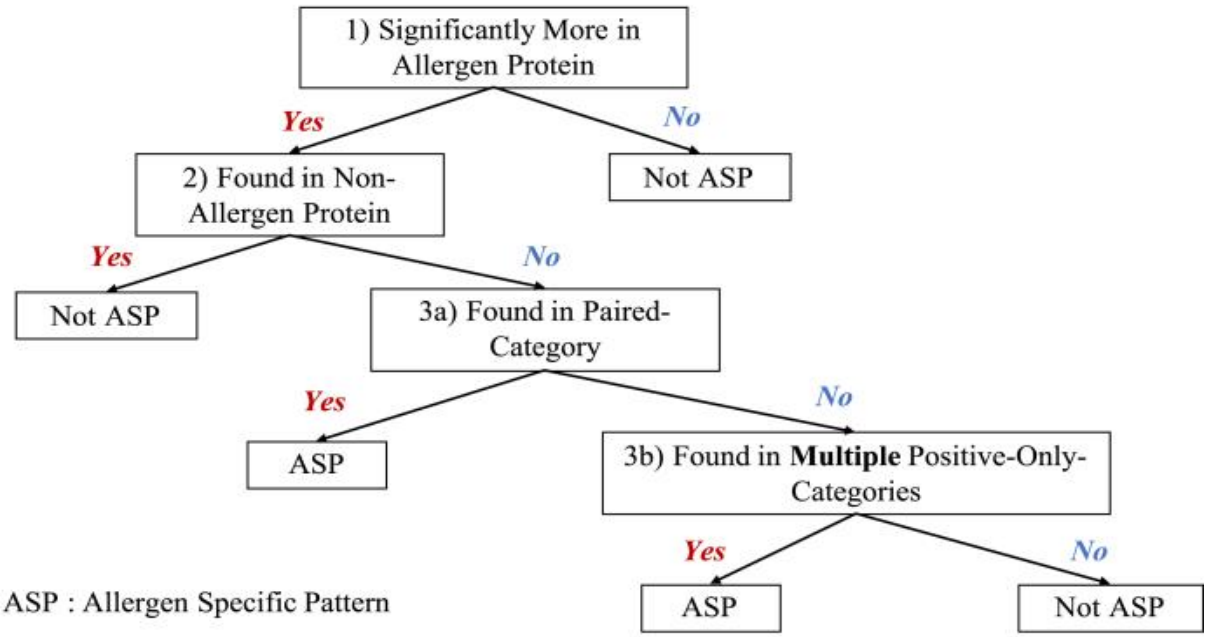
Figure 2 The proposed approach allerStat's data format illustrated.Form for entering data (A). On each line, you can see a protein along with its amino acid sequence, name of biological category, and whether or not it has caused any allergic reactions. A, the structure of the data pertaining to the biological categories. This data analysis approach treats the three categories—paired, positive-only, and negative-only—differently. Category C, pattern examples. We refer to a continuous subsequence of amino acids as a pattern. According to the figure, the amino acid sequence MKRRELEK contains 33 distinct patterns.

Based on the information provided in the Experimental techniques section, we created a dataset of 21,154 proteins that have already been confirmed to cause or not cause allergic reactions. This dataset served as a proof of concept. Data S1 provides the entire dataset in Figure 2A format, whereas Data S2 provides the dataset's biological category information in Figure 1B format. There are 18,906 nonallergenic proteins and 22,248 allergenic proteins in the PoC dataset. On average, the proteins have a length of 421, a minimum of 5, and a maximum of 34,350. There is one negative-only category, twenty pairs of categories, and two hundred and forty-four positive-only categories. Separating allergic from nonallergenic proteins is typically a challenging task. We narrowed our focus to 20 foods because of their extensive allergy testing. We created 17,372 nonallergenic proteins by deleting allergens and their family proteins using evaluated protein information from UniProt. In addition, the thymic medulla offers a one-of-a-kind microenvironment where almost all self-antigens are presented. This helps to eliminate autoreactive T cells before they emigrate to the periphery, thereby building tolerance in the central T cells. The promiscuous production of tissue-restricted proteins by mTECs is a key component of the self-antigen presentation mechanism. Consequently, it is highly unlikely that such a protein synthesized in mTECs will cause allergic reactions. The 1534 nonallergenic proteins were created by integrating the published gene and protein expressions. We must be mindful that each category contains numerous comparable proteins when evaluating the prediction performance using this PoC dataset. We used what we term leave-category-out cross-validation (LCO-CV) to prevent data leaking.

Data S3 displays the feature values for each amino acid, and Fig. S1 displays the distributions of various physico-chemical properties of allergic and nonallergenic proteins. The feature values for each protein are obtained by averaging the amino acid counts in that protein. It is hard to predict allergenicity based on physicochemical properties alone because there is no discernible variation in the distributions of any of these traits across them.

As seen in Figure 2C, there are several patterns and sequences of amino acids. A pattern is defined as a set of consecutive amino acid subsequences of varying lengths. The objective of this research is to identify the patterns that are most strongly linked to allergy reactions as ASPs. The difficulties arise from the sheer volume of potential patterns that need to be examined. Because there are 20 amino acids, there are 1065 potential patterns up to 50 amino acid lengths, for instance. The PoC dataset contains a staggering 3,783,825,994 patterns—and that's only taking them into account that are already there in the dataset. Problems with computation and statistics arise from the enormous number of possible patterns. Finding a solution to these statistical and computational problems is the primary contribution of this work. Figure S2 shows the length of each pattern in the PoC dataset together with the number of patterns contained within it.

A



ASP : Allergen Specific Pattern

B

1. Pattern "KLELS" ⇨ **Not** Allergen Specific Pattern

Sequence	Label	Category	Category Type
…TKLELSSX……	Allergen	Poales	Positive-Only
……ADKLELSP…	Non-Allergen	Bos taurus	Paired

2. Pattern "PSQQ" ⇨ Allergen Specific Pattern

Sequence	Label	Category	Category Type
…SADPSQQS…	Allergen	Bos taurus	Paired
…MAPSQQEL…	Allergen	Bos taurus	Paired

3. Pattern "RRLE" ⇨ Allergen Specific Pattern

Sequence	Label	Category	Category Type
…ELTERRRLETX…	Allergen	Poales	Positive-Only
…MLETSRRLEKS…	Allergen	Oribatida	Positive-Only

4. Pattern "MMKLE" ⇨ **Not** Allergen Specific Pattern

Sequence	Label	Category	Category Type
…TXMMKLES……	Allergen	Poales	Positive-Only
……GABAMMKLEP…	Allergen	Poales	Positive-Only

Figure 3A definition of allergen-specific patterns, along with some instances of them.To define ASPs, a decision diagram is presented. Example of ASPs and non-ASPs is presented in B. The following examples illustrate the conditions that must be met for a pattern to be considered an ASP. The pattern in question must satisfy condition 1. Example 1: The pattern KLELS does not meet the requirements of condition 2, hence it cannot be considered an ASP. In the second example, the PSQQ pattern is an ASP since it satisfies both criterion 2 and condition 3a. In the third example, the pattern RRLE is an ASP since it satisfies both criteria 2 and condition 3b. (Example 4) Pattern MMKLE satisfies condition 2, however it is not an ASP because it is only found in a single positive-only category. In other words, it does not satisfy either condition 3a or 3b. A pattern that is allergen-specific, or ASP.

4. Results And Discussion

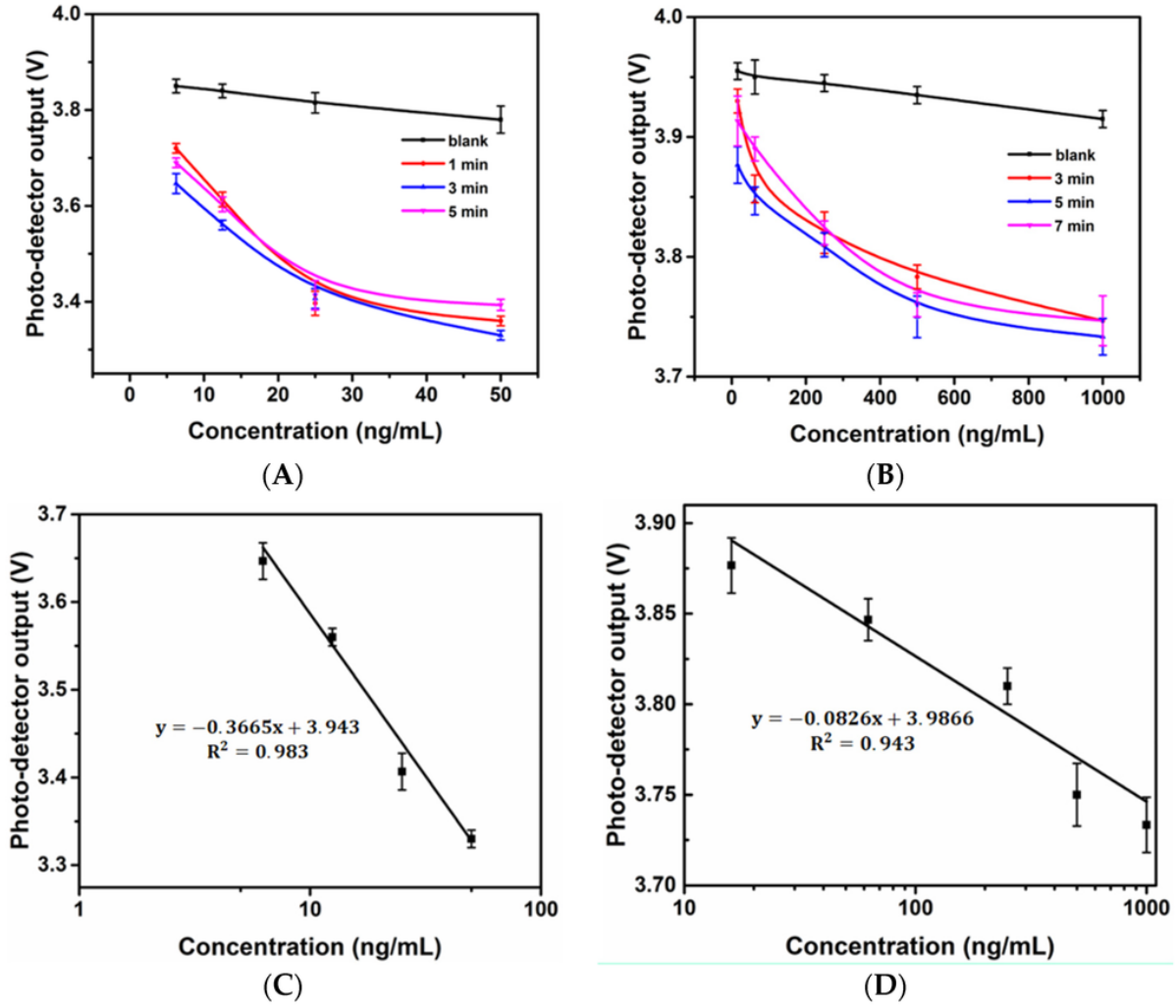


Figure 4. Time-dependent response of the developed optical microfluidic biosensor upon sensing the gluten standard solution (**A**) and Ara h 1 standard solution (**B**); Linear standard curves of gluten (**C**) and Ara h 1 (**D**).

A variety of reaction durations are depicted in Figure 4A, which illustrates the response of the optical sensor to wheat (gluten) standard solutions. Based on the enzyme kinetics for the enzyme reaction under the associated volume, the time period of three minutes may be deemed to be the saturation time. This is evident from the figure, which shows that the outputs of one minute and five minutes were larger than those of three minutes. In a similar manner, Figure 2B illustrates the response of the optical sensor to the Ara h 1 standard solution at a variety of specific reaction times. In this case, the saturation time was considered to be five minutes. The standard curves for gluten and Ara h 1 were determined to be the 3-minute and 5-minute curves,

respectively, while using the biosensor that was built specifically for the purpose. A value of 0.983 was discovered for the R2 coefficient in the linear response zone between 6.25 ng/mL and 50 ng/mL for gluten, and 0.943 was discovered for the R2 coefficient in the linear response region between 16 ng/mL and 1000 ng/mL for Ara h 1. This information is presented in Figure 4C and 4D.

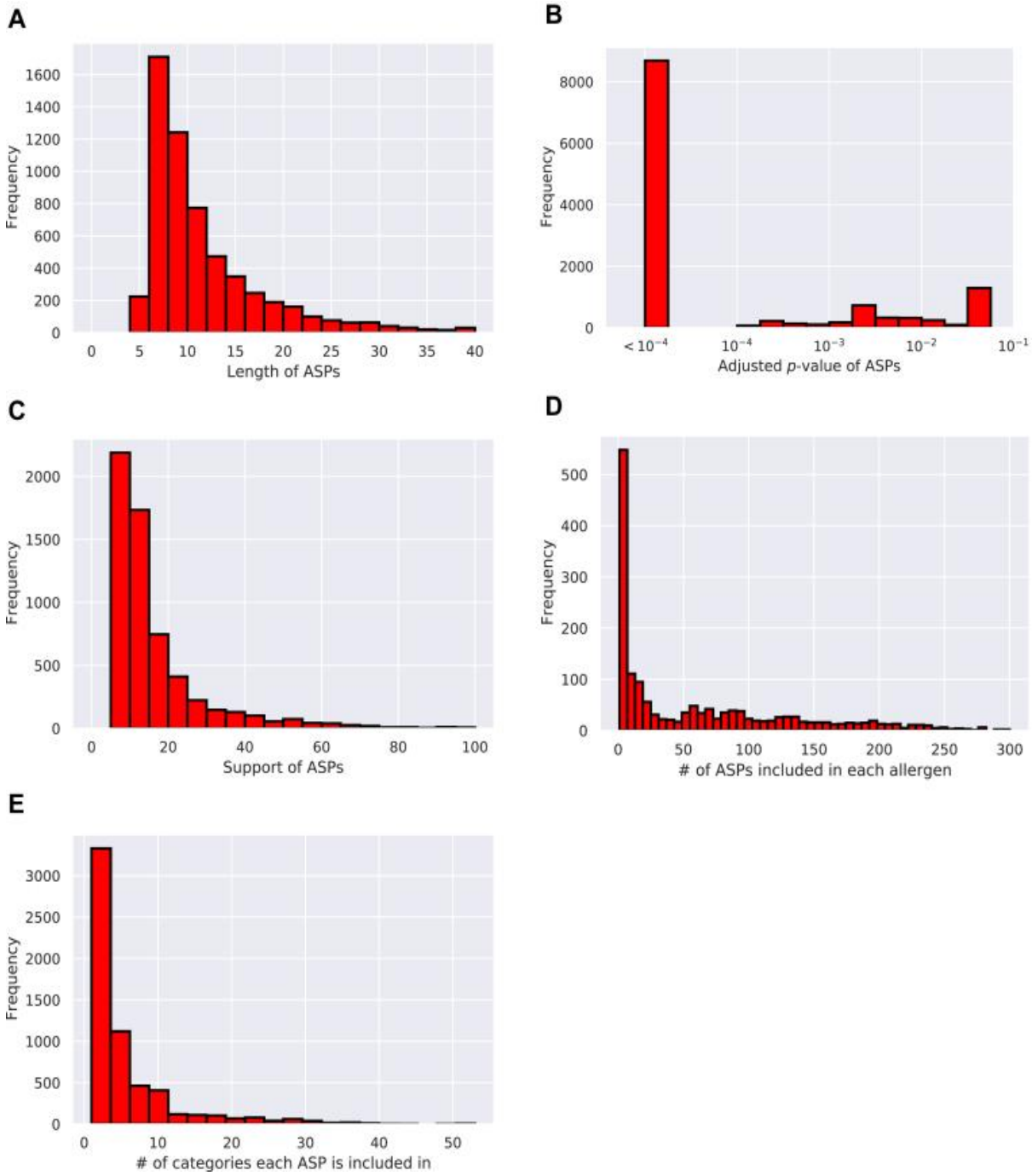


Figure 5 The statistical features of the proof-of-concept dataset's allergen-specific patterns

The ASPs found in the Proof-of-concept dataset are catalogued in Data S4. With $\alpha = 0.01$ and 0.05 as the statistical significance levels, a total of 5064 and 5994 ASPs, respectively, were identified. As shown in Figure 5 (A–C), the detected ASPs' length distributions, modified p-value distributions, and support distributions are as follows. The distributions of the number of allergenic proteins' ASPs are displayed in Figure 5D. The distribution of the number of biological categories to which each ASP belongs is shown in Figure 4E.

5. Conclusions

The majority of cases of food allergies occur in youngsters, however anybody can develop them. Avoiding foods that trigger allergic reactions is the best way to keep yourself safe, but doing so isn't easy or obvious. Even though significant allergies must be listed on food labels, cross-contamination can still happen when food is being made or prepared. When looking for novel allergens or families of allergenic proteins, mass spectrometry is a powerful method for studying the full food proteome. The amount of allergenic protein in food samples can be quantified by MS using marker peptides that are carefully chosen. This allows for the assessment of the severity of allergen contamination. Plus, MS can help with food authenticity by identifying instances of food fraud, adulteration, and undeclared allergies. For people who suffer from food allergies, MS is a potent instrument for helping to ensure that foods are safe to eat. Understanding and potentially predicting the effects of specific epitopes in new foods would be a significant hurdle in effectively utilizing MS data and bioinformatics techniques for allergy detection.

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