



# Human H1 receptor (*HRH1*) gene polymorphism is associated with the severity of side effects after desloratadine treatment in Chinese patients with chronic spontaneous urticaria

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## Abstract

H1 nonsedating antihistamines, such as desloratadine, are first-line treatment options for chronic spontaneous urticaria (CSU). However, desloratadine induces various degrees of sedation side effect in CSU patients, and no biomarkers currently exist for predicting the severity of such side effect. Herein, we evaluated the association between *HRH1* gene rs901865 polymorphism and the severity of sedation side effect following desloratadine therapy in patients with CSU. We found that 20 of the 114 patients (17.50%) showed sedation side effect after desloratadine treatment, and 3 patients (2.63%) experienced serious sleepiness. The frequency of *HRH1* rs901865 G allele was significantly higher in patients who experienced sedation than in patients with rs901865 A allele ( $p = 0.0009$ ). Moreover, patients with the rs901865 G/G genotype suffered a more serious sedation side effect than patients with the rs901865 G/A genotype ( $p = 0.005$ ). These results provide evidence that the *HRH1* rs901865 G/G polymorphism is associated with severe sedation side effect after desloratadine treatment. Thus, the *HRH1* rs901865 allele may potentially be used as a biomarker for predicting the severity of sedation side effect in patients suffering from CSU and treated with desloratadine.

## Introduction

Chronic urticaria (CU) is a common skin disease characterized by the presence of wheals, angioedema, or both for more than 6 weeks. Approximately, 0.5–1% of the general population is affected by CU. Chronic

spontaneous urticaria (CSU), which is a subgroup of CU, has no identifiable trigger [1]. Although self-limiting, CSU lasts longer than 5 years in 10–25% of affected people [2]. Currently, H1 nonsedating antihistamines are considered to be the first choice for the treatment of CSU because they effectively control the symptoms and improve quality of life [3].

Recent publications have suggested that levocetirizine at manufacturer's recommended doses induces modest sedative effect in adults and children when compared with placebo in some population [4, 5], and the degree of sleepiness increases with dose [4, 6]. Earlier studies in vitro suggested that desloratadine is a selective histamine H1 antagonist that does not induce any central nervous system side effect [7]. A study conducted on US population reported that desloratadine produces negligible side effects on patients with chronic idiopathic urticaria [8]. In prospective, randomized, double-blind, three-way crossover trial in the European population, desloratadine was found to be well tolerated, and no increased rate in somnolence with 20 mg of desloratadine was observed [9]. The results of a multicenter study conducted in eight countries across Europe showed that 5 mg of

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desloratadine causes approximately 11.20% of side effects and approximately 3.70% of sleepiness [10]. However, studies in Brazil reported that 5 mg of desloratadine can induce up to 10% of sedative [11]. These studies indicated that nonsedating antihistamines can cause various degrees of sedation in different populations. Notably, “mean results” alone are inaccurate indicators of sleepiness in the population because some patients may show considerable somnolence and some remain unaffected.

The human H1 receptor (*HRH1*) gene encodes a protein receptor that is widely expressed in many different types of cells in the body, including epithelial, vascular, brain, and immune cells [12–14]. *HRH1* binds to antihistamine drugs, and the resulting interaction activates downstream signaling, which mediates the sleep state by blocking neuronal transmission in the histaminergic nervous system in the brain [15–19]. Nonsedating H1 antihistamines, such as desloratadine, have high-H1 receptor selectivity but cannot easily cross the blood–brain barrier to interact with *HRH1*. Therefore, the induction of sedation by nonsedating antihistamines cannot be attributed to high receptor selectivity alone. Recent studies suggested that *HRH1* gene polymorphism contributes the variations among the *HRH1* gene expression levels of patients; in antipsychotic-induced weight gain; and in various pharmacokinetic responses to antihistamine in patients with asthma [20–22]. In the Chinese population, *UGT1A1*, *CYP3A5*, and *ABCB1* gene polymorphisms have been shown to cause varied pharmacokinetic responses after the administration of mizolastine, a nonsedating antihistamine [23].

Our previous studies identified several gene polymorphisms that contribute to different responses to antihistamine drugs in patients with CSU. We showed that *FCERIA* and *C5AR1* gene polymorphisms are associated with high-risk chronic spontaneous urticaria and with the therapeutic efficacy of nonsedating H1 antihistamines in Chinese patients [24, 25]. We also reported that human *ORAI1* SNP is associated with increased susceptibility to CSU and patients who are suffering from CSU and carry the rs3741595 C allele have reduced responsiveness to nonsedating H1 antihistamines [26]. *HRH1*, *HDC*, and *ORAI1* gene polymorphisms are associated with histamine or histamine receptor downstream signaling, in which mutation frequencies are more than 5% according to the NCBI data. Meanwhile, *HRH1* and *HDC* are involved in the mediation of sleep–wake cycle in mouse models [19, 27, 28].

Herein, we studied the effect of *HRH1*, *HDC*, and *ORAI1* gene polymorphisms on sedation side effect in Chinese patients administered with nonsedative antihistamine desloratadine.

## Methods and patients

### Patient group

A total of 139 patients diagnosed with CSU were randomly selected from the patient database of the Department of Dermatology, Xiangya Hospital, Central South University. The study was approved by the Ethics Committees of Xiangya Hospital, Central South University and was registered on the Chinese Clinical Trial Registry under the registration number ChiCTR-OCH-14004518. The protocol is available at URL: <http://www.chictr.org/cn/proj/show.aspx?proj=8045>. The study was performed in compliance with the Declaration of Helsinki guidelines. Written informed consent was obtained from each subject before the start of the study.

### Measurement

The patients were diagnosed by specialist physicians and treated with desloratadine (5 mg per day for 4 weeks; Alerius, Schering-Plough S.p.A.) between August 2012 and October 2013. This cross-sectional study was conducted by personal interview or by phone or both. Physical examination, medical history, and serum biochemical tests were performed on the subjects before the treatment. The concentrations of red blood cell (RBC), white blood cell (WBC), hemoglobin (Hb), and C-reactive protein (CRP) in peripheral blood sample of each patient were measured.

Diagnosis, response, and degree of sleepiness following desloratadine treatment and the clinical efficacy of antihistamines were assessed by two professional dermatologists. The efficacy of the treatment was measured by the change in the score of total urticaria activity in 7 days (UAS7) [26]. The degree of sleepiness was assessed according to the Epworth Sleepiness Scale (ESS) [29]. The UAS7 and ESS scores were measured pre- and post-treatment. Response was defined as a UAS7 score that is equal to or larger than 50% of the baseline score, and scores below this percentage was regarded as nonresponse [26]. In the ESS we used, 1–9 points indicated that a patient is not at all sedated; 10–13, mildly sedated; 14–19, moderately sedated; and 20–23, extremely sedated. The patients were divided into two groups. The patients whose points were 1–9 were included in the non-sleepiness group, whereas the patients with 10–23 points were included in the sleepiness group.

Between the first and fourth week, we invited all the patients for re-examination to check whether they should be included or excluded in the study. The treatment of patients who showed severe sleepiness was terminated, and their ESS score was recorded. The UAS7 scores of these patients were not recorded, and the patients who showed severe sleepiness within 2 weeks of the treatment were excluded from the UAS7 score groups.

**Table 1** Demographic characteristics of CSU patients

| Measure                  | Sleepiness     | Nonsleepiness | <i>t</i> test/chi-square test | <i>p</i> Value |
|--------------------------|----------------|---------------|-------------------------------|----------------|
| Age mean (years)         | 35.55 ± 12.33  | 35.65 ± 12.04 | 0.033                         | 0.974          |
| Gender (male/female)     | 7:13           | 39:55         | 0.911                         | 0.340          |
| Height (cm)              | 162.00 ± 8.78  | 163.70 ± 7.34 | 0.886                         | 0.378          |
| Weight (kg)              | 58.58 ± 8.12   | 59.78 ± 10.51 | 0.469                         | 0.640          |
| BMI (kg/m <sup>2</sup> ) | 22.26 ± 3.03   | 22.23 ± 2.99  | 0.043                         | 0.996          |
| ESS (Pre-)               | 1.45 ± 1.19    | 1.16 ± 1.38   | 0.869                         | 0.387          |
| ESS (Post-)              | 12.45 ± 4.71   | 1.34 ± 1.68   | 10.410                        | 0.000          |
| UAS7 (Pre-)              | 33.00 ± 10.97  | 28.83 ± 10.51 | 1.598                         | 0.113          |
| UAS7 (Post-)             | 12.722 ± 13.45 | 10.38 ± 12.86 | 0.694                         | 0.489          |

*p* Value from the *t* test (continuous) or chi-square test (categorical) comparing values between cases and controls. *ESS* Epworth sleepiness scale, *BMI* body mass index, *UAS7* score of total urticarial activity in 7 days, *Pre-* Pre-treatment, *Post-* post-treatment

### Single-nucleotide polymorphism (SNP) genotyping for allele frequencies of the candidate genes

A total of 5 ml of blood sample was collected from each patient and stored at −80 °C until all the samples had been selected. Genomic DNA was extracted from each blood sample with the FlexiGene DNA kit according to the manufacturer's protocols (Qiagen, Hilden, Germany). SNP genotyping was performed using MassArray (Sequenom, Inc., CA, USA). Three SNPs, namely, *ORAI1* (rs12320939), *HDC* (rs17740607), and *HRH1* (rs901865), were genotyped. SNP rs2298805 was genotyped in non-sleepiness control patients.

### Statistical analysis

A post hoc estimation of power was performed, using the equation proposed by Fleiss et al. that calculate the power of proportion comparison between groups.  $n_1$  and  $n_2$  are the sample size of patients with wild and mutant genotype;  $\pi_1$  and  $\pi_2$  are proportions of case in wild and mutant genotype, respectively;  $\bar{\pi}$  is proportion of case in all genotypes;  $\alpha$  is significance level (0.05), and  $z_{1-\alpha/2}$  is the *z*-score under normal distribution (1.96);  $\beta$  is the probability of type II error;  $\Phi$  is the probability under normal distribution. For rs12320909,  $n_1 = 38$  (GG),  $n_2 = 74$  (GA & AA)  $\pi_1 = 8/38 = 0.21$ ,  $\pi_2 = (9 + 3)/(9 + 3 + 45 + 17) = 0.16$ , and  $\bar{\pi} = 20/112 = 0.18$ , then the pow of test was 10%. Similarly, the estimated power was 99.9% for rs17740607, and 77.5% for rs901865. As a result, the power to test the association of rs12320909 with adverse drug reaction was not sufficient.

$$1 - \beta = \Phi \left( \frac{|\pi_1 - \pi_2| - z_{1-\alpha/2} \sqrt{\frac{\bar{\pi}(1-\bar{\pi})}{n_1} + \frac{\bar{\pi}(1-\bar{\pi})}{n_2}}}{\sqrt{\frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}}} \right).$$

Data were expressed as the mean ± SD. Statistical comparisons between genders were conducted. Independent *t*

test was used for continuous variables and chi-square tests and residual analysis were used for discrete variables. Statistical comparisons between ESS and genotypes were conducted by binary logistic analyze.

## Result

### Clinical characteristics of the study subjects

A total of 139 patients were enrolled in the study, among which 114 patients (82.01%) met the inclusion criteria, 7 patients (3.59%) withdrew consent to participate in the study, and the remaining 18 (12.95%) were excluded for various reasons. The enrolled patients (45 males and 69 females) were between 14 and 63 years old, with a mean age of  $56.50 \pm 7.50$  years. The patients were split into two subgroups according to their ESS scores: the sleepiness group and the non-sleepiness group. A total of 94 patients (39 males and 55 females) were included in the non-sleepiness subgroup, and 20 patients (17.50%, 6 males and 14 females) were included in the sleepiness subgroup. However, three (2.63%, 1 male and 2 females) patients who showed intolerant sleepiness with desloratadine were excluded from the UAS7 scoring. No significant differences between the two subgroups with regard to age, gender, height, weight, and BMI were observed (Table 1).

### HRH<sub>1</sub> gene rs901865 G/G polymorphism is associated with serious sedation side effect after desloratadine treatment

We used the ESS to measure the degree of sleepiness of the patients before and after desloratadine treatment. Before the treatment, the ESS of the sleepiness subgroup was  $1.45 \pm 1.19$ , whereas that of the nonsleepiness subgroup was  $1.16 \pm 1.38$ . No significant difference was observed

**Table 2** The relationship of the *ORAI1*, *HDC*, and *HRH1* gene with sedation side effect after desloratadine treatment

|                           | Genotype         | Case (N = 20) | Control (N = 94) | Chi-square value | p Value |
|---------------------------|------------------|---------------|------------------|------------------|---------|
| <i>ORAI1</i> (rs12320939) | G                | 26 (61.90%)   | 79 (42.47%)      | 5.207            | 0.022   |
|                           | A                | 16 (38.10%)   | 107 (57.53%)     |                  |         |
|                           | GA               | 9 (45.00%)    | 45 (48.91%)      |                  |         |
|                           | GG               | 8 (40.00%)    | 30 (32.61%)      | 0.428            | 0.807   |
|                           | AA               | 3 (15.00%)    | 17 (18.48%)      |                  |         |
|                           | H-W <sup>b</sup> | 0.852         | 0.986            |                  |         |
| <i>HDC</i> (rs17740607)   | G                | 37 (92.50%)   | 106 (56.38%)     | 5.673            | 0.000   |
|                           | A                | 3 (7.50%)     | 82 (43.62%)      |                  |         |
|                           | GA               | 3 (15.00%)    | 82 (87.23%)      |                  |         |
|                           | GG               | 17 (85.00%)   | 12 (12.77%)      | 45.366           | 0.000   |
|                           | AA               | 0 (0.00%)     | 0(0.00%)         |                  |         |
|                           | H-W <sup>b</sup> | 0.717         | 0.000            |                  |         |
| <i>HRH1</i> (rs901865)    | G                | 31 (81.58%)   | 177 (94.15%)     | 6.814            | 0.009   |
|                           | A                | 7 (18.42%)    | 11 (5.85%)       |                  |         |
|                           | GG               | 12 (63.16%)   | 84 (89.36%)      |                  |         |
|                           | GA               | 7 (36.84%)    | 9 (9.57%)        | 9.779            | 0.008   |
|                           | AA               | 0 (0.00%)     | 1 (1.07%)        |                  |         |
|                           | H-W <sup>b</sup> | 0.325         | 0.204            |                  |         |

*ORAI1* ORAI calcium release-activated calcium modulator 1, *HDC* histidine decarboxylase, *HRH1* histamine receptor H1

**Table 3** Association between *HRH1* gene with peripheral blood on CSU

| Measure                  | Sleepiness    | Nonsleepiness  | t test/chi-square test | p value |
|--------------------------|---------------|----------------|------------------------|---------|
| RBC(10 <sup>12</sup> /L) | 4.23 ± 0.44   | 4.49 ± 0.58    | 1.542                  | 0.127   |
| WBC (10 <sup>9</sup> /L) | 7.00 ± 1.68   | 7.54 ± 5.83    | 0.327                  | 0.744   |
| Hb (g/L)                 | 136.4 ± 11.65 | 137.45 ± 15.63 | 0.217                  | 0.829   |
| CRP(mg/L)                | 3.15 ± 3.64   | 3.32 ± 6.11    | 0.097                  | 0.923   |

p value from the t test (continuous) or chi-square test (categorical) comparing values between cases and controls.

RBC red blood cell, WBC white blood cell, Hb hemoglobin, CRP C-reactive protein

between the two groups ( $p = 0.387$ ; Table 1). After treatment, the ESS scores of the two subgroups were significantly different ( $12.45 \pm 4.707$  for the sleepiness group vs.  $1.34 \pm 1.684$  for the nonsleepiness group; Table 1). We first examined whether *ORAI1*, *HDC*, and *HRH1* SNPs in our sample genes are associated with sleepiness. The distribution of *ORAI1* SNP genotype was consistent with the Hardy–Weinberg equilibrium ( $p = 0.852$ , 0.986). No significant difference in *ORAI1* SNPs between the two groups was observed ( $\chi^2 = 5.207$ ;  $p = 0.022$ ). By contrast, *HDC* SNPs for the sleepiness group was significantly different from those of the nonsleepiness group ( $\chi^2 = 5.673$ ;  $p = 0.000$ ). However, genotype distributions with *HDC* SNPs were inconsistent with the Hardy–Weinberg equilibrium ( $p = 0.717$ , 0.000). Meanwhile, genotype distributions with *HRH1* rs901865 alleles were consistent with the Hardy–Weinberg equilibrium ( $p = 0.325$ , 0.204). The chance of having *HRH1* rs901865 alleles was significantly

higher in patients who experienced sedation than in other patients ( $\chi^2 = 6.814$ ,  $p = 0.0009$ ). Moreover, patients with the rs901865 G/G genotype suffered more serious sedation side effect than patients with the rs901865 G/A genotype (odds ratio [OR] = 5.08; 95% confidence interval [CI]: 1.62–16.12;  $p = 0.005$ ; Table 2).

### ***HRH1* gene rs901865 G/G polymorphisms does not affect desloratadine efficacy**

We measured the concentrations of RBC, WBC, Hb, and CRP in the peripheral blood sample of each patient to assess whether *HRH1* gene rs901865 G/G polymorphisms affect any of these factors. We found no significant difference between the subgroups before treatment with regard to the concentrations ( $p$  value = 0.127, 0.744, 0.829, 0.923 for RBC, WBC, Hb, and CRP concentrations, respectively; Table 3). We used the UAS7 score to assess whether the

efficacy of desloratadine is influenced by *HRH1* gene rs901865 G/G polymorphisms.

On pre-treatment, of the sleepiness subgroup was  $1.45 \pm 1.19$ , whereas that of the nonsleepiness subgroup was  $1.16 \pm 1.38$ . No significant difference was observed between the two groups ( $p = 0.387$ ; Table 1). After treatment, the ESS scores of the two subgroups were significantly different ( $12.45 \pm 4.707$  for the sleepiness group vs.  $1.34 \pm 1.684$  for the nonsleepiness group; Table 1). No matter before treatment or after treatment, no significant difference was observed between the UAS7 scores of the sleepiness and the nonsleepiness subgroups ( $p = 0.113$ ,  $0.684$ , respectively; Table 1). This finding suggests that *HRH1* gene rs901865 G/G polymorphisms do not affect the therapeutic efficacy of desloratadine.

## Discussion

Clinical data have shown that some patients who are suffering from CSU and who received the recommended dose of desloratadine experienced serious sedation side effect [10, 13], whereas some patients did not present such side effect even with the overdosed desloratadine [7, 9]. Approximately, 17.50% of the patients felt sleepy after desloratadine treatment, and 2.63%, experienced serious sedation side effect. In the American and European populations, desloratadine has been demonstrated to induce slight side effects in patients with CSU [8–10]. Meanwhile, desloratadine induced sedation in up to 10% of the patients in Brazil [11]. Therefore, patient responses to desloratadine treatment vary among different populations.

However, pathogenesis of sedation in patients after nonsedative H1-antihistamine treatment is still unclear.

Previous studies have found that desloratadine does not effectively cross the blood–brain barrier under normal physiological conditions. However, when the blood–brain barrier is disrupted, desloratadine potentially enters the central nervous system and blocks H1 receptors [7, 10]. The level of H1 receptor occupancy in a patient's brain is associated with the degree of sleepiness [17, 30]. However, according to the percentage of H1 receptor occupancy, desloratadine is classified as a nonsedating H1 antihistamine [17, 30]. Thus, we speculated that desloratadine induces sleepiness through other factors apart from the blood–brain barrier or H1 receptor occupancy. The cause of sedation in patients suffering from CSU and treated with desloratadine remains unclear.

Specifically, altered *HRH1* genes expression changes histamine signaling in the brain, which in turn modulates cognition, sleep–wake cycle, and behavior [31]. Furthermore, *HRH1* rs1552498 and *HRH1* rs17034063 polymorphisms induce sedative effect during clozapine

treatment [32, 33]. The recent research demonstrated that individuals with the *HRH1* gene haplotype rs346074 and rs346070 express the histamine H1 receptor which has a stronger binding affinity to its ligand [21]. This finding may explain why the same drug dose caused weight gain in some patients with rs346074 and rs346070 but not in patients without this haplotype. Further evidence suggests that another *HRH1* polymorphism, rs13064530, is moderately correlated with weight in African patients treated with olanzapine [20]. However, this *HRH1* gene polymorphism was not found to contribute to the antipsychotic-induced weight gain in Caucasian patients with schizophrenia [22]. Meanwhile, studies on asthma suggested that individual variation in *HRH1* polymorphisms may lead to differences in *HRH1* mRNA expression level and response to antihistamine [21, 22]. Thus, different populations had varied pharmacokinetic responses because of *HRH1* polymorphism. Thus, these data suggested that *HRH1* gene polymorphism contributes to the different *HRH1* gene expressions in different populations and potentially affect pharmacokinetic response to different drugs [20].

Herein, we used Sequenom MassArray technology and direct sequencing to genotype and examine the effect of different genetic variants of the *HRH1* gene on the severity of desloratadine-induced sedation side effect. Our findings demonstrated that the presence of a *HRH1* rs901865 G/G variant correlates with increased chance of experiencing sleepiness side effect after desloratadine treatment. This study is the first to report that *HRH1* gene is associated with sedation by desloratadine and indicates that the function of *HRH1* varies among different populations. We also found that the rs901865 (*HRH1*) gene has no effect on the UAS7 scores of patients after desloratadine treatment. Thus, the efficacy of desloratadine was unaffected by the *HRH1* rs901865 G/G variant. A similar finding was observed in patients with asthma [22].

We measured the RBC, WBC, Hb, and CRP concentrations in the peripheral blood samples of patients to further understand the other functions of the *HRH1* rs901865 SNP in CSU. No alterations in the factors were observed in the presence of the *HRH1* rs901865 SNP. Thus, this SNP is unlikely to contribute to the pathogenesis of CSU. We speculated that *HRH1* rs901865 G/G variant affects the affinity of desloratadine to the histamine H1 receptors in the brain, which in turn change the balance of wake–sleepy cycle. Conflicting data on whether desloratadine is a nonsedating antihistamine exist [9–11]. Our findings demonstrated that *HRH1* polymorphisms are associated with the degree of side effect and response to *HRH1*-related drug desloratadine. The drugs may have induced different levels of sedation side effect because of the variation in *HRH1* mRNA expression levels. We concluded that difference in the degree of sedation side effects

after desloratadine treatment is due to variation among the *HRH1* gene expression levels of the patients and this variation affected histamine function in the brain. Nevertheless, whether *HRH1* downstream signaling pathways in the brain causes sedation must be determined preferably through longitudinal studies. In our studies, we found that *HRH1* gene-expression level has no effect on the therapeutic efficacy of nonsedating antihistamines, such as desloratadine [data not shown]. Meanwhile, our results showed that the RBC concentrations in the peripheral blood samples of patients did not differ between the sleepiness and non-sleepiness groups. Overall, our results indicated that rs901865 G/G genotype correlates with sedation side effects after desloratadine treatment. We believe that patients with rs901865 G/G genotype express high levels of *HRH1* mRNA, which induces serious sedation. However, this genotype is a new pathway which is different from the classic *HRH1* pathway.

Our findings also showed that the incidence of sedation following desloratadine treatment increased up to 17.50, and 2.63% of the patients experienced serious sedation. Our incidence was high possibly because all our participants were patients with CSU. Meanwhile, these data are highly consistent with those published with different populations, races, and species of allergy [10, 11, 25]. Our result is crucial in the selection of personalized treatment to such patients.

Our findings demonstrated a new association between increased desloratadine-induced sleepiness and the rs901865 G/G genotype (*HRH1*). Meanwhile, presenting this allele does not affect desloratadine efficacy or the pathogenesis of CSU. These results provide a basis for screening patients who are experiencing sedation after desloratadine treatment. In the future, we will explore the potential mechanism underlying this difference of desloratadine-induced sleepiness, by conducting a multicenter and large sample study to facilitate the selection of therapeutics in order to reduce undesired sedation side effects in patients with CSU.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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| 96 orifice plate position | 384 boards | sample ID | 1205 | 5275 |
|---------------------------|------------|-----------|------|------|
| 1-B02                     | B03        | 2-2       | C    | T    |
| 1-E02                     | E03        | 2-5       | T    | TC   |
| 1-E03                     | E05        | 3-5       | TC   | T    |
| 1-G10                     | G19        | 10-7      | T    | T    |
| 1-B11                     | B21        | 11-2      | TC   | T    |
| 2-A04                     | A08        | 16-1      | TC   | C    |
| 2-A07                     | A14        | 19-1      | T    | T    |
| 2-C11                     | C22        | 23-3      | TC   | TC   |
| 2-D12                     | D24        | 24-4      | TC   | TC   |
| 2-G08                     | G16        | 24-8      | C    | T    |
| 1-G03                     | G05        | 25-5      | C    | TC   |
| 2-A06                     | A12        | 25-8      | T    | T    |
| 1-H03                     | H05        | 3-8       | TC   | T    |
| 2-D05                     | D10        | 17-4      | C    | T    |
| 2-B04                     | B08        | 16-2      | T    | T    |
| 2-H04                     | H08        | 16-8      | T    | T    |
| 2-H07                     | H14        | 19-8      | TC   | T    |
| 2-E11                     | E22        | 23-5      | C    | T    |
| 2-F02                     | F04        | 14-6      | T    | TC   |
| 2-H08                     | H16        | 20-8      | C    | T    |
| 3-C10                     | K19        | 10-3      | G    | C    |
| 3-D10                     | L19        | 10-4      | G    | T    |
| 3-E10                     | M19        | 10-5      | G    | T    |
| 3-F10                     | N19        | 10-6      | G    | TC   |
| 3-A01                     | I01        | 1-1       | G    | T    |
| 3-C11                     | K21        | 11-3      | G    | C    |
| 3-E11                     | M21        | 11-5      | G    | C    |
| 3-F11                     | N21        | 11-6      | G    | C    |
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| 3-H11                     | P21        | 11-8      | G    | TC   |
| 3-D12                     | L23        | 12-4      | G    | TC   |
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| 3-F12                     | N23        | 12-6      | G    | TC   |
| 3-G12                     | O23        | 12-7      | G    | TC   |
| 3-H12                     | P23        | 12-8      | G    | T    |
| 4-B01                     | J02        | 13-2      | G    | T    |
| 4-D01                     | L02        | 13-4      | G    | T    |
| 4-F01                     | N02        | 13-6      | G    | C    |
| 4-G01                     | O02        | 13-7      | G    | TC   |
| 4-C02                     | K04        | 14-3      | G    | T    |
| 4-D02                     | L04        | 14-4      | G    | TC   |
| 4-E02                     | M04        | 14-5      | G    | C    |
| 4-H02                     | P04        | 14-8      | G    | T    |
| 3-E01                     | M01        | 1-5       | G    | TC   |
| 4-A03                     | I06        | 15-1      | G    | T    |
| 4-B03                     | J06        | 15-2      | G    | C    |
| 4-C03                     | K06        | 15-3      | G    | C    |

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| 4-D03 | L06 | 15-4 | G | TC |
| 4-E03 | M06 | 15-5 | G | C  |
| 4-F03 | N06 | 15-6 | G | C  |
| 4-G03 | O06 | 15-7 | G | C  |
| 4-D04 | L08 | 16-4 | G | TC |
| 4-H04 | P08 | 16-8 | G | TC |
| 4-B05 | J10 | 17-2 | G | C  |
| 4-C05 | K10 | 17-3 | G | TC |
| 4-C06 | K12 | 18-3 | G | C  |
| 4-D06 | L12 | 18-4 | G | T  |
| 4-E06 | M12 | 18-5 | G | TC |
| 4-B07 | J14 | 19-2 | G | TC |
| 4-C07 | K14 | 19-3 | G | TC |
| 4-A08 | I16 | 20-1 | G | T  |
| 4-D08 | L16 | 20-4 | G | C  |
| 4-E08 | M16 | 20-5 | G | TC |
| 4-F08 | N16 | 20-6 | G | T  |
| 3-A02 | I03 | 2-1  | G | C  |
| 4-A09 | I18 | 21-1 | G | C  |
| 4-B09 | J18 | 21-2 | G | T  |
| 4-C09 | K18 | 21-3 | G | C  |
| 4-D09 | L18 | 21-4 | G | C  |
| 4-G09 | O18 | 21-7 | G | TC |
| 4-A10 | I20 | 22-1 | G | TC |
| 4-B10 | J20 | 22-2 | G | TC |
| 4-C10 | K20 | 22-3 | G | C  |
| 4-D10 | L20 | 22-4 | G | T  |
| 4-E10 | M20 | 22-5 | G | C  |
| 4-F10 | N20 | 22-6 | G | TC |
| 4-G10 | O20 | 22-7 | G | T  |
| 4-H10 | P20 | 22-8 | G |    |
| 3-C02 | K03 | 2-3  | G | C  |
| 4-D11 | L22 | 23-4 | G | C  |
| 4-F11 | N22 | 23-6 | G | T  |
| 4-G11 | O22 | 23-7 | G | TC |
| 4-E12 | M24 | 24-5 | G | TC |
| 4-F12 | N24 | 24-6 | G | T  |
| 3-D01 | L01 | 25-3 | G | T  |
| 3-D02 | L03 | 25-4 | G | T  |
| 3-H10 | P19 | 25-6 | G | C  |
| 4-A01 | I02 | 25-7 | G | C  |
| 3-F02 | N03 | 2-6  | G | TC |
| 4-A12 | I24 | 26-1 | G | TC |
| 4-B06 | J12 | 26-2 | G | TC |
| 4-C08 | K16 | 26-3 | G | C  |
| 4-E01 | M02 | 26-4 | G | TC |
| 4-F05 | N10 | 26-5 | G | TC |
| 3-B03 | J05 | 3-2  | G | C  |

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| 3-C03 | K05 | 3-3 | G | C  |
| 3-D03 | L05 | 3-4 | G | TC |
| 3-C04 | K07 | 4-3 | G | TC |
| 3-D04 | L07 | 4-4 | G | TC |
| 3-B05 | J09 | 5-2 | G | TC |
| 3-E05 | M09 | 5-5 | G | C  |
| 3-F06 | N11 | 6-6 | G | TC |
| 3-G06 | O11 | 6-7 | G | TC |
| 3-B07 | J13 | 7-2 | G | TC |
| 3-C07 | K13 | 7-3 | G | C  |
| 3-E07 | M13 | 7-5 | G | T  |
| 3-A08 | I15 | 8-1 | G | C  |
| 3-C08 | K15 | 8-3 | G | TC |
| 3-G08 | O15 | 8-7 | G | C  |
| 3-H08 | P15 | 8-8 | G | C  |
| 3-C09 | K17 | 9-3 | G | C  |
| 3-D09 | L17 | 9-4 | G | C  |
| 3-G09 | O17 | 9-7 | G | TC |
| 3-H09 | P17 | 9-8 | G | C  |

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| G    | GA     | AG     | C      | GA     | T      | C       |
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| G    | G      | AG     | C      | G      | T      | TC      |
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| G    | G      | AG     | C      | G      | T      | TC      |
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| TC   | CA     | GA     | G      | CG     | C      | AG      |

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| TC | CA | GA | G  | C  | C  | G  |
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迅捷PDF编辑器

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| G  | T  | G  | AG | GT | G  | C |
| G  | T  | G  | AG | T  | G  | C |
| AG | CT | G  | G  | GT | A  | C |
| G  | T  | G  | G  | T  | GA | C |
| G  | T  | G  | G  | T  | G  | C |
| AG | T  | G  | AG | T  | GA | C |
| G  | T  | G  | AG | GT | GA | C |
|    | T  | G  | G  | T  |    | C |
|    | T  | G  | G  | GT | G  | C |
|    | T  | G  | G  | GT |    | C |
| G  | T  | G  | G  | T  | A  | C |
| G  | T  | G  | G  | GT | GA | C |
| G  | CT | G  | G  | GT | G  | C |
| G  | C  | G  | AG | T  | GA | C |
| G  | CT | G  | G  | T  | G  | C |
| G  | CT | G  | AG | GT | A  | C |
| G  | T  | G  | AG | GT | GA | C |
| AG | C  | G  | G  | T  | G  | C |
| A  | CT | G  | AG | GT | G  | C |
|    | CT | AG | G  | GT | GA | C |
| G  | T  | G  | G  | GT | G  | C |
| AG | T  | G  | AG | G  | G  | C |
| G  | T  | G  | AG | T  | GA | C |
|    | T  | G  | A  | T  | GA | C |
| AG | T  | G  | AG | G  | GA | C |
| AG | CT | AG | AG | GT | GA | C |
| G  | CT | G  | G  | G  | G  | C |

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| AG | T  | G | G  | GT | G  | C |
|    | T  | G | G  | GT | GA | C |
|    | CT | G | AG | T  | GA | C |
|    | T  | G | A  | T  | G  | C |
|    | T  | G | AG | GT | GA | C |
| G  | T  | G | G  | GT | GA | C |
|    | CT | G | G  | GT | GA | C |
| G  | T  | G | G  | T  | GA | C |
| G  | CT | G | G  | T  | A  | C |
| G  | CT | G | AG | T  | G  | C |
|    | CT | G | G  | GT | GA | C |
|    | CT | G | AG | GT | A  | C |
|    | CT | G | G  | T  | G  | C |
|    | T  | G | AG | T  | G  | C |
|    | T  | G | G  | T  | GA | C |
| A  | CT | G | G  | T  | GA | C |
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| AG | CT | G | G  | GT | G  | C |
| AG | T  | G | G  | GT | GA | C |

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| A       | T       | T       | T       | GA       | G        | GT       |
| A       | CT      | GT      | T       | GA       | A        | G        |
| A       | CT      | T       | T       | GA       | G        | GT       |
| A       | CT      | T       | CT      | A        | GA       | T        |
| A       | CT      | GT      | T       | GA       | GA       | T        |
| A       | T       | GT      | T       | A        | G        | T        |
| A       | CT      | T       | T       | A        | G        | T        |
| A       | C       | GT      | T       | A        | A        | GT       |
| A       | T       | T       | T       | GA       | A        | G        |
| A       | CT      | G       | T       | GA       | GA       | G        |
| A       | CT      | T       | T       | G        | GA       | GT       |
| A       | T       | G       | T       | A        | GA       | T        |
| A       | CT      | T       | T       | A        | A        | T        |
| A       | CT      | GT      | T       | A        | A        | G        |
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| A       | T       | GT      | CT      | A        | A        | GT       |
| A       | T       | GT      | CT      | A        | GA       | GT       |
| A       | CT      | T       | T       | A        | A        | G        |
| A       | T       | T       | T       | A        | GA       | G        |
| AG      | G       | T       | T       | G        | C        | C        |
| G       | G       | T       | T       | G        | C        | C        |
| G       | G       | T       | T       | AG       | C        | C        |
| G       | GC      | CT      | T       | G        | C        | C        |
| G       | G       | CT      | CT      | G        | C        | C        |
| G       | G       | T       | CT      | G        | C        | C        |
| G       | G       | CT      | T       | G        | C        | C        |
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| G       | GC      | CT      | T       | AG       | C        | C        |
| G       | GC      | T       | CT      | AG       | C        | C        |
| G       | G       | CT      | C       | G        | C        | CT       |
| G       | GC      | T       | T       | G        | C        | C        |
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| G       | GC      | C       | T       | G        | C        | C        |
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| G       | G       | T       | C       | G        | C        | C        |
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