J Appl Biomed
DOI: 10.32725/jab.2023.012
journal homepage: http://jab.zsf.jcu.cz

Journal of Applied Biomedicine

Original research article

Allele frequency and genotype distribution of the opioid receptor μ-1 (OPRM1) A118G polymorphism in the Western Saudi population

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Abstract
The single nucleotide polymorphism (SNP) A118G (rs1799971) in the Mu Opioid Receptor 1 (OPRM1) gene is associated with significant variations in analgesic doses and adverse effects of opioids. The A118G OPRM1 allele distributions vary significantly between different populations worldwide. The study aimed to assess the allele frequency and genotype distribution of OPRM1 A118G SNP in Saudis. This cross-sectional study included 124 healthy Saudis (62 males and 62 females) visiting the King Abdulaziz University Hospital in Jeddah, Saudi Arabia. The Oragene®-DISCOVER (OGR-600) kits were used to collect saliva samples from the participants. Polymerase chain reaction-restriction fragment length polymorphism was utilized to assess the SNP. Among the tested population, 79.03% (95% C.I. 70.81–85.82) were homozygous wild-type A118A, 16.13% (95% C.I. 10.14–23.80) were heterozygous A118G, and 4.84% (95% C.I. 1.80–10.23) were homozygous mutant G118G. OPRM1 A118G polymorphism allele frequencies were 87% (95% C.I. 79.89–92.44) and 13% (95% C.I. 7.56–20.11) for the 118A and 118G alleles, respectively. A higher frequency of the OPRM1 118G allele was present in females, 21% (95% C.I. 11.66–33.17) compared to males, 5% (95% C.I. 1.01–13.50). Relative to other Asian countries, the Saudi population showed a low prevalence of the OPRM1 A118G polymorphism, with a higher frequency of the 118G allele in females. Our research will contribute to the existing knowledge on the prevalence of OPRM1 A118G polymorphism, which could be considered for the personalized prescribing of opioid analgesics.

Keywords: A118G; Gender; OPRM1; Polymorphism; Saudi Arabia

Highlights:
- The allele frequencies for the A and G alleles of the OPRM1 A118G polymorphism (rs1799971) were 87% and 13%, respectively.
- The G allele of rs1799971 was found at a higher frequency in 21% of females compared to 5% of males.
- The Saudi population showed a low prevalence of the OPRM1 A118G polymorphism relative to other Asian populations.

Abbreviations:
CI: confidence interval; OPRM1: Mu Opioid Receptor 1; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; SNPs: single nucleotide polymorphisms.

Introduction

Pain management remains a significant challenge due to its complex pathophysiology and unexpected responses to drug treatment (Fitzcharles et al., 2021). Opioid analgesics are widely used to treat moderate to severe acute and chronic pains. However, numerous studies have documented a significant inter-individual variability in the clinical responses to opioids and therapeutic opioid dosages required for pain management (Busse et al., 2018; Rosenblum et al., 2008). Both genetic variations and environmental factors contribute to such variabilities. There is growing evidence that the mu-opioid receptor 1 (OPRM1) gene's single nucleotide polymorphisms (SNPs) are related to pain sensitivity and analgesic response to opioids (Magarbeh et al., 2021; Owusu Obeng et al., 2017). The OPRM1 gene encodes the mu-opioid receptor (MOR), one of three opioid receptors expressed in humans. The MORs are expressed throughout the central nervous system and the periphery, as they play an essential role in the pain and reward pathways (Valentino and Volkow, 2018). Both endogenous (enkephalin and beta-endorphin) and exogenous (morphine) opioids can bind and activate the MORs (Darcq and Kieffer, 2018; Sobczak et al., 2014).

Several SNPs have been identified in the OPRM1 gene, though the most common SNP of the OPRM1 gene is rs1799971 (A118G). This SNP occurs at position 118 of the OPRM1 gene, in which the adenine (A) is substituted by guanine (G), result-

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http://doi.org/10.32725/jab.2023.012
Submitted: 2022-10-25 • Accepted: 2023-09-14 • Prepublished online: 2023-09-15
J Appl Biomed 21/3: 160–165 • EISSN 1214-0287 • ISSN 1214-021X

ing in the exchange at position 40 of the protein from asparagine to aspartate (Asn40Asp) (Bond et al., 1998). Alternation in the amino acid sequence significantly alters the MOR properties, for example, ligand affinity and signaling (Beyer et al., 2004; Lopez Soto and Raingo, 2012). Previous studies have shown that the G allele of rs1799971 may affect the response to analgesia. These include commonly prescribed opioid analgesics such as oxycodone, fentanyl, methadone, oxymorphone, hydrocodone, codeine, and morphine, as well as illegal opioids such as heroin. Individuals with the G allele of rs1799971 had higher pain scores and required higher opioid doses with a grade A recommendation for morphine (Campa et al., 2008; Sia et al., 2008). In addition, the G allele was associated with a lower risk of postoperative opioids-induced vomiting, pruritus, and dizziness (Kong et al., 2018). Furthermore, numerous meta-analyses reported that the G allele of rs1799971 is associated with alcohol, opioid, cannabis, cocaine, and nicotine addictions. However, the reported association between the G allele and drug addictions has been inconsistent (Arias et al., 2006; Chen et al., 2012; Coller et al., 2009; Glatt et al., 2007; Haerian and Haerian, 2013; Schwantes-An et al., 2016).

Notable disparities in OPRM1 SNP allele distributions have been documented across global populations. In numerous populations, the G allele of rs1799971 constitutes the minor allele, exhibiting frequencies ranging from 36% to 50% in Asian samples (Ahmed et al., 2018; Loh et al., 2004; Tan et al., 2003), 10% to 30% in European samples (Bart et al., 2005; Bergen et al., 1997; Troisi et al., 2011), and 1% to 17% in African samples (Crowley et al., 2003). Given Saudi Arabia's location in Southwestern Asia, an elevated frequency of the G allele of rs1799971 is anticipated within the Saudi population. Located along the Red Sea coast in the Western region of Saudi Arabia, Jeddah is the largest city in Makkah Province and the nation's second most populous urban center. The population of Jeddah might possess distinct genetic features due to its historical significance as a crucial port city, suggesting the potential for intricate genetic interchanges with diverse cultures. This contrasts with tribes such as the Najdi in the central region and the Al-Murrah in the east, which have undergone fewer historical migrations but engaged in more profound cultural interactions. The limited migratory patterns within these tribes could have conserved specific genetic traits over generations. At the same time, heightened cultural interactions may have contributed to genetic amalgamation and diversity within the Jeddah population. These dynamics potentially underlie disparities in genetic profiles, influencing physical attributes and, conceivably, disease susceptibilities. The prevalence of the OPRM1 A118G polymorphism within the Saudi population remains a significant knowledge gap that warrants attention. Remarkably, its frequency has yet to be comprehensively investigated. Therefore, our study aimed to investigate the OPRM1 A118G polymorphism frequency among healthy Saudis receiving care at King Abdulaziz University (KAAU) Hospital in Jeddah, Saudi Arabia. By focusing on this specific population, we aspire to contribute valuable insights into the genetic landscape of Saudi Arabia and its broader implications.

Materials and methods

Subject selection criteria and sample size calculation

The study was conducted at KAAU in Jeddah, Saudi Arabia, between March and June 2021. The study protocol was reviewed and approved by the Research Ethics Committee at the School of Dentistry (211-01-21). All these subjects were attending KAAU Hospital for check-ups. The inclusion criteria were as follows: Saudi, healthy, non-addicted, and not taking any pain medications. All subjects provided written informed consent before being enrolled in the study. Saliva samples (2 ml) were collected from each subject using the Oragene®-DISCOVER (OGR-600) kit (DNA Genotek Inc, Canada).

According to the study by Alblooshi et al. (2018), the prevalence of the A allele of G118G (rs1799971) in the United Arab of Emirate (UAE) population was 13.2%.

We determined that a random sample of 124 participants would be required to detect the prevalence of A118G OPRM1 in the Saudi population with 95% confidence (Open Epi Version 3.1), assuming the prevalence is 13.2% +/– 5% (Hong and Park, 2012).

Genotyping of A118G single-nucleotide polymorphism (PCR-RFLP)

The genomic DNA was isolated from the saliva using the previously described protocol (Nunes et al., 2012). After the extraction, the A118G polymorphism in the OPRM1 gene was identified using the PCR-RFLP assay, as described earlier (Cheng et al., 2019). Using the forward 5'- GGTCAACTTGTCCCACTTAGATCGC -3' and the reverse 5'-AATCACATACATGACCAGGAAGTTT-3' primers, a 193-bp PCR product was amplified (Macrogen, Korea). The PCR reaction was composed of 1.0 µl genomic DNA (100 ng), 0.8 µl of each primer (0.5 µM), 10 µl of 2× Taq PCR MasterMix (Solarbio Co., China) to a final volume of 20 µl with dH_2O. The PCR program was: 95 °C for 7 min, 35 cycles of 95 °C for 1 min, 62 °C for 30 s, and 72 °C for 30 s, followed by 72 °C for 10 min. Afterward, the PCR reaction product was digested with Bsh1236I (BstUI) restriction enzyme (Thermo Fisher Scientific, USA). The digestion reactions were performed in a 20 µl reaction (10 µl PCR product, 2 µl of 10× Buffer Tango™ in, 0.2 µl Bsh1236I, and 7.8 µl dH_2O) for 3 h at 37 °C. The digested products were separated on 3% agarose gel for 90 min at 100 V and visualized using ultraviolet light. Fig. 1 shows a representative agarose gel image of the *A118G OPRM1* PCR-RFLP assay. The homozygous wild-type genotype (A118A) yields a band of 193 bp, the homozygous genotype (G118G) yields a band of 169 bp, and the heterozygous (A118G) yields two bands of 193 bp and 169 bp. Direct sequencing was used to confirm the results for each genotype in randomly selected samples (Macrogen, Korea).

Data analysis

For statistical analysis, the allele and genotype frequencies of OPRM1 A118G polymorphism were determined by direct counting and compared using a Chi-Square (χ^2) test. The expected values for each genotype were predicted using the Hardy–Weinberg equilibrium (HWE). The allele and genotype frequencies are given with 95% confidence intervals (C.I.). The allele and genotype frequencies and 95% confidence intervals are provided. The normal approximation with continuity correction was used to measure the confidence intervals. Total samples were divided into male and female groups. Comparisons of genotypes and allelic frequencies between the two groups were calculated using the χ^2 test and odds ratios. Statistical significance was set at $P < 0.05$.

Results

This cross-sectional study included 124 participants (62 males and 62 females). All the participants were Saudis, and most of their grandparents were Saudis from a Western ethnic group.

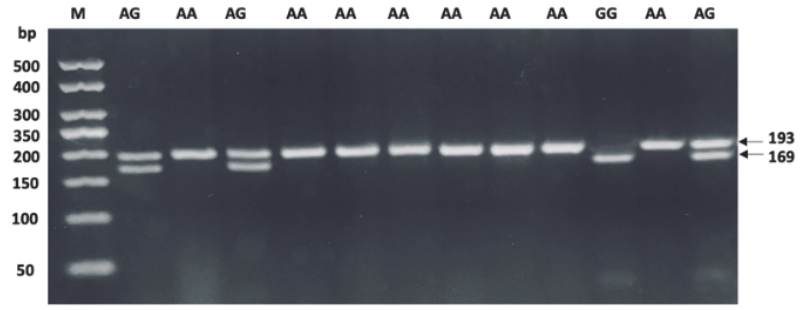

Fig. 1. Agarose gel image showing OPRM1 A118G genotypes determined by PCR-RFLP using the Bsh1236I (BstUI) restriction enzyme. AA genotype (193 bp band); AG genotype (193 and 169 bp bands); and GG genotype (169 bp band). M, DNA molecular weight marker; bp, base pairs.

We examined the genotype distributions for the OPRM1 A118G polymorphism to determine the abundance of the homozygous or heterozygous genotypes (Table 1). In total, the homozygous A118A genotype was present among 79.03% (95% C.I. 70.81–85.82) of the sample. The heterozygous A118G genotype was present among 16.13% (95% C.I. 10.14–23.80), and the G118G genotype comprised the remaining 4.84% (95% C.I. 1.80–10.23). The A118A genotype was most prevalent in this population (P = 0.042).

Next, we determined the gender difference in the genotype distributions for the OPRM1 A118G polymorphism (Table 1). A higher frequency of the heterozygous A118G genotype was present in females, 22.58% (95% C.I. 12.93–34.97) compared to males, 9.67% (95% C.I. 3.64–19.88). While the G118G genotype was present in 9.67% (95% C.I. 3.64–19.88) of the female subjects, it was not detected in the male subjects. Furthermore, the prevalence of the OPRM1 A118G polymorphism varied significantly between genders (P = 0.014).

Table 1. The OPRM1 A118G 6 allele frequency in the Saudi population

Genotypes	Male *N* (%)	Female *N* (%)	Total *N* (%)	*P*-value
AA	56 (90.32)	42 (67.74)	98 (79.03)	
AG	6 (9.67)	14 (22.58)	20 (16.13)	
GG	0 (0)	6 (9.68)	6 (4.84)	P = 0.042*
Total	62 (100)	62 (100)	124 (100)	
HWE (χ^2 value)	0.16 (P = 0.922)	6.29 (P = 0.041*)	9.05 (P = 0.011*)	

Note: HWE: Hardy–Weinberg equilibrium. *P*-values were calculated using the Chi-Square (χ^2) test. * Indicates significance at the < 0.05 level.

The OPRM1 A118G polymorphism genotype distribution in the male subjects was consistent with the Hardy–Weinberg equilibrium (χ^2 = 0.16, P = 0.92) (Fig. 2A). However, the genotype distribution for the OPRM1 A118G polymorphism in the female subjects was inconsistent with the Hardy–Weinberg equilibrium (χ^2 = 6.29, P = 0.041) (Fig. 2B). These data suggest that the OPRM1 A118G polymorphism is more common than anticipated among female Saudis in the Western province.

We also calculated the OPRM1 A118G allele frequency (Table 2). In the total samples, the frequency of the A allele was 87% (95% C.I. 79.89–92.44), and that of the G allele of rs1799971 was 13% (95% C.I. 7.56–20.11). The frequency of

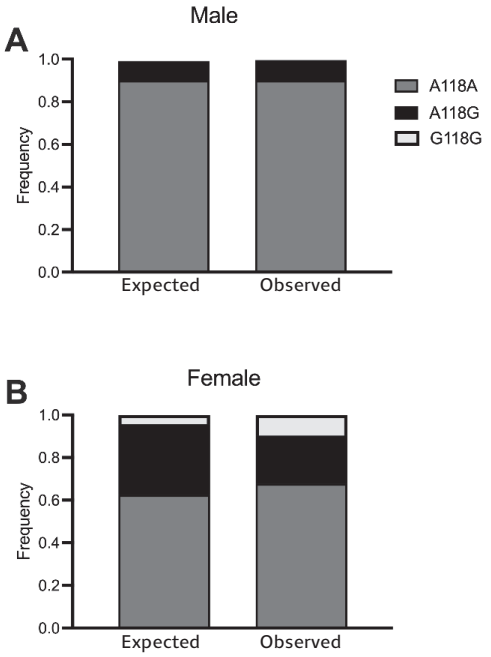

Fig. 2. Expected and observed genotype frequencies for the OPRM1 A118G polymorphisms based on a Hardy–Weinberg distribution

the G allele was significantly higher (OR = 5.22; P = 0.027) in the female subjects, 21% (95% C.I. 11.66–33.17), compared to the male subjects, 5% (95% C.I. 1.01–13.50). These data indicated that the G allele of rs1799971 was more abundant in Saudi females than males in the Western province.

Discussion

The most common SNP within the coding region of the OPRM1 gene is rs1799971 (A118G). The present study used the PCR-RFLP technique to assess the allele and genotype frequencies of OPRM1 A118G SNP in healthy Saudi residents of the Western area of Saudi Arabia. Among the studied population, the homozygous wild-type A118A genotype constituted 79.03%, while heterozygous A118G genotypes were observed in 16.13% of participants, and homozygous G118G genotypes represented 4.84%. Regarding allele distribution, the frequencies of A and G alleles of rs1799971 were 87% and 13%, respectively. Notably, the G allele exhibited a higher occurrence in females, comprising 21% of their alleles, compared to 5%

in males. This differential prevalence underscores potential gender-associated distinctions in the genetic makeup of this particular SNP among the studied Saudi population.

The OPRM1 A118G polymorphism allele frequency was evaluated in different populations (Fig. 3). It is well-known that the G allele frequencies can vary wildly depending on the population ancestry being studied. The highest G allele frequency observed in any population was 49%, according to the 1000 Genome Phase 3, gnomAD, and ESP data (NHLBI GO Exome Sequencing Project /ESP/. Exome Variant Server, 2023; The 1000 Genomes Project Consortium et al., 2015). Remarkably, the G allele of rs1799971 manifested in only 16% and 20% of the European and American populations, respectively. Contrastingly, a mere 1% of African populations carried the G allele. Within Eastern Asian populations, the average G allele frequencies were 36.6%, 49%, and 39% in Japan, Vietnam, and China, respectively. The South Asian population, comprising Bangladesh (44%), Pakistan (37%), India (41%), and Sri Lanka (43%), also exhibited pronounced elevated frequencies of the G allele of rs179997. Therefore, the significant prevalence of the OPRM1 118G polymorphism within the Asian population is readily apparent. Notably, Saudi Arabia is situated in Southwestern Asia. However, our investigation yields intriguing insights, unveiling a distinctive pattern within the Saudi population. In the specific cohort sampled from Jeddah, we observed a relatively modest presence of the G allele of rs1799971, accounting for only 13% of the population. Consequently, our findings underscore that Saudis, particularly in the Western region, exhibit one of the lowest frequencies of the G allele of rs1799971 across the Asian landscape. Strikingly, this frequency aligns more closely with the range observed in European populations, varying from 12% to 18%. This intriguing observation could be attributed to historical and migratory dynamics that have influenced the genetic composition of the Saudi population. Notably, Saudi Arabia's Western region, anchored by the pivotal cities of Makkah and Madinah, has historically attracted a diverse influx of Muslims from various corners of the world. As a result, approximately 10% of Saudis in this region have Afro-Asian ancestry, while most maintain their ethnic Arab heritage. The ancestral origins of the sampled populations in our study suggest a possible fusion of genetic lineages from Africa, Eastern Asia, and Europe. This distinctive interaction of various ancestral contributions adds to the complex genetic tapestry that defines the Saudi population, underscoring the multifaceted essence of genetic inheritance within this geographical area.

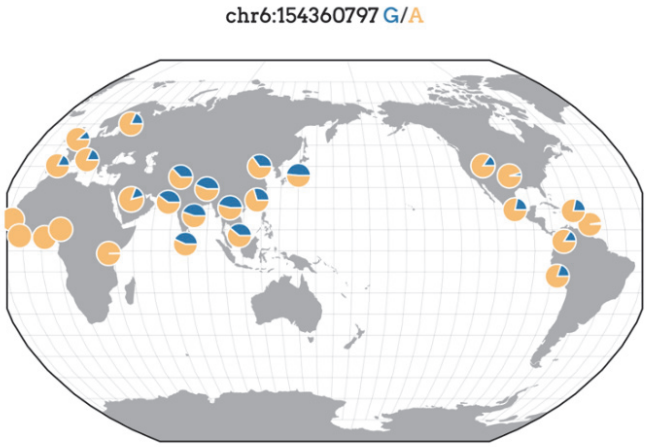

Fig. 3. Allele frequency map for OPRM1 A118G (rs1799971). The frequency proportion for the (**A**) and (**G**) alleles are shown in orange and blue, respectively. The map was obtained from the Geography of Genetic Variants Browser Beta v0.2 42 (Marcus and Novembre, 2017). Data from the current study were included in the map.

A study conducted by Alblooshi et al. (2018) highlighted significant disparities in the prevalence of heterozygous A118G genotypes within the OPRM1 gene in the UAE.

Specifically, their research underscored an elevated occurrence of heterozygous A118G genotypes, accounting for 31.67% of the participants. Conversely, our investigation of Saudi participants from the Western region revealed a comparatively lower frequency of heterozygous A118G genotypes, comprising 16.13% of the sampled individuals. The population of the UAE is characterized by a rich diversity of ethnicities, stemming from its role as an international hub and cultural melting pot. This diversity is further enriched by historical trade, migration, and economic activities, which have played a pivotal role in shaping the genetic composition of the UAE population. As a result, the distribution of genetic variants, including the OPRM1 A118G polymorphism, within the UAE may exhibit variations distinct from those observed in the Saudi population, reflecting the broader genetic heterogeneity intrinsic to the UAE's unique demographic landscape.

An equal number of male and female participants were included in our current study. Intriguingly, our findings reveal a notable gender-related distinction concerning the frequency of the G allele of rs1799971, with females displaying a higher prevalence (P = 0.027) than males. This fascinating pattern is consistent with findings in other populations. Specifically, Cieślińska et al. (2015) reported a twofold higher G allele frequency in females than males within the Polish population.

Conversely, an investigation conducted in Indonesia demonstrated an elevated G allele frequency in males (Puspitasari et al., 2020). The polymorphism showed no significant gender differences in populations from China and the United Kingdom (Bunten et al., 2011; Ding et al., 2013). Together, these varied observations highlight the impact of population-specific factors on the OPRM1 A118G gene polymorphism distribution. The intricate interplay between gender and genetic diversity introduces additional complexity to the overall genetic landscape, underscoring the importance of considering population-specific variations in genetic studies.

Numerous studies have unveiled a compelling association between the A118G OPRM1 polymorphism and its impact on opioid-induced analgesia and therapeutic response. Investigations indicate that cancer patients possessing the G allele of rs1799971 necessitate escalated opioid analgesia for effective pain management compared to carriers of the A allele (Yu et al., 2019). In a recent cross-sectional exploration involving cancer patients within Saudi Arabia, an intriguing gender-based disparity emerged. Specifically, female patients reported experiencing more severe pain and exhibited heightened requirements for opioid analgesics when contrasted with their male counterparts (Alodhayani et al., 2021). The higher prevalence of the G allele of the A118G OPRM1 polymorphism among Saudi females potentially suggests a role for this genetic variant in contributing to the observed escalation of pain levels among female cancer patients. This finding underscores the intricate interplay between genetic factors and pain perception, which warrants further exploration to elucidate its precise implications in cancer-related pain management.

The A118G OPRM1 polymorphism, along with other common variants, represents a set of risk factors associated with opioid addiction. A study by Zhou et al. (2020) reported a significant association between the G allele of rs1799971 and opioid use disorder, including the risk of nicotine depend-

ence, depression, and cognition impairment, among European American individuals.

Conversely, other research, such as the collaborative genetic meta-analysis by Schwantes-An et al. (2016), indicated a protective effect of the G allele against substance dependence liability in populations of European ancestry. This suggests that individuals carrying the G allele may have a reduced risk of developing substance dependence.

In Saudi Arabia, narcotics and alcohol use/possession are forbidden both legally and according to religious law; however, drug addiction still exists (Saquib et al., 2020). Around 7% to 8% of Saudi males report using drugs, though drug addiction is less common among Saudi females (Ibrahim et al., 2018). Saudis' most commonly abused substances are heroin, amphetamines, alcohol, and cannabis. The elevated prevalence of the G allele of rs1799971 among Saudi females could potentially contribute to the observed lower incidence of drug dependence. It is important to note that genetics alone do not solely determine drug dependence. Environmental factors, social influences, mental health, and other genetic variations collectively contribute to an individual's susceptibility to drug dependence. Therefore, while the G allele of rs1799971 may play a role in modulating drug dependence risk, its effect is likely influenced by a complex interplay of genetic and environmental factors. Further research is needed to fully elucidate the precise mechanisms underlying the association between the G allele of rs1799971 and drug dependence across different populations and substances.

Conclusion

This study contributes novel insights into the A118G OPRM1 polymorphism distribution within Jeddah, Saudi Arabia. Subsequent investigations employing larger sample sizes and encompassing diverse geographical regions within the country are recommended to provide a more comprehensive estimation of the prevalence of the A118G OPRM1 polymorphism among the Saudi population. This understanding of polymorphism frequency holds the potential to optimize therapeutic outcomes while minimizing the risk of adverse effects associated with opioid analgesics. Furthermore, this data could prove valuable in predicting susceptibility to alcohol and opioid dependence and influencing breast cancer susceptibility.

Acknowledgments
The authors would like to thank the volunteers for participating in the study.

Conflict of interest
The authors have no conflict of interest to declare.

Ethics statement
The study protocol was reviewed and approved by the Research Ethics Committee at the School of Dentistry (076-03-23).

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