homozygous carriers, respectively, of the *OPRM1* 118G allele would have been expected.

On the other hand, the compliance with the predictions from the Hardy-Weinberg equilibrium does not necessarily make a selected sample a random sample. In a study on the consequences of the G118 allele for the effects of morphine, performed in selected Caucasian subjects consisting of six noncarriers of the *OPRM1* 118G allele, four heterozygous carriers, and two homozygous carriers,[10] the distribution of the genotypes corresponded to the Hardy-Weinberg equilibrium ($\chi^2 = 2.3$, $df = 2$, $P = 0.317$). Nevertheless, the allelic frequency of 22.2% cannot be compared with other reported frequencies of the *OPRM1* 118G allele in Caucasians because by recruitment policy, the sample from which it originates was not a random sample.

To ease comparisons between study populations and to not to burden the reader with calculations of basic genetic statistics, studies of genetics in anesthesia should contain standard genetic statistics and precise information about recruitment procedure of the subjects with respect to genotypes. Violations of the Hardy-Weinberg law should be commented on, and preferably, in those cases, the correctness of the genetic screening should be double checked to avoid violations of distribution predictions due to assay error.

Jörn Lötsch, M.D., *pharmazentrum frankfurt/*ZAFES, Institute of Clinical Pharmacology, Johann Wolfgang Goethe-University, Frankfurt am Main, Germany. j.loetsch@em.uni-frankfurt.de

References

1. Chou W-Y, Wang C-H, Liu P-H, Liu C-C, Tseng C-C, Jawan B: Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. ANESTHESIOLOGY 2006; 105:334–7
2. Hardy GH: Mendelian proportions in a mixed population. Science 1908; 28:49–50
3. Snedecor GW, Cochran WG: Statistical Methods, 8th edition. Ames, IA, Iowa State University Press, 1989
4. Oertel BG, Schmidt R, Schneider A, Geisslinger G, Lötsch J: The mu-opioid receptor gene polymorphism 118A>G depletes alfentanil induced analgesia and protects against respiratory depression in homozygous carriers. Pharmacogenetics 2006; 16:625–36
5. Skarke C, Kirchhof A, Geisslinger G, Lötsch J: Comprehensive mu-opioid-receptor genotyping by pyrosequencing. Clin Chem 2004; 50:640–4
6. Landau R, Cahana A, Smiley RM, Antonarakis SE, Blouin JL: Genetic variability of μ-opioid receptor in an obstetric population. ANESTHESIOLOGY 2004; 100:1030–3
7. Tan EC, Tan CH, Karupathivan U, Yap EP: Mu opioid receptor gene polymorphisms and heroin dependence in Asian populations. Neuroreport 2003; 14:569–72
8. Klepstad P, Rakvag TT, Kaasa S, Holthe M, Dale O, Borchgrevink PC, Baar C, Vikan T, Krokan HE, Skorpen F: The 118 A > G polymorphism in the human micro-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. Acta Anaesthesiol Scand 2004; 48:1232–9
9. Chou WY, Yang LC, Lu HF, Ko JY, Wang CH, Lin SH, Lee TH, Concejero A, Hsu CJ: Association of mu-opioid receptor gene polymorphism (A118G) with variations in morphine consumption for analgesia after total knee arthroplasty. Acta Anaesthesiol Scand 2006; 50:787–92
10. Skarke C, Darimont J, Schmidt H, Geisslinger G, Lötsch J: Analgesic effects of morphine and morphine-6-glucuronide in a transcutaneous electrical pain model in healthy volunteers. Clin Pharmacol Ther 2003; 73:107–21

(Accepted for publication February 19, 2007.)

Anesthesiology 2007; 107:169

In Reply:—We thank Dr. Lötsch for his comments regarding our work.[1] Strictly speaking, his comments for the Hardy-Weinberg equilibrium are correct, but they may not apply to our study. For the Hardy-Weinberg equations to apply, several conditions must be met. No mutations can be occurring, no natural selection pressures must be operating, the population of interest is infinitely large, all members of the population must breed and mating is totally random, and there must be no in or out migration of the populations.* There are several situations in regard to our study sample that may violate one or more of these conditions.

First, we worked with a "convenience" (nonrandom), small (80-subject) sample. Because these were surgical patients (and only women), this sample may not be representative of the "infinite population."

Second, because our patients were drawn from a limited geographic area, they may not be representative of the population as a whole. We cannot exclude the possibility that inbreeding (or in/out migration) may have occurred; in small human groups, such factors cannot be controlled nor easily identified.

Third, the locus of interest is autosomal (males and females have similar allele frequency).

Fourth, because we know so little about the evolutionary impact of these alleles, it is impossible to know whether evolutionary pressures exist within our population or our sample. It is entirely possible that different genotypes in the human opioid receptor A118G polymorphism may convey different degrees of "evolutionary fitness."

If the assumptions underlying the Hardy-Weinberg equilibrium are violated, statistical methods using allele frequencies may not be valid, and methods that use genotype frequencies should be preferred.[2]

In summary, although we thank Dr. Lötsch for his thoughtful comments, we do not believe that they invalidate the basic observations contained in our study.

Wen-Ying Chou, M.D.,† Ping-Hsin Liu, M.D., Chien-Cheng Liu, M.D., Chia-Chih Tseng, M.D., Bruno Jawan, M.D. †Chang Gung Memorial Hospital–Kaohsiung Medical Center, Chang Gung University College of Medicine, Taiwan. wych@ms21.hinet.net

References

1. Chou W-Y, Wang C-H, Liu P-H, Liu C-C, Tseng C-C, Jawan B: The human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. ANESTHESIOLOGY 2006; 105:334–7
2. Xu J, Turner A, Little J, Bleecker ER: Positive results in association studies are associated with departure from Hardy-Weinberg equilibrium: Hint for genotyping error? Hum Genet 2002; 111:573–4

(Accepted for publication February 19, 2007.)

* Dorak MT: Basic population genetics. Available at: http://www.dorak.info/genetics/popgen.html. Accessed April 2, 2007.