Consanguinity in the Contemporary World

Giovanni Romeo^{a, b} Alan H. Bittles^{c, d}

^aAlma Mater Studiorum, and ^bEuropean School of Genetic Medicine, Bologna, Italy; ^cMurdoch University, and

^dEdith Cowan University, Perth, W.A., Australia

In medical genetics literature, a consanguineous marriage is usually defined as the union of a couple related as second cousins or closer ($F = 0.0156$) [1], although in some subpopulation isolates, for example in Finland, it has been demonstrated that more distant genetic relationships may also be important in the expression of rare recessive disorders [2]. Until the middle of the 19th century, close-kin marriage was commonplace and widely accepted in Western countries, albeit with general disapproval from the Orthodox Church and diocesan dispensation required for cousin marriages conducted within the Roman Catholic Church [3].

A significant change in the public attitude occurred thereafter, with a gradual decline in the popularity of consanguineous unions in Western Europe, where affine relationships had previously been regarded with suspicion, in particular between a man and his deceased wife's sister in Victorian England [4]. At the same time, in the USA, an increasing number of states introduced a legislation banning first-cousin marriages [5]. These trends have continued so that, with the exception of recent migrant communities, close-kin unions now account for <1% of marriages in Western countries (www.consang.net; fig. 1).

The rarity of consanguineous marriage in much of the industrialized world, and the current restriction or outright prohibition of first-cousin unions in a majority of US states and in East Asian countries such as China, North and South Korea and the Philippines, has led many commentators to overlook the fact that the Out-of-Africa migration some 60,000–70,000 years ago had been undertaken by quite small numbers of individuals. Current estimates of the numbers of migrants generally agree on a maximum of approximately 10,000 breeding individuals [6–9], but with some simulations suggesting as few as 700 or even 450 emigrating adults [10, 11]. There is some controversy as to whether the migration from Africa was accompanied by one or more bottlenecks [12–14] and the possibility of limited back-migration to North Africa [15], but population expansions over ensuing generations have led to the fact that some 6.0 billion of the current global population of 7.3 billion are Out-of-Africa descendants [16].

It seems inevitable that reproduction would have involved closely related individuals during the early days of these population expansions, when human groups remained small in number, largely nomadic, and geographically scattered, and this pattern of partner choice per-

Fig. 1. Global map of consanguineous marriages.

sisted well into historical times. It therefore is no surprise that genomic studies on samples from the HGDP-CEPH [17] and HapMap panels [18–20] have demonstrated the existence of previously unsuspected genetic relationships. Even in a recent heterogeneous sample of 5,000 Europeans drawn from both isolated and cosmopolitan communities, tens of thousands of second- to ninth-cousin pairs have been identified [21].

From a present-day consanguinity perspective, most attention is paid to populations and societies where close-kin marriage continues to be strongly favored. As illustrated in figure 1, the regions which are mainly involved are North and Sub-Saharan Africa, the Middle East, and West, Central and South Asia, with a conservatively estimated 1.1 billion people resident in countries where 20–50% of marriages or more are consanguineous [3, 22]. This emphasis is reflected in the present special issue of *Human Heredity*, with a strong focus on the populations of these regions and on migrant populations with origins in different parts of Asia and Africa.

Within genetics, contemporary medical and scientific attention on consanguineous marriage continues to be largely focused on rare autosomal recessive diseases. But from an overall population and health perspective, consanguinity is a much more extensive and complex topic

that also involves major social, economic, and demographic influences [23]. Genome analysis is, however, the principal unifying theme, since next-generation sequencing is increasingly indispensable in population profiling [24] and disease diagnosis [25] and is thus central to investigations into the biological and health outcomes of consanguinity. In this context, consanguinity serves as an effective magnifying device for the identification of genes involved in rare autosomal recessive disorders, based on autozygosity mapping and exome homozygosity (EX-HOM) approaches [26, 27].

In endogamous populations, the application of whole genome analysis for genes implicated in the expression of complex genetic disorders will be of major importance to medicine in the coming years. This investigative approach has been elegantly demonstrated in the ongoing Sardinia project [28], which employs a combined strategy of low-coverage whole genome sequencing and SNP arrays to demonstrate highly significant associations between rare or low-frequency genetic variants and specific cellular phenotypes. The genetic contribution of regulatory variants to quantitative traits can in turn be identified, thus helping to elucidate their involvement in disease.

Studies on highly endogamous populations can also be very useful in estimating human mutation rates, as has

recently been reported with the Hutterite community, Anabaptist farmers who have lived in close-knit colonies in the plains of the USA and Canada since the late 19th century. As the descendants of a small group of genetically and demographically well-defined European founders, Hutterite individuals carry large segments of their genome that are autozygous. The accumulation of mutations in alleles in autozygous segments during recent generations thus makes it possible to identify the occurrence of new mutational events [29].

The analysis of disease-causing mutations in the children of consanguineous parents has additionally facilitated the calculation of reliable incidence estimates for autosomal recessive disorders [30–33] by essentially following the same strategy which in the pre-molecular

era was based solely on demographic data [34–37]. During that earlier era, consanguineous marriages showed major variations in space and time for different populations. National data could therefore only be collected in a systematic way for Italy, thanks to the unique resources of the Vatican Archives for consanguineous marriage dispensations available for the whole Italian population for the period of 1600–1964 [38]. Given the rapidly increasing access to next-generation sequencing facilities, together with a very significant lowering of costs, a major expansion of molecular epidemiological studies on disease genes based on consanguineous families and communities can be predicted within the near future.

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