Table 2. PCR for MCV DNA in comparison control tissues ($n = 84$). For detailed description of tissues and tissue sites, see table S2. MCV positivities marked with plus and minus symbols together are as in Table 1. For the various body site tissues, there were 59 samples; for the skin and skin tumor tissues, the sample size was 25 (table S2).

	MCV positivity
Various body site tissues	
Total MCV negative (%)	54/59 (92)
Total MCV positive (%)	5/59 (8)
Appendix control 1	−/+
Appendix control 2	−/+
Gall bladder	−/+
Bowel	−/+
Hemorrhoid	−/+
Skin and skin tumor tissues	
Total MCV negative (%)	21/25 (84)
Total MCV positive (%)	4/25 (16)
Skin	−/+
KS skin tumor 1	−/+
KS skin tumor 2	−/+
KS skin tumor 3	−/+

21. J. Parsonnet, in *Microbes and Malignancy*, J. Parsonnet, Ed. (Oxford Univ. Press, New York, 1999), pp. 3–18.
22. Y. Xu *et al.*, *Genomics* 81, 329 (2003).

23. We thank the National Cancer Institute–supported Cooperative Human Tissue Network for tissues used in this study, M. Aquafondata for tissue staining, P. S. Schnable for sharing cDNA data sets used in DTS pilot testing, O. Gjoerup and R. D. Wood for helpful comments, and J. Zawinul for help with the manuscript. Supported in part by funds from NIH R33CA120726 and the Pennsylvania Department of Health. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

Supporting Online Material
www.sciencemag.org/cgi/content/full/1152586/DC1
Materials and Methods
Figs. S1 to S3
Tables S1 to S5
References

5 November 2007; accepted 8 January 2008
Published online 17 January 2008;
10.1126/science.1152586
Include this information when citing this paper.

Worldwide Human Relationships Inferred from Genome-Wide Patterns of Variation

Jun Z. Li,[1,2]*† Devin M. Absher,[1,2]* Hua Tang,[1] Audrey M. Southwick,[1,2] Amanda M. Casto,[1] Sohini Ramachandran,[4] Howard M. Cann,[5] Gregory S. Barsh,[1,3] Marcus Feldman,[4]‡ Luigi L. Cavalli-Sforza,[1]‡ Richard M. Myers[1,2]‡

Human genetic diversity is shaped by both demographic and biological factors and has fundamental implications for understanding the genetic basis of diseases. We studied 938 unrelated individuals from 51 populations of the Human Genome Diversity Panel at 650,000 common single-nucleotide polymorphism loci. Individual ancestry and population substructure were detectable with very high resolution. The relationship between haplotype heterozygosity and geography was consistent with the hypothesis of a serial founder effect with a single origin in sub-Saharan Africa. In addition, we observed a pattern of ancestral allele frequency distributions that reflects variation in population dynamics among geographic regions. This data set allows the most comprehensive characterization to date of human genetic variation.

In the past 30 years, the ability to study DNA sequence variation has dramatically increased our knowledge of the relationships among and history of human populations. Analyses of mitochondrial, Y chromosomal, and autosomal markers have revealed geographical structuring of human populations at the continental level (*1–3*) and suggest that a small group of individuals migrated out of eastern Africa and their descendants subsequently expanded into most of today's populations (*3–6*). Despite this progress, these studies were limited to a small fraction of the genome, to limited populations, or both, and yield an incomplete picture of the relative importance of mutation, recombination, migration, demography, selection, and random drift (*7–10*). To substantially increase the genomic and population coverage of past studies (e.g., the HapMap Project), we have examined more than 650,000 single-nucleotide polymorphisms (SNPs) in samples from the Human Genome Diversity Panel (HGDP-CEPH), which represents 1064 fully consenting individuals from 51 populations from sub-Saharan Africa, North Africa, Europe, the Middle East, South/Central Asia, East Asia, Oceania, and the Americas (*11*). This data set is freely available (*12*) and allows a detailed characterization of worldwide genetic variation.

We first studied genetic ancestry of each individual without using his/her population identity. This analysis considers each person's genome as having originated from K ancestral but unobserved populations whose contributions are described by K coefficients that sum to 1 for each individual. To increase computational efficiency, we developed new software, *frappe*, that implements a maximum likelihood method (*13*) to analyze all 642,690 autosomal SNPs in 938 unrelated and successfully genotyped HGDP-CEPH individuals (*14*). Figure 1A shows the results for $K = 7$; those for $K = 2$ through 6 are in fig. S1. At $K = 5$, the 938 individuals segregate into five continental groups, similar to those re-

[1]Department of Genetics, Stanford University School of Medicine, Stanford, CA 94305–5120, USA. [2]Stanford Human Genome Center, Stanford University School of Medicine, Stanford, CA 94305–5120, USA. [3]Department of Pediatrics, Stanford University School of Medicine, Stanford, CA 94305–5120, USA. [4]Department of Biological Sciences, Stanford University, Stanford, CA 94305–5120, USA. [5]Foundation Jean Dausset-Centre d'Etude du Polymorphisme Humain (CEPH), 75010 Paris, France.

*These authors contributed equally to this work.
†Present address: Department of Human Genetics, University of Michigan, 5789A MS II, Ann Arbor, MI 48109–5618, USA.
‡To whom correspondence should be addressed. E-mail: marc@charles.stanford.edu (M.F.); cavalli@stanford.edu (L.L.C.S.); myers@shgc.stanford.edu (R.M.M.)

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2007. 11. 22	該当なし	

一般的名称	(製造承認書に記載なし)	研究報告の公表状況	Kato Y, Masuda G, Itoda I, Imamura A, Ajisawa A, Negishi M. J Travel Med. 2007 Sep-Oct;14(5):343-5.	公表国 日本
販売名(企業名)	合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社) 合成血-LR「日赤」(日本赤十字社) 照射合成血-LR「日赤」(日本赤十字社)			

研究報告の概要

○海外帰国者とその妻におけるブルセラ症:*Brucella melitensis*のヒトーヒト感染の可能性

ブルセラ症は世界では一般的な人獣共通感染症で、年間50万例以上のヒト感染症例がある。ブルセラ症の一次感染は、*Brucella*種に汚染された殺菌処理されていない乳製品の摂取によって起こるが、複数の報告で男性から女性パートナーへブルセラ症が伝播した可能性が示唆されており、それらの症例は性交渉による感染と考えられてきた。

症例1:64歳の日本人男性が、6週間続く発熱で1998年6月2日に都内の病院に入院した。過去1週間の激しい腰痛も訴えた。入院時の血液培養からグラム陰性桿菌が検出され、*Brucella melitensis*バイオタイプ2と同定された。ブルセラ菌抗体価は800IUで、骨髄と肝生検からブルセラ症と確定された。患者は同年3月にイラクのバグダッドに10日間の滞在歴があり、滞在中にヒツジのチーズを摂取したことが判明した。抗生物質の投与によって症状は治まり、4ヵ月の投薬で完全に回復した。

症例2:患者1の妻で60歳の日本人女性が、1998年5月31日から発熱と左胸鎖関節の痛みを訴え始めた。血液と関節液の培養で*B melitensis*が生育した。ブルセラ菌抗体価は800IUであったが、抗生物質の投与によって回復した。患者はイラクへの渡航歴はなく、ブルセラ症に関する他のリスク要因もなかった。

考察:イラクを含め中東ではブルセラ症の発生数は多いが、日本では稀なことから、患者1は海外滞在中にブルセラ症に感染したと考えられる。2人の患者の発症には1ヵ月程度の間隔があり、標準的なブルセラ症の潜伏期間と一致する。患者1はイラクから日本に乳製品を持ち込んでおらず、患者2とブルセラ症との疫学的関連はない。患者1は疾患初期に患者2と性交渉があったことを報告しており、おそらく患者1から患者2への性感染が起こったと考えられる。同様に性感染と考えられる症例は過去にも報告されている。

報告企業の意見	今後の対応
イラクからの帰国者からその妻へ、ブルセラ症が性感染した可能性があるとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、問診で発熱などの体調不良者を献血不可としている。今後も引き続き情報の収集に努める。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」
合成血-LR「日赤」
照射合成血-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

Brucellosis in a Returned Traveler and His Wife: Probable Person-To-Person Transmission of *Brucella melitensis*

Yasuyuki Kato, MD, Gohta Masuda, MD, Ichiro Itoda, MD, Akifumi Imamura, MD, Atushi Ajisawa, MD, and Masayoshi Negishi, MD

Department of Infectious Diseases, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

DOI: 10.1111/j.1708-8305.2007.00139.x

Brucellosis is the most common zoonosis worldwide, with more than 500,000 new human cases annually. Although brucellosis is primarily transmitted to humans through the consumption of unpasteurized dairy products contaminated with *Brucella* species, several reports have indicated that brucellosis may be transmitted from a man to his female partner. It has been suggested that sexual intercourse is a means of transmission in these cases. Here, we describe an additional case of probable person-to-person transmission of *Brucella melitensis* in an elderly couple.

Case Report 1

A previously healthy 64-year-old Japanese man with a 6-week history of febrile illness was admitted to hospital in Tokyo, Japan, on June 2, 1998, following a 10-day visit to Baghdad, Iraq, on March 8, 1998. He also complained of severe lower back pain for 1 week. Findings on admission were fever (maximum temperature, 39.5°C) and normal pulse rate (80 beats/min). Neither heart murmurs nor adventitious breath sounds was heard. The liver was palpable 2 cm below the right costal margin; yet, the spleen was not palpated. He had tenderness of the lumber spine without abnormal neurological findings. He had no signs of epididymoorchitis. The white blood cell count was 8,400/μL and hemoglobin concentration 12.5 g/dL. Liver function tests showed elevation of alkaline phosphatase (378 IU/L) and alanine aminotransferase (67 IU/L). The erythrocyte sedimentation rate was 67 mm/h. Urinalysis findings were normal. Chest X-ray showed no opacities. T1-weighted magnetic resonance imaging of the spine revealed decreased signal intensity in the L3, L4, and L5 vertebral bodies and adjacent epidural space. These findings indicated that the patient had spondylitis, complicated by an epidural abscess.

The Gram-negative bacilli yielded by the blood culture at admission were subsequently confirmed as *Brucella melitensis* biotype 2. The *Brucella* antibody titer by the tube agglutination test was 800 IU. In addition, bone marrow and liver biopsy specimens showed evidence of granulomas consistent with brucellosis. A detailed travel history revealed that he had consumed sheep's cheese during his stay in Iraq. After confirmation of brucellosis, he was treated with intramuscular streptomycin (1 g daily), oral doxycycline (100 mg twice daily), and rifampicin (600 mg daily) for 1 month, and the fever and lower back pain gradually subsided. This treatment was followed by oral rifampicin (600 mg daily), trimethoprim–sulfamethoxazole (two standard-strength tablets twice daily), and tosufloxacin (200 mg thrice daily) for 4 months, with complete resolution.

Case Report 2

The wife of patient 1, a previously healthy 60-year-old Japanese woman, began to complain of fever and pain in the left sternoclavicular joint on May 31, 1998. Cultures of blood and the joint fluid grew *B melitensis* biotype 2. The *Brucella* antibody titer by the tube agglutination test was 400 IU. She was successfully treated with oral rifampicin (600 mg daily) and doxycycline (100 mg twice daily) for 6 weeks in combination with intramuscular streptomycin (750 mg daily) for the first 3 weeks. She did not visit Iraq with her husband and had no other risk factors for brucellosis.

Corresponding Author: Yasuyuki Kato, MD, Disease Control and Prevention Center, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku, Tokyo 162-8655, Japan. E-mail: ykato@imcj.hosp.go.jp

Discussion

The Middle East, including Iraq, has the highest incidence of brucellosis in the world, whereas Japan is considered to be a brucellosis-free country.[1] Brucellosis is one of the reportable infectious diseases in Japan. According to the national surveillance data, only three cases of human brucellosis and two of livestock brucellosis were reported between 1999 and 2005 in Japan. No outbreaks of animal or human brucellosis were reported in Japan in 1998. Considering the incubation period of brucellosis (usually 2–4 wk, up to several months), his consumption of sheep's cheese in a brucellosis-endemic country, Iraq, and the rarity of brucellosis in his residential country, Japan, it is likely that patient 1 contracted brucellosis during his stay abroad.

The serial interval of the disease onset between patient 1 and patient 2 was approximately 1 month, which is similar to the mean incubation period of human brucellosis. Although the incubation period of brucellosis varies widely, it is difficult to argue that a common source exposure, such as food poisoning, occurred in these two patients, since patient 1 did not bring any dairy products or animals into Japan from Iraq. Furthermore, patient 2 had no other epidemiological links to brucellosis. Therefore, it is strongly suggested that the disease was transmitted from patient 1 to patient 2.

Through a PubMed search (1966–2005), we found six case reports of probable person-to-person transmission, excluding cases associated with blood transfusion, bone marrow transplantation, and breast-feeding (Table 1). Two of them are associated with international travel. In summary, it seems that men with symptoms of brucellosis are able to transmit the disease to their female partners. It is speculated that sexual transmission occurred in these cases since this is well known in animals. Interestingly, Mantur and colleagues reported that *B melitensis* was isolated from the semen, urine, and saliva of a man with epididymoorchitis, who transmitted the disease to his wife.[6] However, the presence of epididymoorchitis does not seem to be related to the transmissibility of human brucellosis. Furthermore, another report described that *B melitensis* was isolated from the sperm of one patient.[8] Patient 1 reported that he had intercourse with patient 2 during the initial stages of the disease. Therefore, we consider that person-to-person transmission, probably sexual transmission, of *B melitensis* occurred in our case.

Table 1 Published case reports of probable person-to-person transmission of brucellosis between men and women (English literature only)

Case reports	Goossens et al[2]	Stantic-Pavlinic et al[3]	Ruben et al[4]	Lindberg et al[5]	Mantur et al[6]	Thalhammer et al[7]	Present case
Age (y), sex, risk factor of primary case	25, male, laboratory exposure	34, male, laboratory exposure	61, male, laboratory exposure	35, male, travel to endemic area	30, male, animal exposure	25, male, travel to endemic area	65, male, travel to endemic area
Epididymoorchitis	Absent	Absent	Absent	Present	Present	Absent	Absent
Country where primary case was infected	Belgium	Yugoslavia	United States	Spain	India	Syria	Iraq
Age (y), sex, relationship of secondary case	21, female, fiancée	30, female, spouse	61, female, spouse	30, female, girlfriend	22, female, spouse	ND, female, girlfriend	60, female, spouse
Serial interval between two cases	3 mo	3 mo	8 mo	5 mo	1 mo	2 mo	1 mo
Isolated *Brucella* species and biotype	*Brucella melitensis* biotype 3	*B melitensis* biotype 2	*B melitensis* biotype 3	*B melitensis* biotype ND	*B melitensis* biotype 1	*Brucella abortus* biotype ND	*B melitensis* biotype 2
Suspected transmission route	Sexual intercourse	Sexual intercourse	Sexual intercourse	Sexual intercourse	Sexual intercourse	Sexual intercourse	Sexual intercourse

ND = not determined.

Although it has a little role in the epidemiology of brucellosis, person-to-person transmission is rather important in areas where brucellosis is not endemic such as most of developed countries; brucellosis has become a common imported disease in these areas.[9] Febrile-returned travelers should be educated to abstain from sexual intercourse because they could transmit the diseases to their partners. We would like to add brucellosis to the list of travel-related infections that are transmissible through sexual intercourse. This unusual mode of transmission of a common zoonosis requires special attention.

Acknowledgments

The authors thank Dr Yumiko Imada at the National Institute of Animal Health, Japan, for the identification of *B melitensis* and performance of serum agglutination tests for *Brucella*.

Declaration of Interests

The authors state that they have no conflicts of interest.

References

1. Pappas G, Papadimitriou P, Akritidis N, et al. The new global map of human brucellosis. Lancet Infect Dis 2006; 6:91–99.
2. Goossens H, Marcelis L, Dekeyser P, Butzler JP. *Brucella melitensis*: person-to-person transmission? Lancet 1983; 1:773.
3. Stantic-Pavlinic M, Cec V, Mehle J. Brucellosis in spouses and the possibility of interhuman infection. Infection 1983; 11:313–314.
4. Ruben B, Band JD, Wong P, Colville J. Person-to-person transmission of *Brucella melitensis*. Lancet 1991; 337:14–15.
5. Lindberg J, Larsson P. Transmission of *Brucella melitensis*. Lancet 1991; 337:848–849.
6. Mantur BG, Mangalgi SS, Mulimani M. *Brucella melitensis*—a sexually transmissible agent? Lancet 1996; 347:1763.
7. Thalhammer F, Eberl G, Kopetzki-Kogler U. Unusual route of transmission for *Brucella abortus*. Clin Infect Dis 1998; 26:763–764.
8. Vandercam B, Zech F, de Cooman S, et al. Isolation of *Brucella melitensis* from human sperm. Eur J Clin Microbiol Infect Dis 1990; 9:303–304.
9. Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. N Engl J Med 2005; 352:2325–2336.

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2008. 2. 18	該当なし	

一般的名称	新鮮凍結人血漿	研究報告の公表状況	Bertherat E, Bekhoucha S, Chougrani S, Razik F, Duchemin JB, Houti L, Deharib L, Fayolle C, Makrerougrass B, Dali-Yahia R, Bellal R, Belhabri L, Chaieb A, Tikhomirov E, Carniel E. Emerg Infect Dis. 2007 Oct;13(10):1459-1462.	公表国 アルジェリア
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社)			

研究報告の概要

○2003年のアルジェリアにおける50年ぶりのペスト再興
2003年6月から7月にアルジェリアOran地区においてペストの集団感染が発生した。アルジェリアでは、この疾患が50年以上報告されていなかった。腺ペスト症例18名が特定され、*Yersinia pestis*が6名から分離された。初発患者を除き、全員が回復した。標的予防的化学療法、公衆衛生、ベクターコントロールが、感染制御上重要な役割を果たした。疫学的、分子生物学的な知見から、当該期間中、現地の保菌動物の存在が強く示唆されたが、その起源(再興または再持ち込み)については特定できなかった。主要な貿易港における、今回の突然かつ予期せぬペスト再興は、国際的に重要な意味を持つ公衆衛生問題の典型的な例である。また、今回の再興は、ペスト再興の危険性が現在確認されているnatural foci(げっ歯類がペスト菌を保有する地区)に限られるものではないことも示している。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」

血液を介するウイルス、
細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
2003年6月から7月にアルジェリアOran地区において、50年ぶりに腺ペストの集団感染が発生したとの報告である。	日本赤十字社は、輸血感染症対策として献血時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。今後も引き続き情報の収集に努める。

Plague Reappearance in Algeria after 50 Years, 2003

Eric Bertherat,* Souad Bekhoucha,† Saada Chougrani,‡ Fathia Razik,† Jean B. Duchemin,§ Leila Houti,‡ Larbi Deharib,‡ Corinne Fayolle,¶ Banaouda Makrerougrass,‡ Radia Dali-Yahia,† Ramdan Bellal,† Leila Belhabri,# Amina Chaieb,* Evgueni Tikhomirov,* and Elisabeth Carniel¶

An outbreak of plague occurred in the region of Oran, Algeria, from June to July 2003. Algeria had not reported this disease for >50 years. Eighteen bubonic cases were identified, and *Yersinia pestis* was isolated from 6 patients. Except for the index case-patient, all patients recovered. Targeted chemoprophylaxis, sanitation, and vector control played a crucial role in controlling the outbreak. Epidemiologic and biomolecular findings strongly suggested the existence of a local animal reservoir during this period, but its origin (resurgence or re-importation) could not be determined. This sudden and unexpected reemergence of plague, close to an important commercial seaport, is a textbook illustration of a public health event of international importance. It also demonstrates that the danger of plague reoccurrence is not limited to the currently indexed natural foci.

Plague is primarily a bacterial zoonosis affecting rodents. It is caused by *Yersinia pestis* and is transmitted from animal to animal by fleas. Humans usually become infected through the bite of an infected rodent flea. Bubonic plague, a severe infectious disease which, in the absence of appropriate antimicrobial drug therapy, can evolve to a rapidly fatal septicemia or pneumonia, can develop. A pneumonia form, which enables direct transmission to contacts, can be responsible for highly lethal outbreaks.

Currently, plague natural foci persist in Asia, the Americas, and Africa (where most human cases occur) (*1*). Plague foci have previously existed in the northern part of Africa but gradually disappeared in the last century, for unknown reasons. Libya is the only north African country that has experienced human cases in the past 40 years (*2*). In Algeria, archives report epidemics of plague as far back as the 14th century. These epidemics mainly affected ports, particularly that of Oran in 1556 and 1678 (3,000 deaths). In 1899, after an absence of nearly 100 years, plague reappeared in the port of Philippeville (now Skikda). Three large epidemics were subsequently reported in 1921 (185 cases), 1931 (76 cases), and 1944 (95 cases) as well as 158 sporadic cases. All but 2 cases occurred in ports (*3*,*4*). No natural focus of plague had ever been described in Algeria (*5*). We describe an outbreak of bubonic plague that occurred in 2003 in Algeria, where the last reported human case occurred in Oran in 1946 (*6*).

Methods

During June 9–18, 2003, several patients with signs of severe infection and painful inflammatory adenopathy were admitted to the University Hospital of Oran. All came from Kehailia (35°29′N, 0°32′E), a village of 1,300 inhabitants 25 km south of Oran. After eliminating all other possible differential diagnoses, clinicians suspected plague. The diagnosis was confirmed on June 18 by results of analysis of a bubo (lymph node) aspirate. A technical crisis committee was set up, and a case definition was adopted (Table). Any patient with a febrile syndrome and adenopathy who resided in the prefecture of Oran was hospitalized.

Clinical samples collected from patients (blood, bubo aspirate, cerebrospinal fluid) were sent to the Microbiology Department, University Hospital, Oran. Several of the initial cases were first diagnosed with the rapid diagnostic test (RDT) for plague developed by the Institut Pasteur (*7*); however, all samples were also examined with standard bacteriologic methods. Direct examination of smears was performed after Wayson and Gram staining. Blood samples were cultured in Castaneda medium for at least 10 days

*World Health Organization, Geneva, Switzerland; †University Hospital, Oran, Algeria; ‡University of Medicine, Oran, Algeria; §Centre d'Etude et de Recherche pour les Meningocoques et les Schistosomiases, Niamey, Niger; ¶Institut Pasteur, Paris, France; and #Institut Pasteur, Oran, Algeria