

The Relationship between the Causative Allergens of Allergic Diseases and Environments in Korea Over a 8-Year-Period: Based on Skin Prick Test from 2006 to 2015

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Background and Objectives: The present study evaluated the results of skin prick test using 55 allergens at 20 centers in the Republic of Korea in 2006, 2010, and 2014–2015. The aim was to assess changes in the positive rate of allergens according to temporal, regional, and environmental factors.

Materials and Method: In total, 20 hospitals were selected based on the population distribution in the Republic of Korea. A skin prick test panel comprising 55 aeroallergens was distributed to 18 hospitals for this prospective study. The 2006 and 2010 skin prick test results were collected and analyzed retrospectively from 20 hospitals, while the 2014/2015 skin prick test results (from June 2014 to May 2015) were collected prospectively from 18 hospitals.

Results: A total of 14,897 SPT test results were analyzed: 4,319 in 2006, 7,431 in 2010, and 1,852 in 2014/2015. The overall rate of skin prick test positivity to more than two allergens was significantly higher in males than females. The positive rates of alder pollens and birch, oak and ragweed pollen positivity were increased in older patients. Several positive rates were increased

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according to the temperature in spring. The positive rates for beech pollen, birch pollen, hazel pollen, oak pollen, *Tyrophagus putrescentiae*, mugwort, cat, *Acarus siro*, *Lepidoglyphus destructor* and *Tyrophagus putrescentiae* were significantly increased, while those of Cult rye pollen and dandelion were significantly decreased over the three test periods. The overall positive rate for allergens in Jeju province varied significantly from Seoul and other cities.

Conclusion: Change in the positive rate of multiple aeroallergens was evaluated in the Republic of Korea over time. Our findings can be used to recommend aeroallergens suitable for inclusion in skin prick test panels in the Republic of Korea and will facilitate further investigation of changes in the patterns of allergic diseases.

KEY WORDS: Skin prick test · Aeroallergen.

INTRODUCTION

As a result of an increase in the prevalence of allergic diseases (ADs), the associated medical costs have increased,¹⁻³⁾ Therefore many governments and medical associations have been interested in the diagnosis and management of ADs.⁴⁻⁷⁾ Up to date, many nations' living environments have been urbanized and westernized, and global climate has been greatly changing. Consequently, the kinds of the present allergens, which cause Ads, may not be similar to those of allergens of the past; Genetic, regional, and environmental factors can influence the kinds of allergens to cause ADs and the pattern of allergen positive rate.⁸⁻¹¹⁾ Environmental factors, such as changes in climate and air pollution levels, might affect the prevalence of ADs, as shown in a different pattern of allergen sensitization between developed and undeveloped regions.¹²⁾¹³⁾ Because of such reasons, the allergens of skin prick test (SPT) panels should be differently selected based on both regional and environmental factors.¹⁴⁾ Periodic re-evaluations reflecting the current state of causative allergens are important for the diagnosis and effective management of allergic rhinitis (AR). Previous epidemiological studies from different areas have reported the different frequencies and patterns of each allergen's sensitization, and so allergens suggested to be included in SPT panels vary according to the studying areas.⁶⁾¹⁵⁻¹⁷⁾ The fifth Korea National Health and Nutrition Examination Survey (KNHANES) of the general Korean population reported an increase in the prevalence of AR with limited number of allergens (n=12). However, there is no epidemiological study with SPTs in the ROK which has evaluated the changes in allergen sensitization with the course of time.

The aims of this study were to collect and analyze population-based allergen data from 20 centers in 16 regions of the ROK at 3 time points during a 8 year-period, suggesting the most possible aeroallergens in the ROK, evaluate the

change of positive rate of allergens, and to give a basic data for further studies.

MATERIALS AND METHODS

Participants

A prospective study was conducted in the ROK from May 2014 to May 2015 with patients who visited the Otorhinolaryngology-Head and neck surgery (OL-HNS) departments of 18 hospitals in Republic of Korea (ROK) and were suspected to have a history of AD, complained of AR symptoms, and underwent SPTs for diagnosis of AR. Retrospective SPT data obtained from two 1-year periods (January to December, 2006 and 2010) were collected from OL-HNS departments of 20 hospitals in (ROK). A total of 14,897 patients (8,720 males and 6,177 females) participated in this population-based epidemiologic study. The demographic characteristics of the study population are shown in Table 1.

Study design and patients

Total 20 OL-HNS departments in ROK participated in this pros- or retrospective study. Following review and approval of the study protocol by the Ethics Committee for Clinical Studies of each center, retrospective data collections and prospective SPTs were performed by the OL-HNS departments of 20 (retrospective) and 18 (prospective) hospitals. The prospective study was performed between June 2014 to May 2015. After taking a detailed medical and medication history, we complete performed otolaryngological examinations. All patients with suspicious AR symptoms and history were invited to participate in this study. Only patients or the parents who provided written informed consent were enrolled in the study. The 2006 and 2010 SPT results of each center were collected for the retrospective study.

Table 1. Demographic characteristics of the study population

	Total	2006	2010	2014+2015	p-value
Subjects, number	14897	4319	7431	3147	
Sex					
Male	8,720 (58.54)	2,544 (58.90)	4,324 (58.19)	1,852 (58.85)	0.6921
Female	6,177 (41.46)	1,775 (41.10)	3,107 (41.81)	1,295 (41.15)	
Age, years					
Mean±SD	36.38±18.29	33.25±17.82	37.55±18.41	37.94±18.11	<0.0001*†
Median (min-max)	35.00 (2.00–93.00)	32.00 (2.00–90.00)	36.00 (3.00–93.00)	36.00 (3.00–82.00)	
<20	3,385 (22.72)	1,240 (28.71)	1,548 (20.83)	597 (18.97)	<0.0001
≥20–<40	5,164 (34.66)	1,490 (34.50)	2,554 (34.37)	1,120 (35.59)	
≥40–59	4,499 (30.20)	1,218 (28.20)	2,288 (30.79)	993 (31.55)	
≥60	1,849 (12.41)	371 (8.59)	1,041 (14.01)	437 (13.89)	

Data are presented as n (%) or means ±SD. Statistical analysis was carried out using a chi-square test or ANOVA (followed by post hoc Bonferroni correction). Significant difference between *: 2006 vs. 2010 and † : 2006 vs. 2014+2015 by post hoc analysis

Skin prick test

55 allergens were chosen according to previous reports, test duration, laboratory capacity, and test efficiency. 55 allergens are the maximum number of allergens in a SPT covered by the Korean healthcare service. In the prospective study performed from June 2014 to May 2015, all participants underwent SPTs using panels comprising 55 allergen extracts. A positive response was defined as >2+ positive to the allergen (mean wheal diameter 50% of the positive control). Histamine dihydrochloride (10 mg/mL) was used as a positive control and diluent as a negative control, and reactions were interpreted 15 min after application.

Extracts and reagents

Although the aeroallergens tested at each center and the suppliers of allergy test panels varied between 2006 and 2010, the major aeroallergens in the test panels were similar. However, the pollen aeroallergens were different according to supplier and time. From July 2014 to June 2015, the prospective SPTs were performed using the following 55 aeroallergens: 1) trees: maple, locust black, birch, beech, oak, alder, ash, barley, hazel, elder, poplar, plane, elm, willow; 2) grasses: velvet grass, Bermuda, orchard, rye grass, timothy grass, wheat, orache pollen, and Russian thistle; 3) weeds: mugwort, nettle, dandelion, ragweed, rye, and Engl. Plantain; 4) animals: hamster, rabbit, cat, guinea pig, horse, rat, and dog hair; 5) fungi: *Aspergillus fumigatus*, *Botrytis cinerea*, *Candida albicans*, *Cladosporium herbarum*, *Fusarium moniliforme*, *Mucor mucedo*, *Penicillium notatum*, and *Rhizopus nigricans*; 6) mites: *Dermatophagoides farina*, *Dermatophagoides pteronyssinus*, *Acarus siro*, *Lepidogly-*

phus, and *Tyrophagus*; and 7) insects and others: cockroach (G), cockroach (A), and latex (Supplementary Table 1 in the online-only Data Supplement). The allergen panel supplier (Allergopharma, Reinbek, Germany) was selected because it was the most commonly used among the 20 participating OL-HNS departments. A single supplier was used to reduce the probability of errors.

Statistical analysis

We compared gender and age-group between the 3 test-years groups using chi-square test. To compare the age of the 3 test-years groups, we performed one-way ANOVA, followed by post hoc Bonferroni's correction. Differences between age-groups and allergens positive rate were evaluated using the chi-square test. We performed the Cochran-Armitage trend test to compare allergens positive rate among the spring temperature tertile groups or 3 test-years groups. A trend in the prevalence of SPT-positive to two or more allergens over the 3 test-year period was evaluated using Cochran-Armitage trend test. All statistical analyses were performed using the software package SAS Enterprise Guide 4 (SAS Institute, Inc., Cary, North Carolina), and a two-sided $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Subjects

The SPT data of a total of 14,897 subjects (4,319 in 2006, 7431 in 2010, 3,147 in 2014 + 2015 respectively) from 20 centers in the ROK were analyzed. The demographic characteristics of the study population are shown in Table 1.

The 3 test-years differed significantly with regard to age but not to gender. There were the rank differences of allergens between age groups (Supplementary Table 1 in the online-only Data Supplement). The positive rates of Alder pollens and Birch, oak and ragweed pollen were increased in older patients through years but decreased in young patients. The positive rates of Df. And Dp were similar level through 3 years in each age groups. The positive rates of *Acarus siro* and *Lepidoglyphus destructor* were increased dramatically in all age groups through years. The proportion of subjects who were SPT-positive for AR was 51.42% in

2006, 48.12% in 2010, and 56.59% in 2014+2015, and the proportion of subjects who were SPT-positive for two or more allergens was 42.63% in 2006, 40.02% in 2010, and 47.60% in 2014. We analyzed the temperature according to the season. We made three groups (25,50,75th percentile) according to the temperature range in each seasons (Table 2). We divided patients into 3 groups according to temperature as each season. And several pollens positive rates were increased according to the temperature in spring (Table 3). The positive rate of Alder, Beech and Birch pollens was increased in high temperature ($> 13.6^{\circ}\text{C}$) through 2010

Table 2. Summary of mean temperatures in each season

	Spring	Summer	Fall	Winter
1st tertile				
N	1,190	1,261	1,255	1,297
Mean (sd)	5.25 (1.21)	22.71 (0.87)	7.70 (1.42)	-2.60 (1.56)
Median (range)	5.10 (-3.20-7.90)	23.10 (17.20-23.80)	8.40 (-4.20-10.60)	-2.60 (-7.60--0.90)
2nd tertile				
N	1,174	1,178	1,229	1,245
Mean (sd)	10.68 (1.55)	25.23 (0.59)	15.16 (1.87)	0.13 (0.52)
Median (range)	10.00 (8.00-13.50)	25.20 (23.90-26.00)	15.10 (10.80-17.90)	0.00 (-0.80-1.20)
3rd tertile				
N	1,182	1,332	1,285	1,269
Mean (sd)	17.72 (1.20)	26.91 (0.75)	21.40 (1.31)	2.59 (1.56)
Median (range)	17.35 (13.60-20.70)	26.70 (26.10-29.30)	21.60 (18.20-24.90)	2.10 (1.30-26.00)

Table 3. Comparison of allergens positive rate according to temperature tertile

	Spring			p value for trend
	1st tertile ($< 8^{\circ}\text{C}$)	2nd tertile ($\geq 8 - < 13.6$)	3rd tertile (≥ 13.6)	
Pollen				
Alder pollens				
2006	13/331 (3.93)	6/298 (2.01)	16/308 (5.19)	0.4206
2010	31/662 (4.68)	37/646 (5.73)	51/610 (8.36)	0.0069
2014+2015	5/197 (2.54)	12/230 (5.22)	34/264 (12.88)	< 0.0001
p value for trend	0.5812	0.0576	0.0011	
Overall	49/1190 (4.12)	55/1174 (4.68)	101/1182 (8.54)	< 0.0001
Beech pollen				
2006	8/289 (2.77)	8/269 (2.97)	15/275 (5.45)	0.0942
2010	30/650 (4.62)	26/635 (4.09)	46/605 (7.60)	0.0213
2014+2015	7/197 (3.55)	15/230 (6.52)	31/264 (11.74)	0.0009
p value for trend	0.5354	0.0555	0.0075	
Overall	45/1136 (3.96)	49/1134 (4.32)	92/1144 (8.04)	< 0.0001
Birch pollen				
2006	13/331 (3.93)	6/298 (2.01)	20/308 (6.49)	0.1148
2010	37/662 (5.59)	40/646 (6.19)	57/610 (9.34)	0.0093
2014+2015	9/197 (4.57)	16/230 (6.96)	37/264 (14.02)	0.0003
p value for trend	0.5907	0.0079	0.0026	
Overall	59/1190 (4.96)	62/1174 (5.28)	114/1182 (9.64)	< 0.0001

Table 4. Distribution of subjects who are SPT-positive to two or more allergens

	Total	2006	2010	2014+2015	p-value
Subjects, number	14,897	4,319	7,431	3,147	
Number of positive allergens					
1	1,265 (8.49)	380 (8.80)	602 (8.10)	283 (8.99)	0.9161
≥2	6,313 (42.38)	1,841 (42.63)	2,974 (40.02)	1,498 (47.60)	0.0003

Data are numbers (%). P-values were calculated using the Cochran-Armitage trend test

Table 5. Top 15 aeroallergens in 2006, 2010, and 2014

Rank	2006	2010	2014–2015
1	D_pteronysinus (37.07)	D_farinae (32.4)	D_farinae (37.89)
2	D_farinae (34.96)	D_pteronysinus (32.4)	D_pteronysinus (36.58)
3	Mugwort (8.34)	Cat (8.38)	Mugwort (10.99)
4	Cat (6.46)	Tyrophagus (7.74)	Birch (7.83)
5	Oak (5.67)	Birch (7.51)	Tyrophagus (7.83)
6	Dog hair (5.35)	Mugwort (7.3)	Cat (7.50)
7	Alder (5.23)	Oak (6.89)	Acarus siro (6.91)
8	Cockroach (5.09)	Walnut (6.84)	Oak (6.84)
9	Ragweed (4.75)	Dog hair (6.81)	Hazel (6.45)
10	Birch (4.51)	Cockroach (6.72)	Beech (6.18)
11	Dandelion (4.47)	Alder (6.67)	Cockroach (G) (5.92)
12	Beech (4.28)	Beech (5.53)	Alder (5.66)
13	Hazel (4.03)	Ragweed (5.48)	Ragweed (5.00)
14	Tyrophagus (3.92)	Hazel (5.24)	Leidoglyphus (4.8)
15	Willow (2.96)	Acarus siro (4.17)	Dog hair (4.18)

Table 6. SPT positivity according to gender

	Male	Female	p-value*
Subjects, number			
Positive allergens=1			
2006 (n=4319)	236 (9.28)	144 (8.11)	0.1839
2010 (n=7431)	367 (8.49)	235 (7.56)	0.1499
2014+2015 (n=3147)	164 (8.86)	119 (9.19)	0.7473
Overall (n=14897)	767 (8.80)	498 (8.06)	0.1135
p for trend [†]	0.5508	0.3609	
Positive allergens ≥2			
2006 (n=4319)	1,168 (45.91)	673 (37.92)	<0.0001
2010 (n=7431)	1,864 (43.11)	1,110 (35.73)	<0.0001
2014+2015 (n=3147)	933 (50.38)	565 (43.63)	0.0002
Overall (n=14897)	3,965 (45.47)	2,348 (38.01)	<0.0001
p for trend [†]	0.0152	0.0053	

Data are numbers (%). p-values were calculated using the *: chi-square test and † : Cochran-Armitage trend test

and 2014+2015 years. The proportions of subjects who were SPT-positive to only one allergen remained stable from 2006 to 2015, whereas those of subjects who were SPT-positive to more than two allergens changed significantly (Table 4). The top 15 rank of allergens were selected through process as follows; Though the positive value

of some pollens was high in one of test years, they were excluded in top 15 allergens because they were not tested by all OL-HNSs in all test years. The positive rates of Beech pollen, Birch pollen, Hazel pollen, Oak pollen, Tyrophagus putrescentiae, Mugwort, and cat, Acarus siro, Lepidoglyphus destructor and Tyrophagus putrescentiae increased significantly but those of Cult rye pollen, and Dandelion decreased significantly through 3 test-years. D. farina and D. pteronyssinus preserved their ranking and positive rates through years (Table 5). The overall rate of SPT positive to more than two allergens was significantly higher in males than females in all test-years (Table 6). We compared the positive rates of allergens according to gender group (Supplementary Table 2 in the online-only Data Supplement). Although the trend of positive rate is similar between male and female in indoor allergen like D. farina, D. pteronyssinus, and so on, the positive rate to various pollen significantly changed mainly in male; however the positive rates to cat increased significantly in only female. We compared overall positive rates according to regions of ROK. The positive rate of Jeju province was different compared to Seoul and others. Jeju province is an big island away from

Korean peninsula. Although the overall positive rate of Seoul and others was similar among 3 test-years, the overall positive rate of allergen in Jeju province is different compared Seoul and other cities significantly. For example, 1) Positive rates of Alder, Birch and Hazel pollen was increased significantly in Seoul and other cities except Jeju province, 2) to Mugwort only in Seoul, 3) to Cat in Seoul, other cities and Jeju province, 4) to *Acarus siro* in Seoul and other areas. Interestingly, the positive rates to dog hair, *D. farina* and *D. pteronyssinus* much increased in Jeju province compared to Seoul and other areas (Supplementary Table 3 in the online-only Data Supplement).

DISCUSSION

In present study the positive rates of 55 allergens in the ROK were evaluated according to age, gender, region, and time in 3 test-years during a 8 year-period. Although the pattern of allergen sensitization in allergic disease might be too subtle over the short term to be identified, certain changes of pattern might be identified over the long term. Therefore, it can be said that periodic re-evaluation for allergen disease is important to find such subtle change with the course of time. Previous epidemiologic studies in the Korean population reported that house dust mites (HDMs) were the most common allergens. However, these studies had the following limitations: 1) subjects were representative of only certain regions and age groups, 2) the validity of the allergens used was not confirmed, 3) the allergen panels used in those studies could not be regarded as same ones, 4) the variation in allergens over time was not determined.¹⁸⁻²⁰⁾ Another issue is aging, which is associated with modifications of the immune system. Previous studies showed that the rate of SPT positive rate to more than two aeroallergens increased in 20–59 years and decreased with under 20 years and over 60 years.²¹⁾²²⁾ In another papers, the mean eczema area and severity index score of atopy were calculated, and adult patients were found to have higher severity than the other age groups.²³⁾ A cross-sectional study in Spain showed the most common aeroallergen was pollen, though House dust mites are usually reported as the most common allergens in many other studies, which might reflect different geographical and environmental factors.²⁴⁾ In another studies, thunderstorms occurring during the pollen season have been shown to induce severe asthma attacks in pollinosis patients.²⁵⁻²⁷⁾ Therefore,

it is important that each allergen sensitization must be evaluated considering many factors such as age, gender, area, etc. The proportions of subjects who were SPT-positive to only one allergen remained stable from 2006 to 2014, whereas multiple sensitization to more than two allergens changed significantly. Outdoor air pollution, climate and other factors like life-style may also play a role in the development of these conditions. Previous studies have reported that the prevalence rates of asthma and allergic rhinitis have increased over the last two to three decades.²⁸⁾

Among 55 allergens tested in this study, though Der. p and Der. f were top 1 or 2 allergens all through the years, *Acarus siro* increased over time but Alder decreased. These changes might reflect the changes of living environments, global warming, ecosystem, plant distribution et al.²⁹⁾ *Dermatophagoides pteronyssinus*, Cockroach were statistically different according to gender in all test years. Although age-related difference of our result was similar to that of a previous meta-analysis for allergic sensitization to house dust mites, sex-specific difference of AD in that meta-analysis was contrary to our results, showing that the prevalence of allergic diseases in childhood shows a male predominance but switches toward a female predominance in adolescents and adults.³⁰⁾ However, our results showed that the overall rates of SPT positive to more than two allergens and to certain allergens like house dust mites were also significantly higher in males than females in all test-years, which need further evaluations. Von Mutius et al. reported that the number of children with hay fever and atopic sensitization in the former East Germany increased between 1991–1992 and 1995–1996, possibly due to the reunification of Germany when induced greater exposure to a Western lifestyle.³¹⁾ The ROK is one of the most rapidly developing and westernizing nations, which might have reduced exposures to infectious agents in the young age, which might cause an immune deviation from a Th2 to a Th1 response and increase the prevalence of Th2-mediated diseases like atopy, AR, asthma, etc. Therefore, information on the temporal and regional characteristics and changes in allergens is important, and so periodic re-evaluation must be needed. Interestingly, the overall rates of positive rate and certain allergens positive rate tended to be low in 2010. In detail, the positive rate to Dandelion pollen was decreased in 2010 years spring than other years spring significantly. It is possible to assume that it might be caused by the change of environment, because the temperature

was lower and, precipitation and humidification were much more or higher in the spring of 2010 than other 2 test-years. all these environment factors might affect the positive rate of allergen differently in each year.

During 8 year-period, the mean temperature of 2 test-years (2006 and 2014+2015) was higher than that of 2010. For example, allergen positive rate of Alder, Beech and Birch pollens were increased. Because the pollen allergens was increased according to increased temperature of spring significantly. These relation between the positive rate of certain allergens and climate change might be reinforced by global climate change in future, which need further periodic re-evaluations. Considering the spring of ROK gets hotter, it can be predicted that the allergen positive rates to some pollens tend to be lower and to others higher. Based on our results, the positive rate of some allergens that adapt to the warmer climate will increase much higher and others will decrease, which will have to be reflected in SPT in future.

Recently, several papers have suggested common allergens appropriate to their study areas. The National Health and Nutrition Examination Survey (NHANES) provides comprehensive information regarding IgE-mediated sensitization in the general US population. The 2005–2006 NHANES reported that grass-, dust mite-, and ragweed allergen-specific antibodies were the most frequently found antibodies in the US population, as noted by Salo Pi et al.³²⁾ The Global Allergy and Asthma European Network recommended a common standardized panel of allergens for European patients, as noted by Bousquet et al.³³⁾ The revised Japanese allergic rhinitis guidelines recommended different allergic diagnostic for different regions of Japan, as noted by Okubo et al.³⁴⁾ However, in the ROK, only a few aeroallergens have been analyzed with SPT in previous studies, as noted by Park et al.²⁰⁾ Rhee et al.³⁵⁾ Kim et al.³⁶⁾, and Park et al.³⁷⁾ Assessment of allergen-specific IgEs with SPT in the nationwide KNHANES from 2007 to 2009 involved only the following 12 allergens, in which fungi or pollens were not included: *D. farinae*, *D. pteromyssinus*, cockroaches, Alternaria, cat dander, dog dander, oak, birch, grass, mugwort, ragweed, and Japanese hops, as noted by Park et al.²⁰⁾ Therefore, this study is the first nationwide study in the ROK with larger numbers of allergens (n=55) using SPTs with periodic evaluation of SPT results during a 8 year-period. However, unfortunately, every clinic or doctor may not use 55-aeroallergens SPT panel because it may take more times, cost higher, and cause someone inconvenience, especially

children. Therefore, in clinical field, a simple version of SPT with less allergens than 55 may be needed and, based on our results, 15 common allergens in ROK could also be suggested. Finally, it should be noted that this study had the following limitations. First, Although the same allergy panel was used in 2014–2015 and the core panel of airborne allergens was similar in all three test years, the allergy panels used in 2006 and 2010 differed slightly among the 20 participating hospitals. Second, the rate of SPT positive rate was lower 2010 compared to in 2004 and 2014–2015, which might be explained with the differences of climate in 2010. Further re-evaluations that take into consideration climate, lifestyle, and other environmental factors are required. Third, the study population might not be accurate representative of the general population of the ROK. Fourth, many participant hospitals were tertiary-care centers, which might have resulted in referral bias.

CONCLUSION

In summary, positive rate to allergens had changed with time, which may explain why periodic re-evaluations of test aeroallergens in SPT are required and facilitate further population-based studies of positive rate to allergens. The change of factors to affect aeroallergen positive rate, like age, gender, climate change, urbanization, and so on must be considered with times.

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Author Contributions

Conceived and designed the manuscript: CSP, JHC, SWK. Analyzed the data: JHK, JKK, CHK, HJK, HYK, KSR, HJR. Contributed reagents/materials/analysis tools: JHL, SKK, KSK, STK, YDK, DJP, SHS, SCL, JHL, HML. Wrote the paper: HGL, YHK, BYK, CSP.

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