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Contribution of consanguinuity to polygenic and multifactorial diseases

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To the Editor:

A recent Editorial in *Nature Genetics* (**38**, 851; 2006) highlighted the potential of genomic research in Arab countries for understanding monogenic diseases and early-onset genetic disorders of childhood but stated that "it is unlikely that consanguinity contributes significantly to polygenic and multifactorial diseases once socioeconomic variables have been controlled for." We think that this statement is inaccurate and could serve to discourage a very important line of genomic research in which Arab countries are well placed to contribute. The Editorial statement is consistent neither with population genetic principles nor with the results of a large body of research in both experimental organisms and humans[1,2].

There are several reasons why consanguinity should be expected to have a significant effect on polygenic traits influencing human health[1-3]. First, published empirical evidence in animals and humans consistently reports inbreeding effects on numerous multifactorial traits that are both fitness related[1,2,3,5] and post-reproductive (refs. 6,7, and A.V. Hill, personal communication). In the case of complex late-onset traits, inbreeding depression is predicted to be greater than for early-onset traits under at least one plausible model[3]. In humans, there is growing evidence for adverse effects of inbreeding on resistance to infectious diseases, including tuberculosis and hepatitis B virus (A.V. Hill, personal communication), and on traits such as blood pressure and several common late-onset diseases, after controlling for socioeconomic factors[6,7]. Second, inbreeding effects associated with homozygosity at disease susceptibility loci could result in epistatic effects that jointly impair the capacity to adapt to environmental risks, including infectious diseases[5]. Third, there is now evidence that heterozygote advantage at loci such as the major histocompatibility complex, which may be maintained by balancing selection, could be reduced by consanguinity[8]. Finally, the association between socioeconomic factors and consanguinity in societies such as Tunisia and Croatia are highly complex and dependent on many factors, including cultural context and gender[9].

The favorable secular trends in health and life expectancy in human populations worldwide during recent decades coincides both with improved economic growth and development and with massive urbanization, admixture and outbreeding on a global scale. These observed health gains are not solely explained by socioeconomic factors. Therefore, until this issue is better understood, the possible contribution of consanguinity and outbreeding to polygenic traits and complex human diseases should

not be dismissed, and the Arab countries are well-placed to be at the forefront of this endeavor.

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