

Reviewer's report

Title: Consanguinity and Reproductive Health among Arabs

Version: 1 **Date:** 19 May 2009

Reviewer: Alan Bittles

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In Arab societies, clan (hamula) and tribe endogamy is very strongly favoured and practised following centuries-old traditions. Under these circumstances it is highly probable (and has been shown) that founder mutations will be unique to certain clans and tribes. Differences therefore will exist in their overall genetic disease profiles. Failure to consider and control for such differences has been a major oversight in a large majority of studies into the effects of consanguinity on health and disease. It is important that the authors include appropriate comment on this topic.

Specific comments and queries to authors

1. p. 2, para 4: The authors make the very valid point that 'for comparisons of consanguinity rates among (and between) populations, two parameters are best used; the mean coefficient of inbreeding (F) and marriages between first cousins'. Yet with the exception of congenital heart defects (p. 4, para 3), virtually all of the examples provided rely on a simple consanguineous versus nonconsanguineous dichotomy. Given the wide range of F values in the 'consanguineous' group (F = 0.0156-0.125), is this a meaningful comparison? Especially since second cousin offspring (F = 0.0156) are closer to nonconsanguineous (F = 0) than to first cousins (F = 0.0625) or double first cousins (F = 0.125) in terms of percentage homozygosity.
2. p. 3, para 5: Of the 451 genetic disorders recorded in the UAE, Bahrain and Oman 36.6% documented consanguineous marriages, mostly first cousin. But according to Table 1, the levels of consanguineous marriage in these three countries were: UAE 40-54.4%, Bahrain 39.4-45.5%, Oman 56.3%. Should this be interpreted as a significant under-representation of consanguineous progeny with genetic disorders, or is there another more credible explanation? The relationship is especially puzzling since 63% of disorders in the CTGA Database have a recessive mode of inheritance (p. 5, para 4).
3. p. 4, para 2: Given the title of the review, the relevance of data from South America and France is unclear, unless it can be shown that members of the Arab diaspora contributed to and/or were included in these studies.
4. p. 4, para 5: The fact that countries with high rates of consanguineous marriage generally report smaller effects of consanguinity on mortality than populations with low rates of consanguinity is unsurprising, given the limited control for concomitant variables such as socioeconomic status, maternal education, birth intervals and public health facilities and practices in most

consanguinity studies.

5. p. 5, para 1: It would be safer to indicate that there may be equality in the numbers of living children among consanguineous and nonconsanguineous couples: this topic is discussed at some length in other parts of the ms.

6. p. 5, para 2: The comment 'the risk for birth defects in the offspring of first-cousin marriage is expected to increase sharply compared to nonconsanguineous marriage' would only apply to rare autosomal recessive disease genes. If a recessive disease gene is common in the gene pool, there is a high chance that it will be carried by unrelated spouses and expressed in their progeny.

Minor comments to authors

1. Routine editing of the spelling, e.g. 'practiced' and grammar, e.g., p. 2, para 3 'Unlike what is thought' is needed, and the references need to be verified, e.g. nos. 31, 71, 114 and 118, plus a number of references with the suffix '2009'.

2. In ref. 68, the original study cited was: Bittles, A.H., and Neel, J.V. (1994) The costs of human inbreeding and their implications for variations at the DNA level. *Nature Genetics* 8, 117-121.

3. p. 2, the term consanguineous is derived from the Latin con and sanguineus meaning 'with (or of) the same blood'.

4. p. 4, para 1: It would be helpful if the actual level of birth defects reported for Arab countries in the March of Dimes Report was cited.

5. p. 6, para 1: The Mauritanian ethno groups: meaning?