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Hamamy, H., Antonarakis, S.E., Cavalli-Sforza, L.L., Temtamy, S., Romeo, G., Ten Kate, L.P., Bennett, R.L., Shaw, A., Megarbane, A., van Duijn, C., Bathija, H., Fokstuen, S., Engel, E., Zlotogora, J., Dermitzakis, E., Bottani, A., Dahoun, S., Morris, M.A., Arsenault, S., Aglan, M.S., Ajaz, M., Alkalamchi, A., Alnaqeb, D., Alwasiyah, M.K., Anwer, N., Awwad, R., Bonnefin, M., Corry, P., Gwanmesia, L., Karbani, G.A., Mostafavi, M., Pippucci, T., Ranza-Boscardin, E., Reversade, B., Sharif, S.M., Teeuw, M.E. and Bittles, A.H. (2011)  
Consanguineous marriages, pearls and perils: Geneva International Consanguinity Workshop Report. *Genetics in Medicine*, 13 (9). pp. 841-847.

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## Consanguineous Marriages, Pearls and Perils:

### Geneva International Consanguinity Workshop Report

**Short Title:** Geneva Consanguinity Workshop Report

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## **Abstract**

Approximately 1.1 billion people currently live in countries where consanguineous marriages are customary, and among them one in every three marriages is between cousins. Opinions diverge between those warning of the possible health risks to offspring and others who highlight the social benefits of consanguineous marriages. A consanguinity study group of international experts and counselors met at the Geneva International Consanguinity Workshop from 3<sup>rd</sup> to 7<sup>th</sup> May 2010 to discuss the known and presumptive risks and benefits of close kin marriages, and to identify important future areas for research on consanguinity.

The group highlighted the importance of evidence-based counselling recommendations for consanguineous marriages, and of undertaking both genomic and social research in defining the various influences and outcomes of consanguinity. Technological advances ~~infor~~ rapid high-throughput genome sequencing (HTS), and for the identification of copy number variants by comparative genomic hybridization (aCGH) offer a ~~significant~~ ~~unprecedented~~ opportunity to identify genotype-phenotype correlations focusing on autozygosity, the hallmark of consanguinity. The ongoing strong preferential culture of close kin marriages in many societies, and among migrant communities in Western countries, merits an equivalently detailed assessment of the social and genetic benefits of consanguinity in future studies.

**Key words:** Consanguinity, consanguineous marriages, inbreeding, endogamy, fertility, stillbirths, infant mortality, congenital disorders, genetic counseling

## Introduction

Health care providers and genetics specialists have usually judged the overall impact of consanguineous marriage ~~it~~ as being negative when assessed in terms of increased genetic risks to the offspring ~~of consanguineous marriage~~, as opposed to the potential social and economic benefits. A ~~consanguinity~~ study group of international experts and counselors met at the Geneva International Consanguinity Workshop from 3<sup>rd</sup> to 7<sup>th</sup> May 2010 <sup>1</sup> to discuss the known and presumptive risks and benefits of close kin marriages, and to identify important future areas for research on consanguinity.

It has recently been suggested that inbreeding depression, defined as the deleterious effects that result from matings between related individuals, could be associated with epigenetic mechanisms rather than DNA sequence alterations <sup>2</sup>. Most studies have indicated that inbreeding depression in humans is moderate in effect and can conveniently be analysed by studying the 'genetic load', i.e. the reduction in fitness due to deleterious genes maintained in the population by mutation in the face of elimination by natural selection <sup>3</sup>. Recently, however, healthier viable offspring were produced by inbreeding a freshly generated knock-out mouse line for cytochrome P450 genes. This finding indicated a possible beneficial epigenetic role in inbreeding, described as 'inbreeding de-repression' <sup>4</sup>.

Novel technologies and updated perceptions in developmental and functional genetics and genomics may be applied to investigate potential genetic advantages within inbreeding.

Research into the risks and benefits of consanguinity is best undertaken through collaboration between countries with high consanguinity rates and those with appropriate scientific expertise, and the requisite technological and financial resources. Collaborations of this nature should lead to the identification and characterization of many genes responsible for

human diseases, with direct benefits both to the populations investigated and to a better understanding of the genetic bases of human health and disease worldwide <sup>5</sup>.

### **Comparative global consanguinity rates and preferred relationships**

As illustrated in Figure 1, consanguineous marriage is traditional and respected in most communities of North Africa, the Middle East and West Asia, a transverse belt that runs from Pakistan and Afghanistan in the east to Morocco in the west, and in South India, with intra-familial unions collectively accounting for 20-50+% of all marriages <sup>6,7</sup>. First cousin unions ( $F^* = 0.0625$ ) are especially popular, comprising 20-30% of all marriages in some populations (Table 1), in particular the paternal parallel subtype [in Arab societies](#) (Figure 2) <sup>7-9</sup>.

The prevalence of consanguinity and rates of first cousin marriage can vary widely within and between populations and communities, depending on ethnicity, religion, culture, and geography. Consanguineous marriages are also practised among emigrant communities from highly consanguineous countries and regions, such as Pakistan, Turkey, the Maghreb and Lebanon, now resident in Europe, North America and Australia. [In recent years, years however,](#) these marriages have been subjected to [substantial criticism controversy and adverse reactions](#) in a number of Western countries.

In clinical genetics, a consanguineous marriage is generally defined as a union between two individuals ~~who are~~ related as second cousins or closer ( $F \leq 0.0156$ ) <sup>6,10</sup> (Figure 2), but in highly consanguineous populations pedigrees with complex consanguinity loops are commonplace (Figure 3), arising from close kin unions in [preceding successive](#) generations. Reports on consanguinity rates may sometimes include marriages between third cousins or more distantly related individuals ( $F \leq 0.0039$ ) <sup>11</sup>. Although this discrepancy affects the total consanguinity rate, because of the lower coefficients of inbreeding in more remote unions it does not markedly alter the mean inbreeding coefficient ( $\alpha$ )\*.

Unions between individuals with at least one common ancestor, such as those commonly occurring in religious and social isolates, villages and small towns, and within tribes, are referred to as intra-community or endogamous marriages. The custom of endogamous marriage among individuals belonging to the same clan or tribe ~~is, and has been, strongly favoured among certain communities, often~~ results in an unequal distribution of founder mutations ~~across populations~~. Allelic heterogeneity for very rare autosomal recessive disorders also has been observed in an increasing number of highly consanguineous populations, with the co-existence of multiple mutations ~~encoding specific inherited in an increasingly large number of~~ disorders in ~~Middle Eastern the~~ Arab, Jewish and Druze communities ~~in the Middle East~~, findings that have been ascribed to random mutational events and/or selective heterozygote advantage<sup>12;13</sup>.

*\* On average first cousins share 1/8 of their genes inherited from their common ancestors (grandparents), so their progeny are autozygous at 1/16 of all loci which is expressed as an inbreeding coefficient (F) of 0.0625<sup>6</sup>. The mean inbreeding coefficient 'α' = ΣF<sub>i</sub>m<sub>i</sub>, where F<sub>i</sub> is the inbreeding coefficient of a specific category of consanguineous marriage and m<sub>i</sub> is the proportion of this category in the population<sup>3</sup>.*

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### **Consanguinity and social structure**

Socio-cultural factors, such as the maintenance of family structure and property, ease of marital arrangements, better relationships with in-laws, and financial advantages relating to dowry seem to be strong contributory factors in the preference for consanguineous unions. In addition, there is a ~~general belief that marrying within the family reduces the possibilities of hidden uncertainties in health and financial issues~~<sup>10</sup>. Contrary to common opinion, consanguinity is not confined to Muslim communities. Many other religious groups, including the Lebanese, Jordanian and Palestinian Christian populations, also practise consanguineous

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marriage, although to a lesser extent than among co-resident Muslims<sup>9:14:15</sup>, while in the Hindu population of South India over 30% of marriages are consanguineous, with 20+% between uncles and their nieces ( $F = 0.0125$ )<sup>16</sup>.

Close kin marriage can be a strategy of conservation, with cousin marriage providing excellent opportunities for the transmission of cultural values and cultural continuity<sup>17</sup>. For these reasons consanguineous unions are generally thought to be more stable than marriages between non-relatives, although the data so far available on marital discord and divorce are small in number. In most Arab societies, patrilineal parallel cousin marriages are regarded as [important in](#) uniting members of the same descent group, and keeping the education of offspring within the family line. These considerations may be particularly significant under conditions of social change and political or socio-economic insecurity<sup>18</sup>. Thus higher rates of close kin marriage have been observed among certain minority ethnic groups, especially during the initial phases of settlement of emigrant communities and refugees<sup>19</sup>. Conversely, in South India and according to Confucian tradition in China, while marriage between a man and his mother's brother's daughter is permitted, patrilineal parallel cousin unions are viewed as incestuous<sup>10</sup>.

### **Secular and social trends in consanguineous marriage**

The probability of consanguineous marriage is thought to be determined by such factors as the availability of consanguineous kin of comparable age, the similarity of socio-economic conditions and physical traits among relatives, and traditions for or against specific types of consanguineous marriages<sup>3</sup>. In many societies more distant consanguinity (i.e. beyond second cousins,  $F < 0.0156$ ) often arose while people were living in small [rural](#) communities [and villages](#). Although remote levels of consanguinity appear not to have a major adverse impact on health, due to multiple inbreeding loops they can result in a notable increase in



homozygosity. This trend was, however, broken in Western societies due to increasing urbanisation following industrialization in the 19<sup>th</sup> century and in the aftermath of the World Wars of the 20<sup>th</sup> century <sup>20</sup>.

Significant secular changes in consanguinity rates have been reported in recent decades. In Jordan <sup>8</sup>, Lebanon <sup>21</sup>, and among Palestinians <sup>18</sup>, the decrease in the frequency of consanguineous marriage could be attributed to a number of factors, including higher levels of female education, declining fecundity with lower numbers of marriageable relatives, increased rural to urban mobility, and the improved economic status of families. Moreover, public health concerns centered on involving the role of genetic diseases as causes of severe morbidity and mortality are likely to increase with the declining prevalence of infectious diseases.

On the other hand, social, religious, cultural, political and economic factors still play important roles in favouring consanguineous marriages among the new generations. This is particularly the case in rural areas <sup>16;22</sup>, and to an extent among highly educated males but less frequently in tertiary educated females <sup>9</sup>. In fact, consanguinity seems to be increasing in some Arab countries including Qatar <sup>23</sup> and Yemen <sup>24</sup>, possibly because of a belief that the social benefits of consanguineous marriages can outweigh the genetic risks, and also due to misconceptions surrounding the nature of genetic risks among some members of the general public. However, variability in the composition of the populations sampled across generations make such observations difficult to confirm sustain.

The prevalence of consanguinity markedly declined in Europe, North America and Japan in the last century <sup>25;26</sup>, with a more recent reduction among some emigrant populations in Europe. For example, in the Norwegian Pakistani community the proportion of women consanguineously related to their partner decreased from 45.5% in 1995-97 to 27.3% in 2002-2005 for those born in Pakistan, and from 48.3% to 18.8% among women of Pakistani origin

born in Norway<sup>27</sup>. This trend may be explained by acculturation of the immigrant community, with a gradual transition from their traditional consanguineous marriage preferences to those favoured by the dominant group in their adopted country<sup>28</sup>.

### Health impact of consanguinity

Consanguinity does not appear to be associated with elevated rates of miscarriages, since a large majority of studies have failed to detect any significant increase in fetal loss rates among consanguineous couples<sup>29</sup>. A meta-analysis of stillbirths showed an mean excess 1.5% deaths among first cousin progeny, although data from 3 communities resident in a single study site were identified as significant outliers that raised the overall mean value<sup>30</sup>.

In a meta-analysis of the fertility of first cousin and non-consanguineous couples, first cousins had a higher mean number of live births in 33 of the 40 studies, which translated into a mean 0.08 additional births per family ( $r^2 = 0.67$ ,  $p < 10^{-9}$ )<sup>30</sup>. However, multinational studies among first cousin ~~offspring progeny~~ also indicated a mean 1.1% excess in infant deaths ( $r^2 = 0.61$ ,  $p < 10^{-5}$ ) compared to ~~the~~ non-consanguineous progeny<sup>30</sup>, with an equivalent excess of 3.5% in ~~overall~~ pre-reproductive mortality ( $r^2 = 0.70$ ,  $p < 10^{-5}$ )<sup>7</sup>. Currently, it is unclear whether the apparent greater fertility of first cousins couples represents compensation for ~~their~~ increased risk of postnatal losses ~~in related marriages~~ or may primarily be due to their ~~younger earlier~~ mean age at marriage, earlier first pregnancy and longer reproductive span<sup>10, 28; 29</sup>.

The prevalence of congenital anomalies in the offspring of first cousin marriages has been estimated to be 1.7-2.8% higher than the ~~population~~ background ~~population~~ risk, mostly attributable to autosomal recessive diseases<sup>29; 31-33</sup>. An increased 2% risk that first cousin couples will bear a child with an autosomal recessive disorder indicates that approximately 8-16% of these couples have an increased risk of 25% or more, while at least 84-92% of all first-cousin couples have a ~~normal~~ risk, comparable to unrelated parents.<sup>34</sup> Rare and novel

autosomal recessive disorders have been widely reported from communities with high consanguinity rates<sup>35-42</sup>, since the main impact of consanguinity is the increased expression of rare autosomal recessive genetic disorders.

The association of consanguinity with major congenital anomalies, including non-syndromic neural tube defects and cleft lip and/or palate remains controversial. However, after controlling for confounders, there was a significantly increased risk of specific congenital heart defects (CHD) in first cousin offspring<sup>43</sup>. This association could variously suggest a recessive mode of inheritance, some effect on non-coding regulatory DNA, or the contribution of an epigenetic mechanism to CHD. Nevertheless, in South India, where uncle-niece and first cousin marriages are [strongly favoured](#)~~common~~<sup>15</sup>, a genome-wide linkage analysis utilizing high-density oligonucleotide microarrays [was unable to identify a](#) ~~showed~~ [no](#) single gene of major effect in a clinically heterogeneous sample of cases born to consanguineous parents<sup>44</sup>.

Most of the literature on the effects of parental consanguinity on Down syndrome [has](#) concluded that no such association exists~~ed~~. But in some populations an elevated frequency of Down syndrome has been reported and, for example, in an Arab village in Israel multi-generational cases of Down syndrome within a single endogamous kindred could not be explained by advanced maternal age alone<sup>33</sup>.

### **Quantitative traits and complex disorders: is consanguinity a determinant?**

Most quantitative traits, such as height, skin and eye colour, intelligence and blood pressure, fall under the umbrella of multifactorial inheritance, with both genetic and environmental factors contributing to the trait etiology in varying proportions. The association of parental consanguinity with such traits is vague, with few published reports that have consistently controlled for non-genetic variables.

Complex disorders such as hypertension, coronary artery disease, diabetes, schizophrenia, autism and cancer are also etiologically heterogeneous, with multifactorial inheritance suspected in most families and individual cases. High susceptibility genes could play a significant role in the expression of a complex disease, and if such genes are rare and transmitted in an autosomal recessive manner then consanguinity could be a determining factor.<sup>7</sup> To date, little has been published on the effects of consanguinity on the complex late-onset disorders that account for most of the global public health burden<sup>7</sup>. The association of consanguinity with complex disorders can be studied using different approaches. For example, epidemiological surveys could compare the frequency of a disorder in the progeny of first cousin parents to that of unrelated parents; while case-control studies could compare the rates of first cousin-~~parents~~ among affected individuals and controls.

Highly consanguineous populations provide a unique opportunity to detect recessively inherited genes for diseases manifesting in late life, such as a study identifying multiple loci for Alzheimer disease in an Israeli-Arab community<sup>45</sup>. ~~Investigators Studies~~ share the difficulty of adequately defining controls, especially since most complex disorders are late-onset in nature, and there also is the difficulty of controlling for community endogamy, with no guarantee that cases and controls belong to the same sub-population. [Perhaps for these reasons, association studies on consanguinity and breast cancer, and the frequency of BRCA1 and BRCA2 in highly consanguineous populations, have so far produced contradictory opinions](#)<sup>46; 47</sup>.

~~While So~~ some studies have reported higher rates of specific complex disorders among consanguineous progeny, e.g. a small but significant increase in the rate of cousin marriages among the parents of Bedouin Arab schizophrenia patients in southern Israel<sup>48 46</sup>, ~~unambiguous evidence based conclusions are currently difficult to establish.~~

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Similarly, in a religious isolate in The Netherlands, familial aggregation of several complex disorders, including ischemic stroke,<sup>2</sup> was noted. Small effective population sizes and a high cumulative level of consanguinity makes such populations valuable for locating and identifying novel genes, and incipient problems of ensuring rigorous matching of cases and controls are easier to control.<sup>4947</sup> However, in most populations unambiguous evidence-based conclusions have been difficult to establish. The association of consanguinity with breast cancer, and the frequency of *BRCA1* and *BRCA2* in highly consanguineous populations, have so far produced contradictory opinions<sup>48,49</sup>.

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### Prospects for genetic research in consanguinity

Discovery of the functional genomic elements that harbor pathogenic mutations is a major step towards a mechanistic understanding of the physiopathology of the phenotype, and provides targets for therapeutic interventions. The technological advances infer rapid high-throughput genome sequencing (HTS), and for the identification of copy number variants by comparative genomic hybridization (aCGH) therefore offer an unprecedented opportunities<sup>50</sup> to identify a large number of additional links between genotypes and phenotypes in consanguineous families.

In the past, epidemiological studies based on consanguinity could approximately estimate the prevalence of autosomal recessive disorders in a community. Today, new approaches for estimating the frequency of autosomal recessive disorders can utilize molecular characterization of mutations in the affected offspring of consanguineous couples. The rationale of this new approach is based on a comparison of the frequency of identical or non-identical mutations in children born to consanguineous parents. In the latter situation, since two mutated alleles are not identical by descent (IBD) they must have been inherited through two different ancestors of the consanguineous parents, or one is a *de novo* mutation.

A positive correlation has been postulated between the frequency of affected individuals in whom the alleles were not IBD and the frequency of pathological alleles ( $q$ )<sup>50</sup>. The population prevalence of autosomal recessive diseases can be inferred using an equation that incorporates the frequencies of the mutant alleles and the coefficient of inbreeding ( $F$ )<sup>51</sup>, with the results integrated into ~~the~~ Locus-Specific Data Bases that have been rapidly increasing in number during the last decade<sup>52</sup>. Novel research in consanguineous families should similarly focus on the proportion of DNA that is IBD in the parents of affected children compared to the parents of healthy children. Data of this nature potentially could provide more precise disease recurrence information to individual at-risk couples<sup>34</sup>.

~~Over the course of For~~ the past century, Mendelian and multifactorial traits have been perceived as existing at opposite ends of the genetic disease spectrum in humans, ~~and~~ ~~Furthermore~~, the recent emphasis on genome-wide association studies for uncovering variants that underlie common diseases has potentially deepened this divide<sup>53</sup>. It is envisaged that research in highly consanguineous populations could narrow this gap and that new genetic technologies could provide opportunities for comprehensive studies to define coding or regulatory factors implicated in human traits and disease in general, including complex diseases such as autism, diabetes and cancer. Novel technologies and updated perceptions in developmental and functional genetics and genomics could also be applied to investigate the presence of any genetic advantages in consanguinity, which to date have relied heavily on computer modelling.

## Conclusions

A group of experts and international researchers meeting at the Geneva International Consanguinity Workshop from 3<sup>rd</sup> to 7<sup>th</sup> May 2010<sup>1</sup> discussed the known and presumptive risks and benefits of consanguineous marriages, as well as future prospects for research on

consanguinity. The group highlighted the importance of evidence-based counseling recommendations for consanguineous marriages, and for undertaking genomic and social research in defining the various influences and outcomes of consanguinity. There was a consensus that consanguineous marriages are associated with an increased risk of congenital malformations and autosomal recessive diseases, with ~~some resultant~~ increased [resultant](#) postnatal mortality in the offspring of first cousin couples, but demographic and socioeconomic cofounders need to be well controlled. No major adverse associations with reproductive parameters such as miscarriages and fertility have been documented. Associations with quantitative traits and complex adult-onset diseases are vague and inconsistent, suggesting the importance of implementing future research in this area. The group highlighted the importance of present-day robust molecular tools in conducting consanguinity research to better define genotype-phenotype correlations and assess the genetic risks and benefits of consanguinity. The presumptive social benefits of consanguineous marriages need to be confirmed by evidence-based research. The efforts from the scientific community should be more geared to understanding the balance between the risks and benefits of consanguinity. This will help to define issues that are of greatest relevance to people in different lifestyle situations, whether there are situations which justify the discouragement, or possibly even the encouragement of consanguineous marriages and, if so, how best this advice might be given.

**Contributors:**

HH drafted the report, AHB drafted successive versions, and all other contributors revised the report and gave final approval for publication. All contributors actively participated in the workshop.

**Conflicts of interest**

We declare that we have no conflicts of interest

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### Legends for [Table and Figures](#)

[Table 1](#)<sup>6;29</sup>: [Percentage first cousin marriages and closer relationships \( \$F \geq 0.0625\$ \) in representative consanguineous populations. Rates can differ within the same country depending on choice of subjects and methods used.](#)

**Figure 1**<sup>6</sup>: Global total consanguinity rates

~~[Table 1](#)<sup>6;29</sup>: [Percentage first cousin marriages and closer relationships \( \$F \geq 0.0625\$ \) in representative consanguineous populations. Rates can differ within the same country depending on choice of subjects and methods used.](#)~~

**Figure 2**: Categories of consanguineous marriages

**Figure 3**: Complex pedigree illustrating multiple consanguineous marriages

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