The association between oxcarbazepine-induced maculopapular eruption and HLA-B alleles in a Northern Han Chinese population

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Abstract

Background: We investigated the association between oxcarbazepine (OXC)-induced maculopapular eruption (MPE) and HLA-B alleles in a northern Han Chinese population, and conducted an analysis of clinical risk factors for OXC-MPE.

Methods: Forty-two northern Han Chinese patients who had been treated with OXC in Changchun, China were genotyped. Among them were 14 cases with OXC-induced MPE; the remaining 28 were OXC-tolerant. The HLA-B allele frequencies of the normal control group were found in the Allele Frequency Net Database. Polymerase chain reaction-sequence specific primer (PCR-SSP) was used for HLA-B*1502 testing and direct sequencing for four-digit genotype determination.

Results: Four-digit allele sequencing showed that there was no statistically significant difference in the frequency of the HLA-B*1502 allele between the OXC-MPE and OXC-tolerant controls (3.6% versus 7.5%, OR = 0.38, 95% CI = 0.04–3.40, P = 0.65), as well as between OXC-MPE and normal controls (3.6% versus 2.4%, OR = 1.54, 95% CI = 0.20–11.73, P = 0.49). However, a significant difference in the frequency of HLA-B*3802 alleles was found between the MPE group and normal controls (10.7% versus 1.9%, OR = 6.329, 95% CI = 1.783–22.460, P = 0.018). There was no significant difference in terms of age, gender, or final OXC dose between the OXC-MPE and OXC-tolerant groups.

Conclusions: There was no significant association between OXC-MPE and HLA-B*1502 in the northern Han Chinese population in our study. Instead, HLA-B*3802 was found to be a potential risk factor for OXC-MPE.

Keywords: Mild maculopapular eruption, HLA-B* 1502, Northern Han Chinese, DNA genotyping

Background

The new antiepileptic drug (AED) oxcarbazepine (OXC) is a 10-keto analog of carbamazepine (CBZ). The clinical effectiveness of OXC is similar to that of CBZ, but with fewer adverse drug reactions (ADRs), which is attributed to their different metabolic pathways [1]. A common side effect associated with AED use is rash, and has been the leading cause of withdrawal from some AED trials [2-4]. Recently it was reported that the incidence of OXC-related skin rashes is 3-8% in Norwegian [5,6] patients.

Cutaneous adverse drug reactions (cADRs) induced by AEDs range from mild maculopapular eruption (MPE) and hypersensitivity syndrome, to the more severe Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Among these cADRs, MPE is the most common [7], and is generally considered an initial form of the other, more severe, cADRs.

The pathogenesis of AED-induced cADRs is complex—several studies have indicated that T-cell-mediated allergic reactions might be associated with them [8], but genetic susceptibility and the exact pathogenesis are not fully understood and require further investigation. Recent studies have reported that the HLA-B*1502 allele is strongly associated with a dramatically increased risk of CBZ-induced SJS/TEN, but not MPE, among Han
Chinese living in Taiwan and Hong Kong [9,10], that is, in southern China.

Owing to the structural similarity between OXC and CBZ, several studies of genetic susceptibility to OXC have been performed and an association between HLA-B*1502 and OXC-cADRs has been reported. These included studies that suggested that HLA-B*1502 may be associated with OXC-induced SJS/TEN [11,12]. Other studies such as Zhou D [13] reported that the HLA-B*1502 allele may contribute to genetic susceptibility to OXC-induced MPE in the Chinese Han population. However, there are also studies which found no significant association between HLA-B*1502 and OXC-MPE in southern Han Chinese [14]. Because of the inconsistencies among these results and the fact that there has been no study conducted to test the association between HLA-B*1502 and OXC-MPE in the northern Han Chinese population specifically, we carried out the following retrospective study. Herein we report our investigations into the association between OXC-induced MPE and HLA-B alleles. We also analyzed the clinical risk factors for OXC-induced MPE in a northern Han Chinese population.

Methods

Patients

All of the enrolled subjects (patients and normal controls) were of Northern Han Chinese ethnicity. Patients were from towns in Jilin Province (Hua Dian, Pan Shi, Tao Nan, Jiao He, and Shu Lan). The Ethics Committee of Jilin University at Changchun, and the Ethics Committee of Second Affiliated Hospital of Guangzhou Medical University at Guangzhou approved this study. All of the study participants provided written informed consent.

During the years 2010–2012, 14 cases that fulfilled the diagnostic criteria for OXC-induced MPE (OXC-MPE) were identified at the Department of Neurology, First Hospital of Jilin University, Changchun, China. MPE was defined as erythematous exanthema without blistering or postulation. The attribution of MPE to OXC treatment was determined jointly by the treating epileptologist and dermatologist.

We enrolled 28 subjects who had been administered OXC for more than 3 months but had not developed any cADRs (OXC-tolerant). In addition, for the normal control group we used the HLA-B allele frequencies reported in the Allele Frequency Net Database. Two control groups were used in this study, including 618 persons in Beijing, Shijiazhuang, Tianjin and 105 persons in the northern Han population (http://www.allelefrequencies.net).

Data collected from the patients’ records included: age, gender, initial and final dose of OXC, and latency to MPE (starting from the initial dose).

Method

DNA was extracted from peripheral blood using a QIAamp blood mini kit (Qiagen, Hilden, Germany). The presence of HLA-B*1502 was examined via polymerase chain reaction with sequence-specific primers as in previous reports [14,15]. Sequencing for four-digit genotype determination was performed for all of the OXC-MPE and OXC-tolerant patients on an ABI 3730 sequencer (Applied Biosystems, Foster City, CA, USA). The forward and reverse primer sequences were Bin1-TAF (5’-TGGCGGGGCG GCAGGACCTGA-3’) or Bin1-CGF (5’-TGCGGGGGCGC AGGACCCGG-3’) and Bin3-R (5’-CGGAGGCCATCCCC GGCGAACCTAT-3’). Four-digit alleles of HLA-B in all patients were determined by sequence alignment using the immunogenetics/human leukocyte antigen (IMGT/HLA) database (http://www.ebi.ac.uk/imgt/hla) and the software vector NTI 6.0 (InforMax, Gaithersburg, MD, USA).

Statistical analysis

Student’s t-test for independent samples was used to determine the significance of differences in mean age and dosage between the OXC-MPE and the OXC-tolerant groups. The chi-squared test and Fisher’s exact test were carried out to analyze the association between OXC-MPE and HLA-B alleles. To reduce bias in estimating the odds ratio (OR), whenever a zero-count field was encountered, 0.5 was added to all the fields in the 2×2 table [16]. The P-value from continuity correction (n ≥ 40 but 1 ≤ T ≤ 5) or Fisher’s exact test (n < 40 or T < 1), as well as estimated ORs and 95% exact confidence intervals (CIs), were established. P-values less than 0.05 (two-sided) were considered statistically significant. All analyses were performed using SPSS version 16.0 software (SPSS, Chicago, IL, USA).

Results

Fourteen patients who had been diagnosed with OXC-induced MPE (9 females, 5 males; mean age 34.43 ± 12.10 y) and 28 patients who received OXC for at least 3 months without any evidence of adverse drug reactions (17 females, 11 males; mean age 34.04 ± 12.85 y) were enrolled as cases (OXC-MPE) and tolerant controls (OXC-tolerant), respectively. For the normal control group, we used the Allele Frequency Net Database (http://www.allelefrequencies.net, see Table 1).

The genotyping showed that HLA-B*1502 was present in only one of the 14 (7.1%) OXC-MPE patients, whereas 5 of the 28 (17.9%) OXC-tolerant controls carried this allele. The differences in the presence of HLA-B*1502 between the two groups was not statistically significant (OR = 0.35, 95% CI = 0.04–3.36, P = 0.64).

Four-digit allele sequencing showed that there were no statistically significant difference in the frequency of the HLA-B*1502 allele between the OXC-MPE and the OXC-
Table 1 Clinical characteristics and genotypes in the 14 patients with OXC-induced MPE and in the 28 OXC-tolerant controls

| ID No. | Gender | Phenotype | Initial-dose (mg) | Final-dose (mg) | Latency (d) | Concurrent drug | HLA-B 1502 | Four-digit allele |
|--------|--------|-----------|-------------------|-----------------|-------------|-----------------|------------|------------------|
| 1      | M      | MPE       | 300               | 600             | 12          | N               | Negative   | HLA-B*4001/4001  |
| 2      | F      | MPE       | 300               | 600             | 11          | N               | Negative   | HLA-B*1302/4001  |
| 3      | F      | MPE       | 300               | 450             | 16          | N               | Negative   | HLA-B*1302/1302  |
| 4      | M      | MPE       | 300               | 450             | 9           | N               | Negative   | HLA-B*1501/5101  |
| 5      | F      | MPE       | 300               | 450             | 15          | N               | Negative   | HLA-B*1501/1527  |
| 6      | M      | MPE       | 300               | 600             | 12          | N               | Negative   | HLA-B*1501/4403  |
| 7      | F      | MPE       | 300               | 900             | 16          | N               | Negative   | HLA-B*1501/1542  |
| 8      | M      | MPE       | 300               | 600             | 11          | N               | Negative   | HLA-B*4001/1558  |
| 9      | F      | MPE       | 300               | 900             | 17          | N               | Negative   | HLA-B*3802/4403  |
| 10     | F      | MPE       | 300               | 450             | 8           | N               | Negative   | HLA-B*5201/5301  |
| 11     | F      | MPE       | 300               | 600             | 10          | N               | Negative   | HLA-B*5502/5601  |
| 12     | F      | MPE       | 300               | 750             | 14          | N               | positive   | HLA-B*3802/1502  |
| 13     | M      | MPE       | 300               | 750             | 12          | N               | Negative   | HLA-B*1301/1301  |
| 14     | F      | MPE       | 300               | 600             | 9           | N               | Negative   | HLA-B*4402/3802  |

| ID No. | Gender | Phenotype | Initial-dose (mg) | Final-dose (mg) | Latency (d) | Concurrent drug | HLA-B 1502 | Four-digit allele |
|--------|--------|-----------|-------------------|-----------------|-------------|-----------------|------------|------------------|
| 15     | F      | Tolerant  | 300               | 900             | N           | N               |Negative   | HLA-B*4801/3531  |
| 16     | F      | Tolerant  | 300               | 600             | N           | N               |Negative   | HLA-B*4001/4804  |
| 17     | M      | Tolerant  | 300               | 600             | N           | N               |Negative   | HLA-B*4001/5501  |
| 18     | M      | Tolerant  | 300               | 900             | N           | N               |Negative   | HLA-B*3802/4403  |
| 19     | F      | Tolerant  | 300               | 900             | N           | N               |Negative   | HLA-B*3802/1302  |
| 20     | M      | Tolerant  | 300               | 600             | N           | N               |Negative   | HLA-B*4801/3531  |
| 21     | F      | Tolerant  | 300               | 600             | N           | N               |Negative   | HLA-B*4601/1511  |
| 22     | M      | Tolerant  | 300               | 450             | N           | N               |Negative   | HLA-B*1501/4001  |
| 23     | M      | Tolerant  | 300               | 600             | N           | N               |Negative   | HLA-B*1301/4001  |
| 24     | F      | Tolerant  | 300               | 450             | N           | N               |Negative   | HLA-B*1511/4801  |
| 25     | F      | Tolerant  | 300               | 600             | N           | N               |Negative   | HLA-B*4001/5604  |
| 26     | F      | Tolerant  | 300               | 900             | N           | N               |Negative   | HLA-B*1302/5801  |
| 27     | M      | Tolerant  | 300               | 900             | N           | N               |Negative   | HLA-B*1302/0705  |
| 28     | F      | Tolerant  | 300               | 600             | N           | N               |Negative   | HLA-B*3710/4701  |
| 29     | F      | Tolerant  | 300               | 600             | N           | N               |Negative   | HLA-B*3802/1315  |
| 30     | F      | Tolerant  | 300               | 600             | N           | N               |Negative   | HLA-B*3802/3901  |
| 31     | F      | Tolerant  | 300               | 900             | N           | N               |Negative   | HLA-B*5102/3508  |
| 32     | M      | Tolerant  | 300               | 900             | N           | N               |Negative   | HLA-B*5502/3801  |
| 33     | F      | Tolerant  | 300               | 450             | N           | N               |Negative   | HLA-B*1501/1513  |
| 34     | F      | Tolerant  | 300               | 600             | N           | N               |Negative   | HLA-B*2705/5101  |
| 35     | M      | Tolerant  | 300               | 600             | N           | N               |Negative   | HLA-B*4801/4801  |
| 36     | M      | Tolerant  | 300               | 450             | N           | N               |Negative   | HLA-B*1502/4001  |
| 37     | F      | Tolerant  | 300               | 600             | N           | N               |positive   | HLA-B*5801/1502  |
| 38     | F      | Tolerant  | 300               | 750             | N           | N               |positive   | HLA-B*4001/4006  |
| 39     | M      | Tolerant  | 300               | 900             | N           | N               |positive   | HLA-B*1502/5801  |
| 40     | M      | Tolerant  | 300               | 600             | N           | N               |positive   | HLA-B*4601/1502  |
| 41     | M      | Tolerant  | 300               | 450             | N           | N               |positive   | HLA-B*4601/1502  |

OXC, oxcarbazepine; MPE, maculopapular eruption; F, female; M, male.
Discussion

In the present study we found no association between OXC-induced MPE and HLA-B*1502 in our northern Han Chinese patients. Our result is consistent with previous studies of southern Han Chinese [14], but different from another study showing a significant association between OXC-induced MPE and HLA-B*1502 in central Han Chinese [7]. These discrepancies could mainly be due to differences in the frequency of HLA-B*1502 in different populations. Of note, in each of these studies the sample size was small, which limited the power of the statistical analyses.

Among Han Chinese living in Taiwan and Hong Kong (southern China), HLA-B*1502 was strongly associated with a dramatically increased risk of CBZ-induced SJS/TEN, but was not associated with MPE [10]. Recently, three OXC-induced SJS/TEN cases reported from Taiwan were positive for HLA-B*1502 [17], and there was one case of OXC-induced SJS positive for HLA-B*1502 in India [18]. This suggests a very strong association between OXC-induced SJS/TEN and the HLA-B*1502 allele. In our study, we found that the HLA-B*1502 allele was only present in 7.1% of OXC-induced MPE patients in this northern Han Chinese population.

This may be due to the inflammatory immune reactions of MPE different from SJS/TEN. CD4 + T cells are the major cell type found in the skin lesions of MPE [19], whereas CD8 + T-cell-mediated cytotoxic responses appear to be the major event in SJS/TEN [20].

OXC is a new AED which has shown clinical effectiveness similar to that of CBZ but with fewer adverse drug reactions; therefore OXC is now frequently used as a substitute for CBZ. Rash is a common side effect of AED therapy and is the leading cause of withdrawal from AED prescriptions. Some of these rashes can be ameliorated by early-stage therapy with additional management to prevent them from developing into more severe cutaneous reactions that could be fatal, while discontinuing OXC due to skin eruption prevents the long-term use of what would otherwise be an effective drug, and increases the suffering of patients. Hence, identifying the possible risk factors for cADRs will contribute to their prevention and the safe use of OXC.

We therefore compared the frequencies of HLA-B alleles other than HLA-B*1502 between the OXC-MPE and the OXC-tolerant groups. We found an association between the HLA-B*3802 allele and OXC-induced MPE in the northern Han Chinese population we studied; the frequency of the HLA-B*3802 allele was significantly higher in the OXC-MPE group. However, it should be noted that the general northern Han population was used as a control group. When OXC-tolerant subjects were used as a control, there was no statistically significant difference in the frequency of the HLA-B*3802 allele between the OXC-MPE and the OXC-tolerant control groups. This discrepancy may be because this is a small sample study, and therefore the statistical power to detect any significant difference between cases and controls was limited. Whether the HLA alleles identified in this exploratory study would be associated with the development of OXC-induced MPE in a larger sample needs to be investigated.

Hung et al. [9] found that MPE induced by CBZ was associated with single nucleotide polymorphisms (SNPs) in the HLA-E region and the nearby allele HLA-A*3101, but hypersensitivity syndrome was associated with SNPs in the motilin gene located terminal to the major histocompatibility complex (MHC) class II genes [8]. Therefore, the association between OXC-induced skin rashes and other HLA alleles beyond HLA-B should be explored in future research.

Our analysis of potential risk factors for OXC-induced MPE in the present study showed that neither age, gender, nor final dose of OXC were associated with incidence of the skin rash, which is consistent with previous studies in Korea [21]. However, other related studies showed that several clinical variables affected skin reactions, including gender, hormones, the drug titration schedule, and co-medication [22]. Among these variables, a high starting dose and rapid dose escalation were identified as risk factors, especially for the AED lamotrigine, and particularly when administered concurrent with valproate [23]. In addition, it has been reported that a reaction to one AED may induce hypersensitivity to a previously tolerated AED, and a previous AED-related skin reaction appears to be a considerable risk factor for occurrence of another rash [24]. The differences between our study and those cited above may be because all of the patients in our study were given monotherapy, treated with the same initial dosage, and the small sample size.
## Table 2 Frequencies of HLA-B alleles and their associations with OXC-induced MPE

| Alleles | MPE a | OXC-tolerant controls b | Population controls c,d | MPE cases compared with OXC-tolerant controls | MPE cases compared with normal population controls |
|---------|-------|-------------------------|-------------------------|---------------------------------------------|---------------------------------------------|
|         | Frequency | OR (95% CI) | P | OR (95% CI) | P |
| 0705    | 0/28 (0) | 1/56 (1.8) | 4/1236 (0.4) | 0.65 (0.03–16.45) | 1.00 |
| 1301    | 2/28 (7.1) | 2/56 (3.6) | 44/1236 (3.6) | 2.08 (0.28–15.58) | 0.86 |
| 1302    | 3/28 (10.7) | 5/56 (8.9) | 69/1236 (5.5) | 1.22 (0.27–5.54) | 1.00 |
| 1315    | 0/28 (0) | 1/56 (1.8) | – | 0.65 (0.03–16.45) | 1.00 |
| 1501    | 4/28 (14.3) | 2/56 (3.6) | 86/1236 (7.0) | 4.50 (0.77–26.27) | 0.18 |
| 1502    | 1/28 (3.6) | 5/56 (8.9) | 29/1236 (2.4) | 0.38 (0.04–3.40) | 0.65 |
| 1511    | 0/28 (0) | 2/56 (3.6) | 21/1236 (1.7) | 0.38 (0.02–8.24) | 0.55 |
| 1513    | 0/28 (0) | 1/56 (1.8) | 1/1236 (0.1) | 0.65 (0.03–16.45) | 1.00 |
| 1527    | 1/28 (3.6) | 0/56 (0) | 2/1236 (0.2) | 6.16 (0.24–156.27) | 0.33 |
| 1542    | 1/28 (3.6) | 0/56 (0) | 0/210 (0) | 6.16 (0.24–156.27) | 0.33 |
| 1558    | 1/28 (3.6) | 0/56 (0) | 2/1236 (0.2) | 6.16 (0.24–156.27) | 0.33 |
| 2705    | 0/28 (0) | 1/56 (1.8) | 6/1236 (0.5) | 0.65 (0.03–16.45) | 1.00 |
| 3508    | 0/28 (0) | 1/56 (1.8) | 1/1236 (0.1) | 0.65 (0.03–16.45) | 1.00 |
| 3531    | 0/28 (0) | 2/56 (3.6) | 0/210 (0) | 0.38 (0.02–8.24) | 0.55 |
| 3710    | 0/28 (0) | 1/56 (1.8) | – | 0.65 (0.03–16.45) | 1.00 |
| 3801    | 0/28 (0) | 1/56 (1.8) | 8/1236 (0.7) | 0.65 (0.03–16.45) | 1.00 |
| 3902    | 3/28 (10.7) | 2/56 (3.6) | 23/1236 (1.9) | 3.24 (0.51–20.63) | 0.42 |
| 3901    | 0/28 (0) | 1/56 (1.8) | 23/1236 (1.9) | 0.65 (0.03–16.45) | 1.00 |
| 4001    | 3/28 (10.7) | 4/56 (7.1) | 100/1236 (8.1) | 1.56 (0.32–7.51) | 0.89 |
| 4006    | 0/28 (0) | 1/56 (1.8) | 39/1236 (3.2) | 0.65 (0.03–16.45) | 1.00 |
| 4402    | 1/28 (3.6) | 0/56 (0) | 11/1236 (0.9) | 6.16 (0.24–156.27) | 0.33 |
| 4403    | 2/28 (7.1) | 5/56 (8.9) | 32/1236 (2.6) | 0.79 (0.14–4.32) | 1.00 |
| 4601    | 1/28 (3.6) | 3/56 (5.4) | 118/1236 (9.6) | 0.65 (0.07–6.59) | 1.00 |
| 4701    | 0/28 (0) | 1/56 (1.8) | 0/210 (0) | 0.65 (0.03–16.45) | 1.00 |
| 4801    | 0/28 (0) | 5/56 (8.9) | 24/1236 (2) | 0.16 (0.01–3.08) | 0.25 |
| 4804    | 0/28 (0) | 1/56 (1.8) | 0/210 (0) | 0.65 (0.03–16.45) | 1.00 |
| 5101    | 1/28 (3.6) | 1/56 (1.8) | 66/1236 (5.4) | 2.04 (0.12–33.83) | 0.10 |
| 5102    | 0/28 (0) | 1/56 (1.8) | 6/1236 (0.5) | 0.65 (0.03–16.45) | 1.00 |
| 5201    | 1/28 (3.6) | 0/56 (0) | 21/1236 (1.9) | 6.16 (0.24–156.27) | 0.33 |
| 5301    | 1/28 (3.6) | 0/56 (0) | 0/210 (0) | 6.16 (0.24–156.27) | 0.33 |
| 5501    | 0/28 (0) | 1/56 (1.8) | 7/1236 (0.6) | 0.65 (0.03–16.45) | 1.00 |
| 5502    | 1/28 (3.6) | 1/56 (1.8) | 35/1236 (2.9) | 2.04 (0.12–33.83) | 0.10 |
| 5601    | 1/28 (3.6) | 0/56 (0) | 2/1236 (0.2) | 6.16 (0.24–156.27) | 0.33 |
| 5604    | 0/28 (0) | 1/56 (2.5) | 1/1236 (0.1) | 0.65 (0.03–16.45) | 1.00 |
| 5801    | 0/28 (0) | 3/56 (5.3) | 74/1236 (6) | 0.27 (0.01–5.38) | 0.55 |

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**Notes:**

- a n = 28.
- b n = 56.
- c n = 1236, from a China Beijing Shijiazhuang Tianjin Han population of 618 persons (http://www.allelefrequencies.net).
- d n = 210, from a China North Han population of 105 persons (http://www.allelefrequencies.net). Note: The frequency of these alleles has not been reported by the former.

**OXC:** oxcarbazepine; **MPE:** maculopapular eruption; **OR:** odds ratio; **CI:** confidence interval.

**P < 0.05** (two-sided) was statistically significant.

- **–** no data available.

## Conclusion

In conclusion, we found no significant association between OXC-induced MPE and the HLA-B*1502 allele in the northern Han Chinese patients we studied. Instead, in this Han Chinese population HLA-B*3802 was identified as a potential risk factor for OXC-MPE. Furthermore, no association was found between OXC-MPE and age, gender, or dosage. It should be noted that this is a small-sample study, which limited the statistical power to detect any
significant difference. Therefore, our results need to be further confirmed by a future study with a larger sample size.

Abbreviations
AED: Antiepileptic drug; cADR: Cutaneous adverse drug reaction; CBZ: Carbamazepine; CI: Confidence interval; MPE: Mild maculopapular eruption; OR: Odds ratio; OXC: Oxcarbazepine; PCR: Polymerase chain reaction; SJS: Stevens-Johnson syndrome; TEN: Toxic epidermal necrolysis.

Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship, finance and/or publication of this article.

Authors’ contributions
All authors have read and approved the final manuscript. YDL and FLM contributed equally to this work, as First Authors. YDL contributed to the conception, design, acquisition of data, and writing. FL M contributed to analysis, interpretation of data, and writing. D-HM and YWS contributed equally as corresponding author. D-HM contributed to giving final approval of the version to be published; Y-WS contributed to manuscript revision, equally as corresponding author. DHM contributed to conception, design, acquisition of data, and writing. D-HM and YWS contributed to conception, design, acquisition of data, and writing. D-HM contributed to giving final approval of the version to be published. WK participated in the design of the study. NH performed the statistical analysis and revising. TZ participated in the sequence alignment.

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