The Effect of Consanguinity on Reproductive Fitness and Selection Intensity in the Muslim Population of Western Uttar Pradesh, India

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ABSTRACT The study sought to ascertain the adverse effects of consanguinity among Muslim parents of Aligarh city located in western Uttar Pradesh in India. More than 478 families were visited and data were collected from only 100 of them being inbred to varying degrees of consanguinity. It was found that increasing degree of consanguinity decreases fertility ($R^2 = 0.2671$, $r = -0.1568$), but increases mortality ($R^2 = 0.3161$, $r = 0.5622$). Selection intensity ($R^2 = 0.1734$, $r = 0.4164$) and secondary sex ratio ($R^2 = 0.3757$, $r = 0.6129$) also go up as the degree of consanguinity increases. However, the genomic basis of Runs of Homozygosity (ROH) is a more accurate method of calculating homozygosity. Next Generation Sequencing may help better understand ROH and their utility as a tool for inbreeding detection. To avoid the inbreeding load, there is a need to raise public awareness of reproductive health and the potential negative effects of consanguinity.

INTRODUCTION

The attribute of descending from the same ancestor as another individual is known as consanguinity. Matrimony between closely related individuals is known as consanguineous marriage. In a clinical context, consanguineous marriage is one in which two family members are second cousins or closer. Children born to consanguineous marriages are more likely to inherit diseases caused by homozygous recessive genes (Fareed and Afzal 2017, and as a result, suffer from autosomal recessive genetic disorders. The closer a biological bond between parents is, the more likely they are to suffer from such disorders (Shawky et al. 2013). Consanguineous marriages also have a negative impact on foetal survival indicators and result in the birth of progenies that are disadvantaged in terms of health parameters (Afzal et al. 2018; Anwar et al. 2020). Parental consanguinity is a risk factor for a variety of multifactorial problems, including obesity, cardiovascular disease, diabetes, and certain malignancies, all of which can affect reproductive output (Oniya et al. 2019). Some studies, however, question

the impact of consanguineous marriages on complicated and multivariate health problems (Romdhane et al. 2019). The assessment of its overall negative impact is very inconsistent and difficult to distinguish from the epidemiological context (Oniya et al. 2019; Romdhane et al. 2019; Anwar et al. 2020). Consanguineous marriages have been conducted in many cultures around the world for thousands of years. According to UN figures, in 2005, about 2.35 million children died in India, globally accounting for more than twenty percent of all deaths among children under the age of five (Black et al. 2010). It has been suggested that consanguineous spouses should be informed about their children's higher risk of congenital defects. First cousins have a 1.7 to 2.8 percent increased chance of raising a child with an autosomal recessive disorder (Bittles et al. 2010). Consanguinity rates vary widely among and within countries, but it is most common in North Africa, the Middle East, South Asia, and migrant communities in North America, Europe, and Australia (Bittles 2011).

The reproductive activity of a population is an important aspect of its life cycle, and it has an effect on the population's overall demographic trend (Badaruddoza 1991). It can be analysed in two ways at the population level, that is, through reproductive performance and reproductive fitness. In order to understand changes in a popu-

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lation's genetic structure, fertility and mortality are critical determinants of population development. Henry (1961) specified natural fertility as fertility that occurs in the absence of intentional use of birth control methods. The significant differences in child mortality and sex ratio in India's various regions have previously been recorded (Jha et al. 2006). Fertility loss is a major public health problem that has been related to socioeconomic problems in most Asian and African countries (Majumder and Ram 2015). The secondary sex ratio is the male-to-female ratio observed at birth. The number of males per hundred females is what it is. In American whites, the secondary sex ratio is about 106 (Stern 1973; McKusick 1978). In different classes of Indians, it ranges from 103 to 124 (Ansari 1980; Sinha 1982). Crow (1958) demonstrated that estimates of differential fertility and differential infant mortality could be used to determine the efficacy of natural selection in a population. There will be fewer changes in a population's genetic composition if the cumulative selection strength index reaches zero. Crow's index has long been used to measure the relative biological fitness of small human populations quantitatively. The total amount of selection, which is expressed by Crow's index, is made up of two components, that is, the mortality component (Im) and the fertility component (If). Individual fitness can be measured in human populations based on the number of healthy offspring (Crow 1958).

Objective

The aim of this study was to look into the effects of inbreeding on reproductive fitness and selection intensity in the Muslim population of western Uttar Pradesh in India.

MATERIALS AND METHOD

Study Design and Data Collection

A door-to-door survey using a standardised questionnaire was conducted from August 2019 through November 2019 in Aligarh (located in western Uttar Pradesh, India, approximately 130 kilometres southeast of the capital city of New Delhi). More than 478 families were visited for the study on random basis, and out of them, total 100 families were found inbred, while re-

maining 378 families were excluded from the study, as they were not fulfilling the desired criteria (widowed (n=59), family planning (n=84), did not permit (n=108), non-consanguineous (n=127)). All the surveyed individuals gave their written informed consent. Only Muslims families were included in the study, as consanguinity is preferable only among the Muslim community in North India. Data were collected from mothers of the family, enquiring about their degree of consanguinity. State, localities, caste, sects, ages, and genders of subjects were recorded. Total number of offspring (live and dead) of each mother was recorded and pedigrees were drawn, and in addition, any sort of illness was noted. All the information was subsequently crosschecked with the fathers of the particular family. From the information provided in the questionnaire, a master chart was created, and frequency tallies were taken.

Pedigree Analysis

Genealogical information volunteered by the subjects up to five generations back aided in determining their marriage's consanguinity pattern. Wright's path (Wright 1922) relationship method was used for determining the inbreeding coefficient (f) for various mating types in the order of first cousin (f = 0.0625) > first cousin once removed (f = 0.03125) > second cousin with value 0.0156) > third cousin (f = 0.0039).

Calculation of Fertility, Mortality, Secondary Sex Ratio and Selection Intensity (SI)

Fertility (live births per mother), mortality rate and percent mortality were calculated independently and collectively for children of both male and female sexes. The secondary sex ratio is the proportion of males to females in a population at the time of birth. The ratio of males per hundred girls born was determined after the sex of the infants born alive or dead was reported. Crow's formula was used to calculate the index of selection intensity (Crow 1958) as follows.

$$I = Im + \frac{If}{Ps}$$

Where, $Im = \frac{Pd}{Ps}$, $Im = \frac{vi}{(x)^2}$ and Ps = 1- Pd.

Here, "I" is the total selection index, "Im" is the mortality selection index, "If" is the fertility

selection index, X is the mean number of live births per woman until the age of 45 years and above, that is, menopause, "Vf" is the variance in the number of live births due to fertility, and "Pd" is death before the age of 18 years.

The researchers thus studied the following parameters:
1. Coefficient of inbreeding (both for autosomal locus 'fa' and sex-linked locus 'fs').
2. Offspring's fertility, mortality and secondary sex ratio.
3. Selection intensity and percent mortality with different degrees of 'f'.

Statistical Analysis

Statistical evaluation of the data was conducted using Microsoft Excel version 2019. Mean, median, mode, standard deviation and standard error were calculated for different degrees of inbreeding. Fertility, mortality, percent mortality and secondary sex ratio were calculated. Selection intensity was calculated by using the given formula. Correlation is used to denote association between two quantitative variables and (linear) regression is used to estimate the best straight line to summarise the association. Hence, correlation and regression analysis were performed for fertility, mortality, selection intensity and secondary sex ratio separately for males and females and cumulatively as well with varying degrees of consanguinity, to find out the association among these variables. Coefficient of determination (R^2) and coefficient of correlation (r) was also determined and the results are presented.

RESULTS

Incidence of Marriage and Coefficient of Inbreeding (f)

Data were collected from a total of 100 Muslim mothers from Aligarh city. Out of the surveyed individuals, Sunnis are dominating, though a significant number of Shias are also present. Syed, Sheikh, Mughal and Pathan make up around one-fourth of the Sunni population, while the other three-quarters are from various lower castes. Out of 100 married women surveyed, seventy-seven percent marriages were of first cousin (FC) type, five percent of them were first cousin once removed (FCR) type, eleven percent of second cousin (SC) type and only seven percent of third cousin (TC) type (Table 1). Out of 77 marriages of first cousin type, highest percentage was of matrilateral cross (MC) or mother's brother's daughter type (42%), while lowest percentage was of patrilateral cross (PC) or father's sister's daughter type (14%) (Table 2). The combined value of 'f' for first cousin marriages for autosomal locus is 0.048125 and for sex-linked locus it is 0.0625, and average 'fs' of all four types is 0.078125 (Table 1). Combined value of 'f' for all seven types of marriages for autosomal locus is 0.051675 (Tables 1 and 2).

Fertility

The value for average number of children born per couple was found to be highest in case of second cousin (5.27) and lowest for patrilateral parallel (4.0), but for all seven categories of the observed consanguinity rate, it is 4.40 (Table 3).

Table 1: Observation of different types of consanguinity and their incidence recorded during survey with coefficients of inbreeding

Types of consanguinity	Coefficient of inbreeding	Incidence of marriage			Coefficient of inbreeding counted
		Number	Percentage	Fraction	
Patrilateral parallel (PP)	0.0625	15	15	0.15	0.009375
Patrilateral cross (PC)	0.0625	11	11	0.11	0.006875
Matrilateral parallel (MP)	0.0625	19	19	0.19	0.011875
Matrilateral cross (MC)	0.0625	32	32	0.32	0.02
First cousin once removed (FCR)	0.03125	05	5	0.05	0.0015625
Second cousin (SC)	0.0156	11	11	0.11	0.001716
Third cousin (TC)	0.0039	07	7	0.07	0.000273
Combined	0.051675	100	-	1.0	0.051675

Table 2: Different types of first cousin marriages and their coefficients of inbreeding for autosomal (fa) and sex-linked (fs)

Types of consanguinity	Incidence of marriage		Coefficient of inbreeding for autosomal locus (fa)		Coefficient of inbreeding for sex-linked locus (fs)	
	Number	Percentage	Fraction	Decimal	Fraction	Decimal
Patrilateral parallel (PP)	15	19	1/16	0.0625	0	0
Patrilateral cross (PC)	11	14	1/16	0.0625	1/16	0.0625
Matrilateral parallel (MP)	19	25	1/16	0.0625	3/16	0.1875
Matrilateral cross (MC)	32	42	1/16	0.0625	1/16	0.0625
Average	-	-	1/16	0.0625	5/64	0.078125
Combined	77	-	-	0.048125	-	0.0625

Table 3: Average number of males, females and total child born and died per couple with respect to the type of consanguinity

Type	Average male child born / couple	Average female child born /couple	Average child born /couple (M+F)	Average male child died/ couple	Average female child died / couple	Average child died /couple (M+F)
P P	1.8	2.20	4.0	0.066	0.133	0.20
PC	2.0	2.63	4.63	0.181	0.272	0.454
MP	2.0	2.05	4.05	0.210	0.263	0.473
MC	2.21	2.06	4.28	0.25	0.125	0.375
FCR	2.0	2.20	4.20	0.00	0.20	0.200
SC	2.09	3.18	5.27	0.363	0.00	0.363
T C	1.85	2.57	4.42	0.142	0.00	0.142
COMB.	1.99	2.41	4.40	0.173	0.113	0.315

Fertility for females is higher (2.41) as compared to males (1.99) (Table 4). The regression analysis of fertility shows that combined fertility (both for males and females) decreases as the degree of consanguinity increases ($R^2 = 0.2671$) (Table 6) and shows negative value (with low magnitude) coefficient of correlation ($r = -0.1568$) (Table 6). Similar pattern was also observed in case of females but of moderate magnitude ($R^2 = 0.3744$, $r = -0.6118$) (Table 6), but the males showed different trend and positive correlation (low magnitude) between fertility and degree of consanguinity ($R^2 = 0.0265$, $r = 0.1626$) (Table 6).

Mortality

The highest value for average number of children deceased per couple was observed in

Table 4: Percent mortality of males, females and combined (males and females) for different degrees of consanguinity

Type	Male				Female				Combined			
	Born	Dead	Total	% mortality	Born	Dead	Total	% mortality	Born	Dead	Total	% mortality
PP (n=15)	26	1	27	3.70	31	2	33	6.06	57	03	60	5.00
PC (n=11)	20	2	22	9.09	26	3	29	10.34	46	05	51	9.80
MP (n=19)	34	4	38	10.52	34	5	39	12.82	68	09	77	11.68
MC (n=32)	63	8	71	11.26	62	4	66	6.06	125	12	137	32.43
FCR (n=05)	10	0	10	0.00	10	1	11	9.09	20	01	21	4.76
SC (n=11)	19	4	23	17.39	35	0	35	0.00	54	04	58	6.89
TC (n=07)	12	1	13	7.69	18	0	18	0.00	30	01	31	3.22
Combined	184	20	204	9.80	216	15	231	6.49	400	35	435	8.04

case of matrilateral parallel, which is 0.473 and lowest for third cousin type (0.142) but cumulatively for all the seven categories, it is 0.315 (Table 3). Mortality for males is found to be higher (0.173) as compared to females (0.113) (Table 4). The regression analysis of mortality illustrates that mortality increases as the degree of consanguinity increases, which means a positive correlation was found between these two attributes. The values of determination coefficient and correlation coefficient corresponds to $R^2 = 0.0444$, $r = 0.2108$ (low magnitude) for males, and it is $R^2 = 0.2789$, $r = 0.5281$ (moderate positive correlation) for females, while it is $R^2 = 0.3161$, $r = 0.5622$ (moderate) for both males and females cumulatively (Table 6). Table 5 shows the percent mortality for both sexes and progeny. In case of males, the maximum value of percent mortality was observed to be 17.39 for second cousin type, and in females, it is 12.82 for matrilateral parallel, and for both the sexes, it is 32.43 for matrilateral cross (Table 4).

Selection Intensity

For selection intensity, 0.376 (the lowest value) was observed in third cousin type marriage and the highest value (2.5663) for matrilateral parallel (Table 5). It is clear from the data that males have higher selection intensity (5.657) than the females (4.762) (Table 3). The regression analysis of selection intensity shows that combined selection intensity ($R^2 = 0.1734$, $r = 0.4164$) and for females ($R^2 = 0.6929$, $r = 0.8324$) increases as the degree of consanguinity (value of inbreeding coefficient) increases and moderately positive correlation was observed between these two variables (Table 6). Selection intensity for males shows a different trend ($R^2 = 0.5753$, $r = -0.7584$), as it decreases with increase in consanguinity degree and moderately negative correlation was observed (Table 6).

Secondary Sex Ratio

Secondary sex ratio is found to be highest in matrilateral cross type that is 107.57 while it is lowest in second cousin that is 65.71. The combined value for secondary sex ratio was recorded as 88.31 (Table 5). The graph of regression analysis depicts that secondary sex ratio increases as degree of consanguinity increases ($R^2 = 0.3757$, $r = 0.6129$), and a moderately positive correlation was found between secondary sex ratio and degree of consanguinity (Table 6).

Table 5: Consisting different types of consanguinity, total male and female child, secondary sex ratio and selection intensity for males, females and combined

Type	Total male child	Total female child	Secondary sex ratio	Selection Intensity (Males)	Selection intensity (Females)	Selection intensity (Combined)
P P	27	33	81.81	0.561	0.976	0.530
PC	22	29	75.86	0.495	1.182	1.178
M P	38	39	97.43	0.824	0.942	2.563
MC	71	66	107.57	0.711	0.543	0.754
FCR	10	11	90.90	0.497	0.80	1.207
SC	23	35	65.71	1.596	0.237	0.827
TC	13	18	72.22	1.330	0.080	0.376
COMB.	204	231	88.31	5.657	4.762	6.880

Table 6: Values of correlation coefficient (r) and coefficient of determination (R^2) of males, females and combined for fertility, mortality, selection intensity and secondary sex ratio

Attributes of the population surveyed	Males		Females		Combined	
	r	R^2	r	R^2	r	R^2
Fertility	0.1626	0.0265	-0.6118	0.3744	-0.5168	0.2671
Mortality	0.2108	0.0444	0.5281	0.2789	0.5622	0.3161
Selection Intensity	-0.7584	0.5753	0.8324	0.6929	0.4164	0.1734
Secondary Sex Ratio	–	–	–	–	0.6129	0.3757

DISCUSSION

The estimation of inbreeding is critically dependent on the estimation of the inbreeding coefficient 'f', which represents the expected percentage of homozygosity of an individual in a given breeding system. First cousins, for example, are expected to share 12.5 percent of their genes. As a result, their offspring will be homozygous at 6.25 percent (1/16) of gene loci on average (Bennett et al. 2002; Hamamy 2012). The values 'f' for sex-linked (fs) and autosomal locus (fa) correspond to homozygous regions of the sex-chromosome (1 pair) and autosomes (22 pairs), respectively. It is clear that progeny of close consanguineous unions has a higher proportion of homozygous gene loci in their genomes and are thus more vulnerable to harmful inbreeding effects.

Fertility

Hussain and Bittles (2004) examined 21 studies conducted in India and Pakistan that discovered significant differences in mean fertility levels. However, little is known about the effects of inbreeding on reproduction and fertility in modern human societies, and the majority of studies were conducted over 30 years ago, with little follow-up since (Jaber and Halpern 2014). The linear regression and correlation analysis from the data revealed that fertility decreases as the degree of consanguinity increases in the case of females and cumulatively for both sexes (Table 4), supporting the fact that mean fertility rates are low in consanguineous couples (Hussain and Bittles 1999; Charlesworth and Willis 2009; Jaber and Halpern 2014). The findings indicate a slight negative correlation between fertility and degree of consanguinity for females (r = -0.6118) and for both sexes (r = -0.1568) but for males it is showing positive correlation (r = 0.1626) but of very low magnitude (Table 4). According to some reports, decreased fertility was probably caused by a failure to begin pregnancy when the pair shared particular HLA haplotypes (Ober et al. 1992), or through the production of harmful genes during the early stages of embryonic or foetal development, as a result, periconceptual losses occur (Ober 1999). In general, consanguineous couples have higher total fertility rates

(Bhasin and Nag 2002; Reddy et al. 2007; Labouriau and Amorim 2008 a, b; Jaber and Halpern 2014).

Mortality

The linear regression analysis and mortality correlation analysis reveal a positive relationship between mortality and degree of consanguinity (Table 4). The highest mortality rate was found in the case of first cousins (f = 0.0625), while the lowest value was observed in the case of third cousins (f = 0.0039) (Table 4), supporting previous findings (Fareed et al. 2017). Although the correlation between degree of consanguinity and mortality is mild in males (r = 0.2108), it is moderate in females (r = 0.5281) and combined for both sexes (r = 0.5622) (Aarzoo and Afzal 2006; Bharathi 2014). In short, inbreeding has a negative impact on offspring mortality, with increased homozygosity levels posing more serious risks (Anwar et al. 2020).

Selection Intensity

With increasing degree of consanguinity, there was an increase in selection intensity. The following is the trend, that is, third cousin (f = 0.0039, SI = 0.376) < second cousin (f = 0.0156, SI = 0.827) < first cousin once removed (f = 0.03125, SI = 1.207) < first cousin (f = 0.0625, SI = 1.256) that is average across all four types. A similar pattern of results was reported in a previous study from northern India (Fareed et al. 2017; Anwar et al. 2020). The correlation and linear regression analysis revealed a moderately positive correlation of selection intensity with increasing degree of consanguinity in females (r = 0.8324) and for cumulative in both sexes (r = 0.4164), but a negative correlation in males (r = -0.7584) (Table 3). However, this negative correlation is unusual, which could be due to the small sample size. Males (5.657) have higher total SI values for all seven categories (PP, PC, MP, MC, FCR, SC, and TC) than females (4.762) (Table 3) (Fareed et al. 2017).

Secondary Sex Ratio

The linear regression and correlation analyses show a moderate positive correlation (r =

0.6129) between degree of consanguinity and secondary sex ratio (Table 3), which is consistent with previous research showing an increase in SSR up to a level inbreeding coefficient group (Fareed et al. 2017; Anwar et al. 2020). Although the trend is clear, an SSR value with a random pattern may be linked to a small sample size.

According to the data presented above, inbreeding is detrimental to the demographic profiles of inbred individuals. To mitigate the negative effects of this, one should be aware of the proportion of homozygosity in the genomes of affected individuals. Using pedigree information, the coefficient of inbreeding "f" discusses homozygosity in individuals. With the advent of dense, genome-wide marker maps, it is now possible to estimate a person's level of homozygosity (Leutenegger et al. 2011). This method provides a genome-based alternative to genealogy (Leutenegger et al. 2003; Purcell et al. 2007) and is thought to be more accurate than pedigree-based information for estimating the realised proportion of the genome that two individuals share (Howard et al. 2017). ROH (Runs of Homozygosity) is a more accurate method of calculating homozygosity, but it is an expensive technique that was first identified by Broman and Weber (1999) as long stretches of homozygous segments in the human population. This is roughly equivalent to the inbreeding coefficient (f) (Curick and Solkner 2014). ROH are not evenly distributed across the genome, but they are found in ROH islands (Nothnagel et al. 2010) and as ROH hotspots (Pemberton et al. 2012). NGS (Next Generation Sequencing) has the ability to increase the knowledge of ROH and its application in inbreeding studies (Curick and Solkner 2014). It is a very expensive technique, and one does not have any financial assistance to carry out this work, otherwise, it would have compared the homozygosity from ROH data and calculated 'f' from pedigree, which the researchers will try to do in the future.

CONCLUSION

The research provides insight into the well-being of the Muslim population of Aligarh in western Uttar Pradesh, India. The aim of this study was to discover the negative effects of consanguinity on Aligarh's population. Consan-

guinity puts a strain on reproductive fitness and increases the strength of selection. However, due to the limited sample size, the significance level is not reached, despite the fact, the patterns are apparent. As the degree of consanguinity increases, fertility decreases. For both autosomal and sex-linked loci, the degree of consanguinity increases mortality and selection intensity. The difference between the two forms of first cousin marriage indicates that the matrilateral parallel type has the highest mortality and the matrilateral cross type has the highest fertility. Sex ratio shows an increase due to inbreeding, that is, males are born higher than females, however, mortality is more among female. Inbreeding is detrimental to the demographic pictures of inbred individuals, according to the above data. The greater the degree of consanguinity, the greater the impact on the children. Public awareness of the genetic risk of cousin marriage, as well as genetic counselling are required to regulate the negative effects of consanguinity among humans in countries with a high proportion of consanguineous marriages. The findings can help healthcare providers and policymakers to train and educate public about the risk of this practice.

RECOMMENDATIONS

Consanguineous unions should be discouraged to prevent negative consequences for an individual's reproductive health, such as high mortality, low fertility, high selection intensity, and other recessive genetic disorders.

LIMITATIONS

Due to the relatively small size, the significance level is not reached in this study, but the trends are clear. A larger sample size, however, is required for a better understanding and significant results. ROH seems to be the most accurate technique for determining an individual's homozygosity, however it is not feasible without additional funding due to its high cost.

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