Commentary

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# Time to Get Real: Investigating Potential Beneficial Genetic Aspects of Consanguinity

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The extensive and well-documented application of close genetic crosses in animal and plant breeding has amply demonstrated that, from a biological perspective, inbreeding is not necessarily detrimental, although a substantial price may have to be paid with respect to reduced viability and vigor in some progeny. However, in terms of specific phenotypic characteristics, and as long as the intensity of inbreeding does not become excessive, the benefits of selecting for specific recessive traits can outweigh the disadvantages.

Dynastic and less commonly non-dynastic sib and half-sib marriage has been described in Egypt and other early civilizations [1], and first cousin marriage is commonplace in many present-day countries and communities, with uncle-niece and double first cousin unions also popular in specific populations [2; www.consang.net]. Despite the widespread prevalence of these practices, it has been widely, if uncritically, assumed in modern Western society that in evolutionary and historical terms non-consanguineous mating and marriage was the human norm, with the further implicit belief that outbreeding represents the 'civilized' marital option.

Recent estimates derived for the effective size of the out-of Africa founder population have varied from 10,000 to as few as 700 individuals [3–6], which indicates that humans are much more 'inbred' than previously suspected [2, 7]. This contention is supported by genome-wide SNP analyses that have demonstrated the existence of uninterrupted runs of homozygosity (RoH), frequently exceeding 5 Mb in length in Europeans [8] and >26 Mb in a Han Chinese individual [9]. Further, in a northern European island population, RoH up to 4 Mb were commonly identified in individuals with no record of ancestral consanguinity during the previous 5–10 generations [10].

Against this background, the review of consanguineous marriage by Dr. Denic and his colleagues [11] is something of a mixed bag. As noted above, I have considerable sympathy for their premise that consanguinity may be genetically beneficial, especially under specific ecological circumstances, but the case they have presented is less than totally convincing. There are several basic reasons for my lack of enthusiasm. The first major reservation relates to the overuse of statements purporting to be factual, but with no supporting evidence presented or appropriate reference to published articles for verification. This is important, because in seeking to compare the health outcomes of consanguineous and non-consanguineous progeny, it is essential that credible non-consanguineous baseline estimates are employed.

Thus the statement that 'The incidence of genetic birth defects in non-consanguineous families is approximately

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2%' is at variance with the widely cited estimate for congenital malformation of 36.5/1,000 in populations of northern European origin [12]. Furthermore, a recent review endorsed by the American Academy of Pediatrics conservatively estimated that 50/1,000 live births have a congenital heart defect [13], which suggests that the overall incidence of congenital defects is significantly higher than previously expected and far exceeds that assumed by Denic et al. Similar vague and unsubstantiated assertions, such as 'An average individual has one to two lethal recessive mutations'; 'The human genome is around 70% homozygous'; and 'If human fitness is partly based on homozygosis of beneficial recessive alleles, then inbreeding could help it by increasing homozygosity', do little to inspire confidence.

A second shortcoming is the uncritical conflation of markedly different sources of evidence to illustrate alleged contradictions in the perceived social and economic benefits of consanguineous marriages, e.g. comparing 19th century England with late 20th century Pakistan. Thus in 19th century England the higher rates of consanguinity among 'the richer classes' are treated with surprise by the authors, on the grounds that, 'If inbreeding preserves wealth, the opposite should have been true, i.e. the less well-off should have been more inclined towards intra-family marriages as the poor are more in need to safeguard their wealth'. This rationale is doubly unconvincing. With the laudable exception of the philanthropy exhibited by a few of today's richest US citizens, I am unaware of any overwhelming or even general tendency among the financially well-to-do to freely dispense their wealth to others. And since financial well-being was a state that few of the 19th century English poor would ever have experienced, it is difficult to perceive how they naturally would have aspired to retain their non-existent 'wealth'.

At the same time, the understandable wish of poorer people to preserve whatever capital and worldly resources they possess through intra-familial marriage has been widely reported across many consanguineous societies, including present-day Pakistan [14, 15], usually in conjunction with sociodemographic characteristics such as rural residence, maternal illiteracy, young parental age at marriage, lower contraceptive usage, and short birth intervals. It is these latter factors, acting independently, which have been shown to significantly contribute to the excess postnatal death rates in consanguineous progeny [16], rather than simply, 'The excessive number of deaths in consanguineous families is ascribed to the homozygosity of lethal recessive alleles', as asserted by the authors. Given the internal complexity of human societies, and the fact that few studies into consanguineous marriage have employed adequate control for sociodemographic covariables, there seems little justification to further conclude, 'This suggests that economic status and a sense of security are neither very important nor specific drivers of intra-familial marriages'.

A third, and probably the most contentious issue in the review is the reliance on computer modeling to determine whether consanguinity could convey a genetic benefit. For example, to assess how $\alpha^+$-thalassemia mutations might influence malarial parasitism in regions with a high prevalence of consanguineous marriage, a question already addressed by the authors in previous journal articles [17–20]. Computer modeling can be a very useful tool. But even the most sophisticated models are caricatures of reality, especially when dealing with the multiple genetic and environmental issues faced by poorly educated populations, following largely subsistence agricultural lifestyles, and beset by a wide range of endemic and epidemic diseases, including malaria. Uncritical acceptance of the findings of such a modeling exercise is questionable, particularly when important features of consanguinity, such as reproductive compensation, were not incorporated. For this reason, statements such as '… inbreeding increases the speed of fixation of recessive and co-dominant alleles …' merit appraisal with due caution.

Dr. Denic and colleagues have published a number of quite imaginative hypothetical articles on the topic of consanguinity. These articles include the supposed existence of a gene which in wild-type suppresses sexual attraction between near relatives. However, as a mutant 'consanguinophilia' allele co-selected with genes protective against malaria, its expression is claimed to result in relaxation of the incest taboo to the extent that biological kin, such as first cousins, successfully procreate [21]. This is a rather surprising concept, because in an earlier paper it was proposed that cervical cancer was common in populations with a high prevalence of cousin marriage due to mutual sexual aversion between consanguineous spouses, which caused males to seek extra-marital liaisons and thus expose themselves to the risk of human papilloma virus (HPV) infections and their wives to the consequent risk of cervical cancer [22]. The improbability of this scenario has been addressed [23], and given the social sensitivity of the topic it is understandable that a detailed case-based study would be difficult in practice, even if ethics approval was forthcoming.

By comparison, a clinic- or field-based study into the interaction of $\alpha^+$-thalassemia mutations, malaria and

consanguinity should not attract adverse attention, especially if as cited by the authors, '… $\alpha^+$-thalassemia is the most common single monogenic condition of mankind'. Providentially, there is a very high reported prevalence of α-globin gene defects in the UAE where Dr Denic and his colleagues are based, with 49% of newborns showing an α-globin gene mutation [24]. Studies on β-thalassemia also have demonstrated a very significant degree of compound heterozygosity in the UAE population [25], which in common with other Middle Eastern countries is characterized both by population stratification arising from clan and tribal endogamy, and high rates of consanguineous marriage [26, 27].

Given these unique circumstances, literally on their doorstep, and with malaria a recently controlled disease in the region, the time seems ripe for Dr. Denic and his colleagues to commit their computer models to practical test. In the certain knowledge that the results of such an investigation would be of very great interest both in terms of public health genomics and evolutionary medicine.

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