

## Association of Consanguinity with Abnormalities in the Descendants

Ammara Rafique, Hajra Naz

### ABSTRACT

**Objective:** Consanguinity is often related to several abnormalities in descendants. This survey assessed the frequency of abnormalities in the descendants of consanguinity couples.

**Study Design & Setting:** The cross-sectional survey was conducted from 01-Feb-2021 to 01-Oct-2021 with consanguinity couples residing in Pakistan or abroad.

**Methodology:** Institutional Bioethics Committee (IBC) of Karachi University approved the study. Extensive research on PubMed, Scopus, Medline, Web of sciences, Direct Science, Springer, and Google scholar was carried out to design a structured survey after exploring major factors for special children. The form was divided into three sections encompassed fundamental and marriage-associated demographics, pre- and post-natal characteristics of normal and special children, extended family details, and perceptions regarding cousin marriage. Using snowball sampling, particularly the chain-referral method, data was collected. SPSS v.28 was used to predict the association of each variable with the existence and non-existence of special child/children.

**Results:** Among 503 consanguinity couples, 92.6% had none or normal descendants whereas 7.3% had special descendants of their own or from other cousin marriages in their extended families. Abnormalities including ADHD (n=9, 24.3%), Autism (n=4, 10.8%), cardiac issues (n=1, 2.7%), CP (n=5, 13.5%), deafness (n=3, 8.1%), Down's syndrome (n=1, 2.7%), dumbness (n=5, 13.5%), impaired vision (n=6, 16.2%), and mental retardation (n=3, 8.1%) were reported. However, no case of multiple sclerosis, thalassemia, Tay Sach's disease, or Schizophrenia was reported.

**Conclusion:** Consanguinity precipitated several abnormalities in 0.073% of the population.

**Keywords:** Abnormalities, Causes, Consanguinity, Cross-sectional survey, Pakistan

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### INTRODUCTION:

Consanguinity is the marriage, sexual relationship, or close union between people having the same biological ancestors usually up to about second cousins. Consanguinity is a debatable topic as consanguineous marriages are exceptionally common in North Africa, the Middle East, and West Asia as well as among the emigrants from these countries now residing in Australia, Europe, and North America. Since the mid of 19<sup>th</sup> century, the subject of consanguineous marriage is of major scientific and public interest. There are several cultural, clinical, and social implications for consanguinity couples, which represent about 20-30% of total marriages.<sup>1</sup> Globally, cousin marriage is a tradition and

respected social trend for a marital union and most women prefer cousin marriages for their progeny for the same reasons.<sup>2</sup> The frequency of first-cousin marriages differs within and between different communities and populations, based on their respective culture, geography, race, and religion.<sup>3</sup> Parents prefer cousin marriages due to the ease to find a spouse, family pressure, less expenditure of money, financial security reasons, same caste, and strengthening of family bonds.<sup>2</sup>

Pakistan has a substantial portion of consanguineous marriages in the world.<sup>4</sup> During the last 3 decades, 63% of the rise in the prevalence of consanguineous marriages has been reported in Pakistan and was more prevalent amongst uneducated and young women, in rural areas, less privileged, or unaware people.<sup>4</sup> A significant association between consanguinity and congenital defects is likely Charcot Marie tooth syndrome, congenital heart defects, Down's syndrome, mental retardation, and thalassemia in Pakistan.<sup>5</sup>

Consanguinity has been reported to develop several single-gene and multifactorial disorders such as Bloom syndrome, Becker muscular dystrophy, cancers, cardiovascular diseases, Cerebral Palsy, children's hypertension, cleft lip, cystic

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fibrosis, phenylketonuria, diabetes, muscular dystrophy, impaired vision, hearing issues, mental retardation, obesity, severe combined immunodeficiency, hemoglobinopathies, Tay-Sachs disease, and many others.<sup>6-9</sup>

Consanguinity also has several favorable attributes at the scientific level besides threats. It may preserve advantageous genetic traits by causing homozygosity of alleles in descendants. Consanguinity improves gross fertility, but the number of surviving descendants in both nonconsanguineous and consanguineous mating are similar due to increased morbidity and mortality.<sup>7</sup> The awareness and perception regarding the health risks associated with cousin marriages remains low and therefore about 60% of women prefer marrying their sons or daughters in relatives.<sup>10</sup>

There are often major health concerns if first-cousin marriages continue over several generations in a family. Therefore, this survey was designed to evaluate whether consanguinity can precipitate the descendants' mental and physical abnormalities.

#### **METHODOLOGY:**

Ethical approval was obtained from the Institutional Bioethics Committee (IBC) of Karachi University. For unlimited population size, the calculated sample size was 385 responses with a confidence level of 95%. The idea was to collect a maximum number of responses from consanguinity couples through the snowball sampling method. The initial consanguinity couples referred us to more alike couples which served as a chain-referral method for data collection. Using snowball sampling, this cross-sectional survey was conducted from 01-Feb-2021 to 01-Oct-2021 with consanguinity couples residing in Pakistan or abroad. The inclusion criteria were consanguinity couples i.e. cousins with first cousin marriage were included, and the exclusion criteria were those married to second or third cousins.

An extensive search on PubMed, Scopus, Medline, Direct Science, Springer, and Google scholar to explore established risk factors for special children. Twenty-seven variables were chosen to design a structured survey form which was divided into three sections.

It was mentioned on the top of the form that the survey was only for those consanguinity couples who were first cousins. The first section encompassed fundamental and marriage-associated demographics such as consanguinity relation among spouses, residence, age of spouses by the time of marriage, maternal age, health during pregnancy, and blood groups of parents. The second section encompassed details of pre-and post-natal characteristics of normal and special children such as type of delivery, birth weight, birth state, type of specialty, I.Q, miscarriage, and abortion particulars. The third section encompassed extended family details and perceptions regarding cousin marriage including details of the number of first cousin marriages in the extended family, number of special children, type of specialty, the major

reason for cousin marriages, perception about cousin marriage, and their consideration of marrying their children with their cousins. Since they were all categorical variables so, multiple choices were given to the respondents.

The form was designed in English but later translated into Urdu too. Primarily hard-copy responses were prioritized but later the responses were also collected through Google forms in both languages. The form link was publicized on many social media platforms including Facebook, Instagram, Twitter, WhatsApp, Snapchat, LinkedIn, ResearchGate, and many others to acquire a better response rate. The survey forms were floated in hardcopies in five big universities in Karachi including the Bahria University Medical and Dental College, NED University of Engineering and Technology, Institute of Business Management, University of Karachi, and Ziauddin University with due permission.

For statistical analysis, Pearson chi cross-tabulation values were obtained via SPSS version 28 to predict the association of each variable with the existence and non-existence of special child/children.

#### **RESULTS:**

About five hundred and twenty hardcopy forms were floated in the universities. Four hundred and thirty-three were returned finished, nine were unfinished, and seventy-eight were reverted blank. We got a minimal response online as only seventy respondents responded online form in eight months. Therefore, the response rate for hardcopies was 83.2% and for web-based was 13.4%. All special children were reported from Pakistanis residing in Pakistan whereas 3.86% of Pakistanis residing abroad reported no special children (Figure 1). Out of five hundred and three respondents, (92.6%) had none or normal descendants whereas (7.3%) had special descendants of their own or from other first-cousin marriages in extended families (Figure 2).

Multiple cross-tabulations were performed but only significant associations are presented in Table 1-3. The frequency of consanguineous marriages was higher in the age bracket of 23-24 years for women (33.9%) and 27-28 years of men (30.2%). Among parents of special children, most mothers were within the age bracket of 23-24 years at the time of marriage (35.1%) and husbands in the age bracket of 25-26 (18.9%), 27-28 (18.9%) or above 30 years (18.9%).

The statistical analysis for fundamental or marriage-associated demographics indicated that the existence of special children was only statistically associated with the blood group of mothers ( $p < 0.01$ ) (Table 1).

The analysis further showed that the presence of special children was statistically associated with the delivery type of normal ( $p < 0.05$ ) and special child/children ( $p < 0.001$ ), gestational age of special child/children ( $p < 0.001$ ), birth weight of normal ( $p < 0.01$ ) and special child/children ( $p < 0.001$ ), type of specialty in special child/children ( $p < 0.001$ ),

and I.Q of both normal and special children ( $p < 0.01$ ) (Table 2). Mental and physical abnormalities reported as ADHD (24.3%), Autism (10.8%), cardiac issues (2.7%), CP (13.5%), deafness (8.1%), Down’s syndrome (2.7%), dumbness (13.5%), impaired vision (16.2%), and mental retardation (8.1%). However, no case of multiple sclerosis, thalassemia, Tay Sach’s disease, or Schizophrenia was reported.

Table 3 presents that the presence of special child/children was statistically associated with first cousin marriages in the extended families of both spouses ( $p < 0.01$ ), special child/children in those marriages ( $p < 0.001$ ), type of abnormality ( $p < 0.001$ ), reasons for cousin marriage ( $p < 0.05$ ), views about cousin marriage ( $p < 0.001$ ), and non-willingness to marry their child/children in cousins ( $p < 0.001$ ).

Figure 1: Pakistanis residing in Pakistan or abroad

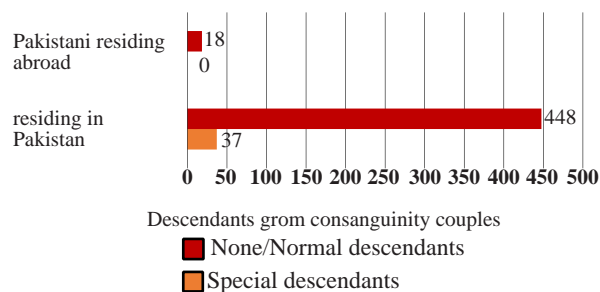


Figure 2: Descendants from consanguinity couples

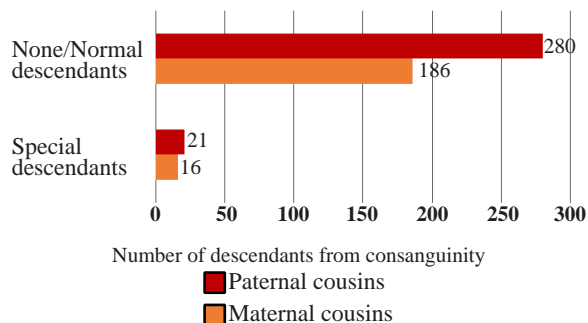


Table 1: Fundamental and marriage-associated demographics

Variables	Special child		p-value
	Present	Absent	
	N (%)	N (%)	
<i>Wife's blood group</i>			
B+	5 (13.5)	160 (34.3)	0.002
A+	9 (24.3)	83 (17.8)	
O+	3 (8.10)	99 (21.2)	
AB+	18 (48.6)	91 (19.5)	
B-	1 (2.70)	10 (2.14)	
A-	1 (2.70)	12 (2.57)	
O-	0	7 (1.50)	
AB-	0	4 (0.85)	

Values are cross-tabulations significant at  $p < 0.01$

Table 2- Pre- and post-natal characteristics

Variables	Special child		p-value
	Present	Absent	
	N (%)	N (%)	
<i>Delivery type of normal child/children</i>			
Normal	24 (64.8)	188 (40.3)	0.018
Other	11 (29.7)	175 (37.5)	
Both	1 (2.70)	53 (11.3)	
Not applicable/no child	1 (2.70)	50 (10.7)	
<i>Delivery type of special child/children</i>			
Normal	16 (43.2)	0	0.000
Other	21 (56.7)	0	
Not applicable/no child	0	466 (100)	
<i>Special child's gestational age</i>			
Full-term	27 (72.9)	0	0.000
Pre-term	10 (27.0)	0	
<i>Normal child/children's birth weight</i>			
Normal	18 (48.6)	276 (59.2)	0.002
Low	14 (37.8)	68 (14.5)	
Both	4 (10.8)	72 (15.4)	
Not applicable/no child	1 (2.70)	50 (10.7)	
<i>Special child/children's birth weight</i>			
Normal	20 (54.0)	0	0.000
Low	17 (45.9)	0	
Not applicable/no child	0	466 (100)	
<i>Special child's disability</i>			
ADHD	9 (24.3)	0	0.000
Impaired vision	6 (16.2)	0	
Cerebral Palsy	5 (13.5)	0	
Dumbness	5 (13.5)	0	
Autism	4 (10.8)	0	
Mental retardation	3 (8.10)	0	
Deafness	3 (8.10)	0	
Cardiac issues	1 (2.70)	0	
Down Syndrome	1 (2.70)	0	
<i>IQ of both normal and special children</i>			
Not applicable/no child	0	51 (10.9)	0.008
Low IQ	1 (2.70)	2 (0.42)	
Both low and high IQ	11 (29.7)	66 (14.1)	
Average	12 (32.4)	143 (30.6)	
High IQ	0	40 (8.58)	
Intelligent	13 (35.1)	164 (35.1)	

Values are cross-tabulations significant at  $p < 0.05$ , and  $p < 0.001$

**DISCUSSION:**

The study revealed that the probability of a special child in consanguineous marriage is 0.073%. Most of the consanguinity couples (83.3%) reported first cousin marriages in their extended family as well (which helped in data collection via a snowball method) with the predominance of the absence of special children as disclosed by 43.2% of

Table 3: Extended family details and perception

Variables	Special child		p-value
	Present	Absent	
	N (%)	N (%)	
<i>Presence of special child/children in other cousin marriages</i>			
One	15 (40.5)	44 (9.44)	0.000
Two	0	1 (0.21)	
None	16 (43.2)	296 (63.5)	
Not applicable	6 (16.2)	125 (26.8)	
<i>Abnormality in children from other cousin marriages</i>			
ADHD	4 (10.8)	5 (1.07)	0.000
Impaired vision	0	6 (1.28)	
Cerebral Palsy	0	3 (0.64)	
Dumbness	0	1 (0.21)	
Autism	2 (5.40)	3 (0.64)	
Mental retardation	2 (5.40)	5 (1.07)	
Deafness	3 (8.10)	5 (1.07)	
Down Syndrome	2 (5.40)	5 (1.07)	
Genetic abnormalities	2 (5.40)	4 (0.85)	
Respiratory distress	0	5 (1.07)	
Sickle cell anemia	0	1 (0.21)	
None of the above	0	2 (0.42)	
Not applicable/no child	22 (59.4)	421 (90.3)	
<i>Views about cousin marriage</i>			
Discourage	14 (37.8)	63 (13.5)	0.000
Genetic defects	9 (24.3)	69 (14.8)	
Uncertain views	6 (16.2)	89 (19.0)	
No comments	3 (8.10)	96 (20.6)	
Good, reliable	5 (13.5)	149 (31.9)	
<i>Reasons for cousin marriage</i>			
Easy to find a spouse	7 (18.9)	113 (24.2)	0.024
Family pressure	2 (5.40)	106 (22.7)	
Same caste	11 (29.7)	86 (18.4)	
Property	0	4 (0.85)	
Less expenditure of money	0	3 (0.64)	
None of the above	4 (10.8)	74 (15.8)	
All above	13 (35.1)	80 (17.1)	
<i>Like marrying your children in cousins</i>			
Not applicable/no child	0	50 (10.7)	0.000
No	29 (78.3)	137 (29.3)	
May be	6 (16.2)	180 (38.6)	
Yes	2 (5.40)	99 (21.2)	

Values are cross-tabulations significant at  $p < 0.05$  and  $p < 0.001$

parents of special children and 63.5% parents of the normal children. In our survey, the parental demographics data showed maternal cousins reported more special children (56.7%) as compared to paternal cousins (43.3%) which are not concordant with Ben-Omran et al reporting paternal cousins have a higher risk of autosomal recessive disorder in the descendants.<sup>12</sup> When a large amount of DNA is shared,

there is an increased probability of sharing a certain pathological allele identical by descent and a probability of having affected descendants with an autosomal recessive disorder.<sup>11</sup> Yet it is impossible to characterize low or high-risk couples among maternal or paternal consanguineous marriages.

In our survey, the majority of mothers with special children were within the age bracket of 23-24 years at the time of marriage but the literature supports that woman and their descendent experience significant problems if maternal age progresses above forty.<sup>13</sup> Several risk factors like consanguinity, parental age, and history of previous congenital anomalies have been identified in the central nervous system, renal, gastrointestinal, and other anomalies of descendants.<sup>14</sup> Numerous studies have claimed that the risks of illness and premature mortality are 3-4% greater in cousin marriages as compared to the general population. Consanguinity may be alarming for the descendants as it can rise the three-fold risk of CP, and the nine-fold risk of other disorders.<sup>15</sup>

Our data reported a significant association between a mother's positive Rh blood and special offspring. A study has reported that the blood incompatibility between mother and fetus (maternal blood with negative Rh and fetal blood with positive Rh) increased the probability to be born with disorders.<sup>16</sup> But this certainly cannot be asserted we only surveyed the blood group of parents. Rh incompatibility can trigger hyperbilirubinemia which may lead to chronic stress if not treated well. We anticipate that Rh incompatibility may have developed specialties reported in our survey (Table 2). Our data reported miscarriages (7.75%) and it has been reported that there is a higher incidence of abortions, miscarriages, and stillbirths in consanguineous marriages.<sup>17</sup>

There is a higher rate of miscarriages in cousin marriages as compared to non-consanguineous marriages which might be the reason for such a high ratio of miscarriages reported in our data.<sup>7,18</sup>

Most of the special children in our data were born full-term (72.9%) with normal delivery (43.2%) however normal delivery is safest for both fetus and mother if a baby is delivered at full-term.<sup>19</sup> Among special cases, (35.1%) were intelligent as claimed by the respective parents and it has been reported that more than half of children from consanguineous marriages have intellectual disabilities.<sup>20</sup> The intellectual abilities can only be assessed through IQ tests so, there is a chance that the parents may have marked IQ levels without assessment.

Most consanguinity couples agreed to the fact that the main reason for cousin marriage is that it is easier to find a partner (24.2%). Most respondents with special children expressed that cousin marriages should be discouraged (37.8%) and (78.3%) of them denied marrying their children to cousins suggesting their concerns for future generations. A study has reported that most women in Pakistan still prefer cousin

marriages due to traditions and family security regardless of their education or social status.<sup>21</sup>

Unfortunately, there is inconsiderable awareness in mothers about the risk associated with consanguinity.<sup>10</sup> It is necessary to aware people of reproductive health to combat the deleterious effects of consanguineous marriage.<sup>3</sup> It is suggested that nonconsanguineous marriages are safer and may delay the manifestation of abnormalities until scientists attain a practical solution.<sup>22</sup>

Our study has a few limitations. Possibly some consanguinity couples may not have been fully truthful about every inquired detail. Our survey data collection was limited to the chain-referral sampling method thereby, more data is required to further validate our reported findings. The I.Q reported by the parents of special may be marked without assessment.

We believe that our findings will be beneficial in creating massive research about the abnormalities associated with consanguinity. It is questionable area how many descendants of consanguinity couples manifest abnormalities on a daily, monthly, or yearly basis in Pakistan. Government shall assign researchers from all provinces of Pakistan to establish an integrated manual or electronic database of abnormalities in the descendants of consanguinity couples.

## CONCLUSION:

Descendants from consanguinity couples depicted several abnormalities including ADHD, Autism, cardiac issues, CP, deafness, Down's syndrome, dumbness, impaired vision, and mental retardation in 0.073% of the population. Extensive research is essential to identify the exact mechanism of the reported abnormalities. We anticipate that genetic counseling is prudent to reduce the genetic, social, and economic burden of abnormalities often associated with consanguinity.

### Authors Contribution:

**Ammara Rafique:** Conception, developed the study design, interpretation, manuscript drafting, literature review, and bibliography

**Hajra Naz:** Research Supervisor, conception, and interpretation

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