

Research Article

Impact of consanguineous marital unions on risk of bronchial asthma

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Abstract | Asthma is a common respiratory disorder which has a documented influence of genetic factors on its overall prevalence. As asthma is an autosomal recessive disorder therefore it is highly influenced by consanguinity. Many unknown genetic disorders were first identified in endogamous populations, which is mainly due to the role of basic alteration which may be unique to a particular community. The efficacy of genetically isolated populations (population isolates) provide a useful resource for understanding genetics of common diseases such as asthma and their component traits. Following review explores the risks associated with bronchial asthma and consanguineous marital unions, with special emphasis on Arab, South Asian and Muslim populations.

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Introduction

Consanguinity is a Latin word derived from "con" which means same and "sanguineus" which means blood. Thus consanguinity refers to a correlation between two individuals with a shared ancestry. In addition, consanguineous unions also refer to marriages between biologically-associated individuals (Tadmouri *et al.*, 2009) such as cousins, second cousins or close relatives. Consanguineous unions may occur between individuals with shared ancestor such as those living in small towns, tribes resulting in inter-marriages and population isolates (Alwan and Modell, 1997; Modell and Darr, 2002).

Consanguineous or family marriages have been practiced since early times. Presently, around 20% of the World populations

express preference for consanguineous unions (Modell and Darr, 2002). Consanguineous marriages are most common in, traditional rural communities characterized by poor and least educated societies (Bittles *et al.*, 1993; Tadmouri *et al.*, 2009). The rates of consanguinity vary in the populations depending up on culture, religion, social factors and even geography (Hafez *et al.*, 1983). The reasons behind cousin marriages are ease of marriage, decision-making and to make family bonds stronger generation after generation (Bener and Alali, 2006). Studies show a prevalence of certain diseases in couples having inter-marriages belonging to communities with high rate of consanguinity (Bener *et al.*, 1996; Bener and Alali, 2006; Bener and Mohammad, 2017). Inbreeding produces homozygotes thus increasing the chances for autosomal recessive disorders (Fareed and

Afzal, 2017; Mansouritorghabeh, 2021). Consanguineous marriages causes an increased birth rate of infants with extreme recessive diseases such as asthma (Benera and Mohammad, 2017), heart diseases (El Mouzan *et al.*, 2008), intellectual disability (Harripaul *et al.*, 2017), neurodevelopmental disorders (Reuter *et al.*, 2017), *diabetes mellitus* (Jaber *et al.*, 1997; Gosadi *et al.*, 2014), Retinal Dystrophies (Li *et al.*, 2017), developmental delay in children (Sadeghi and Shevell, 2017), Autism (Alshaban *et al.*, 2017; Harripaul *et al.*, 2017) and cancers (Jastaniah *et al.*, 2016). Although the social importance of consanguineous marriages cannot be overlooked, recorded statistics have prompted medical practitioners to propose that consanguineous marriage should be controlled on medical basis. (Bakhshani, 2021).

Large immigrant communities currently residing in Northern America, Western Europe and Oceania have retained their preference for consanguineous marriages due to cultural and religious beliefs (Bittles *et al.*, 2008). Historically, high frequency of inter-marriages in the World take place in Northern African, Middle Eastern South Asian communities (Tadmouri *et al.*, 2009; Sharma *et al.*, 2021). A transverse belt in east running through Pakistan and Afghanistan to the west in Morocco and Southern India accounts for 20–50% of all global consanguineous marriages and intra-familial unions (Benera and Mohammad, 2017). Double first cousins marriages are most common in Arabs whereas, uncle–niece marriages are common in South India where the inbreeding coefficient (F) reaches 0.125 (Hamamy *et al.*, 2011). Arabs set a trend of consanguinity (Sharkia *et al.*, 2008). Absence of uncle–niece marriage among Arabs is due to its prohibition in Islam (Tadmouri *et al.*, 2009).

Consanguineous marriages where both parents share a common ancestor drastically increase the chances of inheriting mutant alleles at the same locus (Bakhshani, 2021).

The extent of common genetic material is dependent upon the closeness in relationship between parents. Siblings share 50%, uncle and niece share 25% whereas first cousins share 12.5% of their inherited genetics. Children born as a result of such marriages are therefore at a significantly higher risk of inheriting homozygous genes and subsequently undergo in autosomal recessive genetic diseases (Alvarez *et al.*, 2011). Apart from diseases, death rate in first-cousin off springs is greater (3.5%) than in non-consanguineous progeny, although several factors such as demography, environmental factors and financial conditions considerably influence the outcome (Fareed and Afzal, 2017).

Consanguinity and Religion

Consanguinity and the range of inbreeding differs from population to population and are determined by geography, religion, ethnicity and culture. When taking religion in to account, views about consanguineous marriages varies according to beliefs and practices (Fareed *et al.*, 2017; Begum, 2021). Except for prohibited relationships, marriages between close and distant relations, as well as between those not related have been practiced among the Muslims. The high incidence of close kin marriages (consanguineous marriages), including those with first cousins, is a well-known feature of a Muslim society (Afzal *et al.*, 1994; Begum, 2021). Consanguineous marriages are not only practiced by Muslims but also by people of many other religious affiliations (Saadat *et al.*, 2004). In Christianity, the Orthodox churches claimed to avoid consanguineous marriage, the Roman Catholic church presently needs a Diocesan order for marriage between first cousins, and the Protestant values allow marriages up to and having first cousin relationship (Bittles, 2001). The Levitical law allows the uncle–niece marriage, which alongside with first-cousin marriages are practiced in various Sephardi Jewish societies. First-cousin marriage is

commonly acceptable within Buddhism religion, but in Hinduism, marriage rules are more difficult (Bittles and Black, 2010).

Consanguinity in Arab populations

Consanguineous or inter-marriages are customary in many societies Modell and Darr, (2002) however, mostly the Arab countries are highly prevalent with consanguineous marriages (Benera and Mohammad, 2017). In Arab populations, the belief of consanguinity is high due to social and cultural factors. The tradition of consanguinity among the people of same tribe has been highly preferred among Arabs, with the highest rates of consanguineous marriages in the world (20-50%) (Tadmouri *et al.*, 2009). There is a general thought of high success rate of consanguineous marriages as compared to marriages between non relative Arabs; however there are no studies to show the comparison of divorce rates between these two types of marriages among Arabs (Tadmouri *et al.*, 2009). Not only the Muslim communities in Arab world practice the consanguinity but many other communities, like Palestinian Christian populations, Lebanese and Jordanian also practice consanguinity, but to a less degree as compared to Muslims (Khlat, 1988; Khoury and Massad, 1992; Vardi-Saliternik *et al.*, 2002; Begum, 2021).

In Bahrain, Iraq, Kuwait, Egypt, Libya, Lebanon, Palestine, Jordan and Tunisia increasing trends of consanguineous marriages have been recorded among previous and present generations. On the other hand, increasing consanguinity rates have been recorded among generations in Algeria, Morocco, Qatar, Oman, Saudi Arabia, Syria, Sudan, the UAE, and Yemen (Tadmouri *et al.*, 2009).

Low parental education, smoking and family history of asthma are significant threat factors for asthma development among

Studies carried out in various countries and communities of Middle Eastern cultures show that the frequencies of consanguineous marriages range from 20% to greater than 70% (Khlat, 1988; Khoury and Massad, 1992; Tadmouri *et al.*, 2009; Alshaban *et al.*, 2017). In some of the Arab countries including Yemen, Israel, Qatar, Jordan and UAE consanguinity is increasing in the present generation (Khoury and Massad, 1992; Jaber *et al.*, 1994; Tadmouri *et al.*, 2009). Among all the consanguineous type marriages, first cousin unions are the most common with overall rate of 20-30% which is the highest rate ever recorded (Bittles, 2001; Bittles, 2002; Tadmouri *et al.*, 2009).

Results from a study examining 200 Middle Eastern couples showed that the frequency of inbreeding and inter-cultural marriages is 23.5% and 24% respectively, while the percentage of inter-cultural marriages and inbreeding in the control group is 22.5% and 5%. Consequently autosomal recessive disorders are twice as common in the inbred as compared to non-inbred families, constant with autosomal recessive inheritance (Hoodfar *et al.*, 1996).

The rate of consanguineous marriages is quite high in Israeli Arabs with 44.3% prevalence. This prevalence is greater in the rural regions (Jaber *et al.*, 1994). The consanguineous marriage rate is 54% in Qatar (Bener and Alali, 2006; Bener, 2012). Urban to rural first cousin marriage frequency in Algeria are 10% and 15% respectively (Zaoui and Biemont, 2001), 8.3% and 17.2% in Egypt Hafez *et al.* (1983) and 29.8% and 37.9% in Jordan Khoury and Massad, (1992) respectively. There is high occurrence of asthma and consanguinity in Saudi Arabia. Prevalence of bronchial asthma was reported to be 23% in 1995 and prevalence of consanguinity was between 54 and 56% (El Mouzan *et al.*, 2008).

children (Al-Kubaisy *et al.*, 2005). in Qatari schoolchildren, the prevalence rate of asthma which is 19.8%, is very close to that

in the neighboring Gulf country, Oman (20.7percent), and is greater than in some of the developing countries (Janahi *et al.*, 2006).

Consanguinity in Pakistan

Conditions similar to Arab countries are also observed in South and west Asia where consanguineous marriages are strongly preferred. Recent survey of Pakistan Demographic and Health Survey (DHS) reported that in Pakistan, two-thirds of marriages are consanguineous. A study from a big city of Pakistan (Karachi) showed that about 60% of marriages are consanguineous, over 80% of which are the first cousins marriages (Hussain and Bittles, 1998). It is reported that all ethnic and religious groups prefer the consanguineous marriages. One of the main cause for this preference are sociocultural and not an economic benefit, either in the form of link of family property or less dowries and expenses (Hussain, 1999).

Another survey study was conducted in the year 2012 in different areas of the Federally Administered Tribal Areas (FATA), Bajaur Agency and Khyber Pakhtunkhwa (KP), Pakistan including Alijan, Anatkali, Chamerkand, Gandaw, Loisam, Manudera, Nawagai, Nawaikali, Raghagan and Sadiqabad. Data was collected from 123 consanguineous married couples. During cousin marriages, 52% of the couples' parents are married to their first cousin while 49% are married to their second cousin. About 87% couples were first cousins while 13% were second cousins (Farzana *et al.*, 2012).

Higher rates of consanguinity are related to several factors including illiteracy, low education, and residency in rural areas along with consanguineously married parents. First cousin marriages are observed in responsiveness and raised blood eosinophil amount (Jong-Uk *et al.*, 2015). The triad of eczema, allergic rhinitis and asthma is called

second-generation British Pakistanis. High rates of such marriages are not a simply a cultural preference but it varies according to region of origin, caste, socio-economic status, and upbringing (Shaw and Alison, 2001). The preference for consanguineous marriages is not restricted to Islamic societies only but is also common in other communities. Significantly high consanguinity was observed in a Hindu community (Southern-India) where the normal range of inbreeding co-efficient (F) in the urban and rural areas was 0.0204 and 0.0371 (Rao and Inbaraj, 1979; Bittles *et al.*, 1991).

Bronchial Asthma

Asthma was first described as a disease by the Ancient Egyptians (Manniche, 1999). The word asthma comes from the Greek word ἄσθμα, which means "panting" (Murray, 2010). It is an obstructive inflammatory disease of the lungs airways WHO, (2013) characterized by variable and recurring symptoms, bronchospasms (NHLBI Guideline, 2007), wheezing, coughing, chest tightness, and shortness of breath (Martinez, 2007). The rates of asthma have increased significantly since the 1960s (Anandan *et al.*, 2010). The global prevalence of asthmatics increased from 183 million in 1990 to 358 million people in 2015 (GBD, 2016) resulting in an estimated 397,100 deaths in 2015 (GBD, 2016).

Asthma is a multifactorial disease and is common in countries with higher consanguinity rates (Bener *et al.*, 1996; Bener and Alali, 2006; Bener, 2012). Asthma is associated with genetic and environmental factors (Bener *et al.*, 1996; Miller and Ho, 2008). These factors result in inflammation of various types and involve eosinophils, mast cells, macrophages (Bener *et al.*, 1996). Atopy and asthma are closely related with an increased bronchial hyperatopy (Rapini *et al.*, 2007). These intermediate phenotypes are generally heritable and focus to demanding genetic

research. Asthmatics cluster in families, indicate that a genetic element is likely to be involved (Jong-Uk *et al.*, 2015).

Asthma is not directly related to consanguineous or non-consanguineous parents. Several studies show that consanguineous marriage and family history of asthma are important determinants in the development of asthma in the offspring (Mahdi *et al.*, 2010). Childhood asthma is highly prevalent in families with consanguineous marriages (Joseph *et al.*, 2009). Individuals born from consanguineous parents inherit the same chromosomal segments and hence have a number of homozygous chromosomes (Alvarez *et al.*, 2011). First-cousin marriage in some families can ease the expression of infrequent recessive disease genes inherited by both parents which causes major childhood disorders like asthma (Bittles, 2009).

High rate of consanguineous marriage (21.1 %) is observed in Turkey, A strong preference for this traditional practice has contributed to the high rates of total fertility and infant mortality in Turkey. High rate of fertility among consanguineous marriages compensates for the high frequency of genetic disorders and mortality in offspring. Apart from high fertility and mortality, the risk for autosomal recessive disorders (asthma) also increases in intermarriages (Tuncbilek and Koc, 1994).

First cousin marriages are mostly preferred in Arab countries, resulting in a higher chance of autosomal recessive traits to be expressed among offspring of first degree related parents (El Mouzan *et al.*, 2008). Impact of consanguineous marriages on asthma inheritance was studied in the Qatif region, one of the seven regions of Eastern Province in the kingdom of Saudi Arabia. Data revealed that more than 52% couples are related to each other (consanguineous; cousins of all degrees) (Mohammed *et al.*, 1995). The ratio of consanguineous

marriage is 50.5% in Al Ain and Dubai, two cities in the United Arab Emirates. Consanguineous union's off springs also has significantly high occurrences of diseases such as asthma, than those of non-consanguineous unions. This study also shows that there is great impact of inbreeding on asthma inheritance in offspring (Abdulrazzaq, 1997).

The impact of consanguinity on asthma inheritance was investigated as a part of the study on association between child health and consanguinity in the State of Qatar. It was observed that the consanguineous marriage percentage were 54.0% with expected population confidence limits of 52.3–55.7%. The most common form of cousin marriage is the First cousin unions. There is a high level of parental consanguinity (both in the respondent's parents and her parents-in-law). The occurrence of asthma is comparatively high in the offspring of all consanguineous than in non-consanguineous couples (Bener and Hussain, 2006).

Conclusion

Consanguineous marriages and family history of bronchial asthma are important determinants in the development of asthma. Occurrence of childhood asthma is significantly higher in consanguineous families. There is also a higher risk for bronchial asthma in first cousin marriages when compared to second cousin marriages. The global prevalence of asthmatics is increasing due to increasing prevalence and preference of cousin marriages. In order to avoid the load of inbreeding, some improvements are needed in educational and socioeconomic status and also to increase public awareness about reproductive health and predicted harmful effects of consanguinity. Pre-marital and pre-conception counseling of consanguineous populations should be an important part of health policy to educate people and make them aware of its harmful effects. A range

of social factors, including improved female education, urbanization, and smaller family sizes may contribute in decline of consanguineous unions. This change in marriage patterns will not only result in reduced homozygosity but will be accompanied by a decrease in the expression of recessive disorders such as bronchial asthma.

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