Interleukin-8 is an inflammatory cytokine that promotes angiogenesis and increases capillary leakage. The *IL-8* rs4073 and *VEGF* rs699947 are promoter polymorphisms connected to transcriptional activity of the genes.[3,4] The A allele in *IL-8* rs4073 has been associated with higher levels of circulating and secreted IL-8, and a poorer response to bevacizumab in ovarian cancer.[3] The C allele in *VEGF* rs699947 has been associated with higher VEGF production.[4] In our patients, the C allele was associated with somewhat less CS gain. However, the A allele was more strongly associated with persisting macular fluid and more frequent reinjections. The reason for the possible dichotomous effect of this *VEGF* polymorphism on the anatomic and functional outcomes is unclear.

Complement activity stimulates IL-8 production in endothelial and retinal pigment epithelial cells.[5] The combination of a deficient regulation of alternative complement pathway and greater IL-8 production may lead to IL-8 stimulated angiogenesis and capillary leakage. The cumulative effect of the risk alleles suggests that IL-8 signaling may serve as a compensatory proangiogenic mechanism during anti-VEGF treatment. An explanation for the less producing VEGF genotype to require more injections could be that it may make such potential compensatory mechanisms more active.

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Presented at: the Meeting of the European Association for Vision and Eye Research, Nice, France, September 18-21, 2013.

Financial Disclosures: Asta Hautamäki: Compensation of travel/accommodation/meeting expenses − Novartis, Bayer; Sanna Seitsonen: Compensation of travel/accommodation/meeting expenses − Novartis; Ilkka Immonen: Consultant − Novartis and Bayer − Compensation of travel/accommodation/meeting expenses − Novartis and Bayer.

Supported by grants from The Eye Foundation, Helsinki, Finland, The Eye and Tissue Bank Foundation, Helsinki, Finland, The Evald and Hilda Nissi Foundation, Helsinki, Finland, and Mary and Georg C. Ehrnrooth Foundation, Helsinki, Finland. The funding organizations had no role in the design or conduct of this research.

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Predictors of Matching in Ophthalmology Residency for International Medical Graduates

International medical graduates (IMGs) comprise approximately 25% of the United States' (US) physician workforce and play a vital role in US healthcare by serving in medically underserved areas and by increasing diversity among physicians.[1] However, it has become increasingly difficult for IMGs to train in the US. In ophthalmology, IMG applications represent a large number of the total application pool, but only approximately 5% of the total matched positions.[2] Given the competition among IMGs for US residency positions and the opaque nature of the selection process, factors that influence matching are important for IMG applicants and their mentors. It is our hope that quantifying the predictors of successfully matching will assist in guiding applicants who hope to train in a US ophthalmology program.

To investigate this question, we used deidentified data collected by the San Francisco Ophthalmology Residency Match from 2003 to 2008. All successful IMG applications (i.e., successful matching into a US ophthalmology residency) from 2003 to 2008 served as cases, and a random sample of unsuccessful applications from the same time period served as controls. An author (T.H.D.) blinded to the match outcome coded redacted and deidentified information from the applications. Institutional board exemption was obtained from the University of California, San Francisco Committee on Human Research. We conducted univariate analyses using logistic regression to determine the variables associated with successfully matching into an ophthalmology program and included all variables with $P < 0.1$ into a multivariate model (Tables 1 and 2, available at www.aaojournal.org). We selected the final multivariate model using a backward-stepwise algorithm until all variables had a $P < 0.05$. We used a modified sandwich variance estimator for cluster-correlated data to account for within-applicant correlation because some applications were submitted by the same applicant but in different years of the study.[3] Statistical analyses were performed using Stata 12.1 statistical software (STATA Corp, College Station, TX).

In multivariate analysis, having 3 letters of recommendation from US ophthalmologists increased an IMG's odds of matching

6-fold (odds ratio [OR], 6.20; 95% confidence interval [CI], 2.54−15.16). Higher US Medical Licensing Examination (USMLE) Step 1 score (OR, 3.22; 95% CI, 1.38−7.49), academic awards (OR, 1.12; 95% CI, 1.03−1.22), high-impact journal publications (OR, 2.99; 95% CI, 1.51−5.72), and US research experience (OR, 2.95; 95% CI, 1.31−6.67) were also associated with increased odds of matching. Postgraduate clinical training, including years spent as surgical interns in the US, was associated with 4-fold reduced odds of matching (OR for ≥3 years, 0.26; 95% CI, 0.12−.0.58; Table 3, available at www.aaojournal.org).

The strongest predictor of matching was having 3 letters of recommendation written by US ophthalmologists, which conferred 6-fold adjusted odds of matching. Although our study was not designed to determine why letters from US ophthalmologists were important, we hypothesize that they could have been more highly valued than non-US letters for multiple reasons, including (1) residency committees may feel more comfortable giving credence to letters written by US physicians with whom they had professional relationships; (2) the letters may represent the applicant's ability to develop a productive mentoring relationship with a US physician; (3) the letters represent the approval of a physician who trained in a US program; (4) letters from non-US physicians who are not familiar with the US match process may not adequately comment on valued applicant characteristics; and (5) cultural differences in the expected level of advocacy routinely seen for US applicants. Also, letters of support from US ophthalmologists are not likely a simple independent variable, but rather may reflect several complex factors, including work ethic, collaboration, and interpersonal skills.

This study also quantified the importance of research for IMGs applying in a surgical specialty such as ophthalmology. In our study, publishing in high-impact journals and having US research experience were both associated with 3-fold adjusted odds of matching, similar to having a high USMLE step 1 score. Additionally, having ≥1 high-impact publication was associated with 3-fold adjusted odds of matching.

In contrast with previous research regarding postgraduate clinical experience, our study showed that postgraduate clinical experiences in the US such as a surgical internship year reduced an IMG's odds of matching 4-fold. We defined "postgraduate clinical experience" as formal, accredited clinical training in internship, residency, or fellowship. Conversely, time informally spent in clinic with research mentors was not included in this variable. Previously, a survey of >100 internal medicine residency program directors showed that they believed postgraduate clinical experience in the US was 1 of the top 4 predictors of IMG success in residency.[4] Although our study was not designed to determine the causes of this effect, the implication of this finding may suggest that IMG applicants should focus on gaining research experience rather than clinical experience to improve their odds of matching into ophthalmology.

The results from this study confirm the findings of prior work regarding the importance of USMLE scores for applicants applying to US residency programs. For both USMLE steps 1 and 2, those applicants who scored in the highest quartile had a >2-fold odds of matching compared with those who scored in the lowest quartile. Previous research regarding US medical students applying for residency found that higher marks in cognitive domains such as higher USMLE Step 1 score and Alpha Omega Alpha membership were significantly associated with matching.[5]

The strengths of this study include the large sample size, as well as the inclusion of a wide variety of predictors (e.g., not only USMLE scores, but also research experience, clinical experience, publications, and letters of recommendation). The study is limited in that some qualities potentially valued by selection committees—such as interpersonal communication skills or professionalism—could not be directly measured in this dataset. In addition, we were unable to analyze the role of the applicant's rank in their foreign medical school graduating class because of variability in how this was reported.

To the best of our knowledge, this study represents the first attempt to investigate the factors associated with a successful ophthalmology residency application for IMG applicants. The 3 most influential predictors of successful matching were 3 support letters from US ophthalmologists, highest quartile USMLE scores, and ≥2 high-impact publications; additional postgraduate clinical training reduced the likelihood of matching. These data suggest that developing relationships and conducting research with US physicians would increase the likelihood of matching for IMGs seeking ophthalmology training in the US.

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Table 1. Test Scores, Academic Achievement, and Clinical Training Experience of Successful and Unsuccessful Applications of International Medical Graduates Applying for US Ophthalmology Residency

Characteristic	Unsuccessful, n (%) or Mean ± SD	Successful, n (%) or Mean (SD)	Unadjusted OR (95% CI)	*P* Value
USMLE step 1 score quartile				0.0019
<200	48/164 (29.3)	38/167 (22.8)	Ref	
200–215	49/164 (29.9)	33/167 (19.8)	0.85 (0.47–1.54)	
216–235	41/164 (25)	41/167 (24.6)	1.26 (0.69–2.32)	
≥236	26/164 (15.9)	55/167 (32.9)	2.7 (1.44–4.94)	
USMLE step 2 score quartile				
<196	36/139 (25.9)	39/150 (26)	Ref	0.0006
196–216	47/139 (33.8)	25/150 (16.7)	0.49 (0.25–0.95)	
217–233	34/139 (24.5)	37/150 (24.7)	1.00 (0.52–1.94)	
≥234	22/139 (15.8)	49/150 (32.7)	2.06 (1.04–4.08)	
Academic awards (per 1-increase)	3.8±2.9	4.9±3.2	1.13 (1.05–1.22)	0.002
Nonacademic awards	0.22±1.05	0.32±1.02	1.09 (0.86–1.39)	0.45
Advanced degree	24/170 (14.1)	29/170 (17.1)	1.25 (0.70–2.23, 0.45)	0.45
Postgraduate clinical training				0.065
None	34/170 (20.0)	52/170 (30.6)	Ref	
In US	18/170 (10.6)	15/170 (8.8)	0.54 (0.24–1.23)	
Outside US	74/170 (43.5)	54/170 (31.8)	0.48 (0.27–0.84)	
Both in and outside US	44/170 (25.9)	49/170 (28.8)	0.22 (0.40–1.31)	
Years US or international clinical postgraduate training				0.012
0	31/170 (18.2)	55/170 (32.4)	Ref	
1–2	48/170 (28.2)	40/170 (23.5)	0.47 (0.26–0.86)	
≥3	91/170 (53.5)	75/170 (44.1)	0.46 (0.27–0.79)	
Postgraduate US or international ophthalmology training	91/170 (53.5)	82/170 (48.2)	0.81 (0.53–1.23)	0.32
US clinical electives	72/170 (42.4)	95/170 (55.9)	1.72 (1.12–2.64)	0.012
Fellowship in US (clinical or research)	76/170 (44.7)	128/170 (75.3)	3.77 (2.38–5.98)	<0.001

CI = confidence interval; OR = odds ratio; SD = standard deviation.

Table 2. Research Experience and Characteristics of Letters of Recommendation of International Medical Graduates Applying for US Ophthalmology Residency

Characteristic	Unsuccessful, n (%)	Successful, n (%)	Unadjusted OR (95% CI)	*P* Value
Any US research training	107 (62.9)	155 (91.2)	6.08 (3.29–11.26)	<0.001
Years of research postgraduate training				<0.0001
0	103/170 (60.6)	53/170 (31.2)	Ref	
1–2	42/170 (24.7)	75/170 (44.1)	3.47 (2.12–5.71)	
≥3	25/170 (14.7)	42/170 (24.7)	3.26 (1.83–5.82)	
Total publications impact factor >3				<0.0001
0	133/170 (78.2)	81/170 (47.7)	Ref	
1	18/170 (10.6)	35/170 (20.6)	3.19 (1.73–5.90)	
≥2	19/170 (11.8)	54/170 (31.76)	4.67 (2.66–8.18)	
First-author publications impact factor >3				0.0003
0	146/170 (85.9)	117/170 (68.8)	Ref	
1	15/170 (8.8)	24/170 (14.1)	2.00 (1.01–3.93)	
≥2	9/170 (5.3)	29/170 (17.1)	4.02 (1.97–8.18)	
Total publications				<0.0001
0	88/170 (51.8)	43/170 (25.3)	Ref	
1	29/170 (17.1)	22/170 (12.9)	1.55 (0.80–3.01)	
≥2	53/170 (31.2)	105/170 (61.8)	4.05 (2.51–6.56)	
Total first-author publications				<0.0001
0	113/170 (66.5)	78/170 (45.9)	Ref	
1	22/170 (12.9)	19/170 (11.2)	1.25 (0.63–2.47)	
≥2	35/170 (20.6)	73/170 (42.9)	3.02 (1.88–4.87)	
Total scholarly works				<0.0001
0	61/170 (35.9)	22/170 (12.9)	Ref	
1	18/170 (10.6)	14/170 (8.2)	2.16 (0.92–5.05)	
≥2	91/170 (53.5)	134/170 (78.8)	4.08 (2.36–7.05)	
Letter written by US author	134/170 (78.8)	162/170 (95.3)	5.44 (2.46–12.02)	<0.001
Letters written by US ophthalmologist (n)				<0.001
0	63/170 (37.1)	18/170 (10.6)	Ref	
1	40/170 (23.5)	21/170 (12.4)	1.84 (0.87–3.90)	
2	40/170 (23.5)	61/170 (35.9)	5.34 (2.74–10.38)	
3	27/170 (15.9)	70/170 (41.2)	9.07 (4.63–17.76)	
Waived right to access letter	93/169 (55)	138/169 (81.7)	3.64 (2.24–5.89)	<0.001

CI = confidence interval; OR = odds ratio; SD = standard deviation.

Table 3. Predictors of Successful International Medical Graduate Match after Multivariate Adjustment

Predictor	Adjusted OR (95% CI)	*P* Value
Letters written by US ophthalmologist		<0.0001
3	6.20 (2.54–15.16)	
2	3.98 (1.75–9.04)	
1	1.00 (0.38–2.69)	
0	Ref	
USMLE step 1 score		0.008
≥236	3.22 (1.38–7.49)	
216–235	1.80 (0.84–3.84)	
200–215	0.78 (0.38–1.59)	
<200	Ref	
Total publications impact factor >3		0.0005
≥2	2.99 (1.51–5.72)	
1	3.07 (1.45–6.51)	
0	Ref	
US research experience	2.95 (1.31–6.67)	0.009
Waived right to access letter	2.18 (1.21–3.93)	0.009
Academic awards (per 1-increase)	1.12 (1.03–1.22)	0.01
Years clinical postgraduate training		0.003
≥3	0.26 (0.12–0.58)	
1–2	0.31 (0.14–0.71)	
0	Ref	

CI = confidence interval; OR = odds ratio; SD = standard deviation.