Assessment of association between degree of consanguineous marriages and late-onset diseases in Sivagangai population

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Abstract

Consanguineous marriage is an intra-familial relationship between two people with a common ancestor. This practice occurs in most populations, with varying percentages among all marriages in South India. In the present study, the impacts of endogamous marriage against genetic late-onset diseases among the selected population of Sivagangai were studied. The 11327 families were selected and interviewed face-to-face in the local language according to the standard procedures to determine the effect of endogamy on diabetes mellitus, hypertension, asthma, heart diseases, cancer, blood disorders, gastrointestinal diseases, and hearing impairment. In the total population, 29.88% of couples were recorded as consanguineous and 70.11% non-consanguineous. The difference was statistically significant (P<0.00001). The effect of Endogamy on late-onset diseases among the total affected individuals was 57.25% of the product of consanguinity and 42.75% of the product of non-consanguineous. The highest degree of consanguinity recorded was third degree followed by second degree.The study indicated a statistically significant difference between the two groups, with a higher prevalence of genetic disorders in families with a history of consanguinity. Overall, the study emphasizes the need for awareness and action to address the prevalence of genetic disorders related to consanguineous marriages through education and counseling to ensure the well-being of future generations.

Keywords: Endogamy, Consanguinity, Degree of Consanguinity, Intra-familial relationship, Diabetes mellitus.

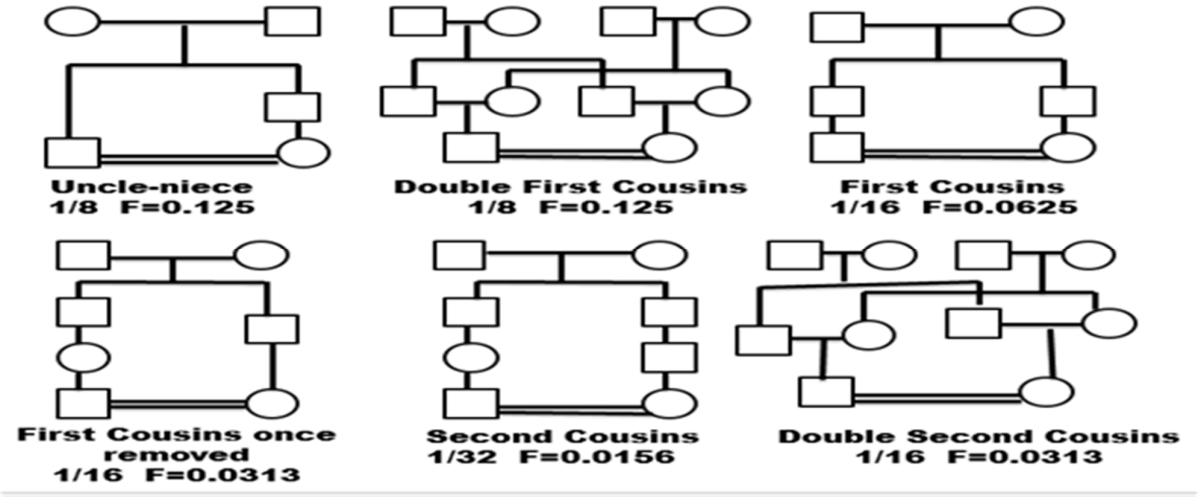
Introduction

Consanguinity is a type of customary relationship between two people who share a common ancestor. At present, one billion of the global population live in communities with a preference for consanguineous marriage (Bittles and Black 2010, Modell and Darr 2002). Consanguineous marriages have been practised for hundreds of years in many communities throughout the world (Jaber *et al.,* 1998). The rate of consanguinity differs in different countries (Bener *et al.,* 1996). Consanguineous marriage is one of the traditional practices in most of the communities of North Africa, the Middle East and West Asia. This intra-familial union collectively account for 20–50% of all marriages (Bittles 2011, Hamamy *et al.,* 2011, Tadmouri *et al.,* 2009) According to NFHS (2015), fourteen percent of marriages in India are consanguineous marriages, which are more prevalent in southern states except Kerala. The people of Kerala strictly avoid such interrelationships. About one-third of women in Tamil Nadu, Lakshadweep, Andhra Pradesh, and Telangana have been indulged in consanguineous marriages. Pondicherry records the highest level

of uncle-niece marriage at 54.9% (Puri *et al.,* 1978). There is a wide variation in inbreeding levels within the northern and southern states of India. According to NFHS 4 (2015-16), Tamil Nadu and Lakshadweep reach the highest level of inbreeding up to 33%. Arcot district of Tamil Nadu recorded the highest frequency of cognate marriage. In most of the northern states of India, only 10-12% prefer inbreeding except in Jammu and Kashmir, which reach up to 20% (before separation into union territory in the year 2019). Among the different forms of consanguineous marriages, the uncle-niece marriage is most common in South India. Uncle-niece marriages are practised in high proportions, particularly in the coastal areas of southern India. When we look into the ethnic group, the Dravidian have the Indo-Scythian, and Mongoloid ethnic groups (Saheb and Bhanu, 1984). Consanguineous unions are preferred in some communities as it is believed to strengthen family relations. The fear of marrying strangers, maintenance of the family property, requirement of less economic transaction (dowry) and cultural practices favour intra-familial marriages (Bittles, 1994). Marriages among relatives are also believed to be more stable, have better relationships with in-laws, and favour the practice and continuity of cultural practices. Parents believe that in close kin relationships, the physical traits of the bride will be less important and in-laws will be more caring and supportive (Bittles, 1994).

Marriage may seem like an individual matter involving only future spouses. But in reality, this practice depends on several factors such as early marriage. (Sidi-Yakhlef & Metri 2013) Consequently, this behaviour will contribute to the impoverishment of the genetic variability and will offer a possibility of manifestation of deleterious or harmful genes in the genotype of the population, and therefore a harmful effect on health profile (Fareed, Ahmad, Anwar, & Afzal, 2017). Several studies confirm diabetes rate increase among the offspring of consanguineous couples (Bener *et al.,* 2007; Elhadd, Al-Amoudi, & Alzahrani, 2007; Bener & Mohammad 2017) In populations with high consanguinity rates and common inherited blood disorders, community programs for premarital screening to detect carriers of hemoglobinopathies such as thalassemia and sickle cell anaemia are in progress as in Jordan (Hamamy *et al.,* 2007), Determining the degree of relationship between the proband and the affected individual is also important. The individuals of first cousin, second cousin and first cousin once removed have shared a significant amount of genetic information with a proband and the risk for a recessive condition in consanguineous mating. The current study was carried out to find out the impact of kinship relationships on the transmission of identical lethal recessive genes associated with late-onset diseases among the population of Sivagangai.

Figure 1 Type of Consanguineous Marriages.



Methodology

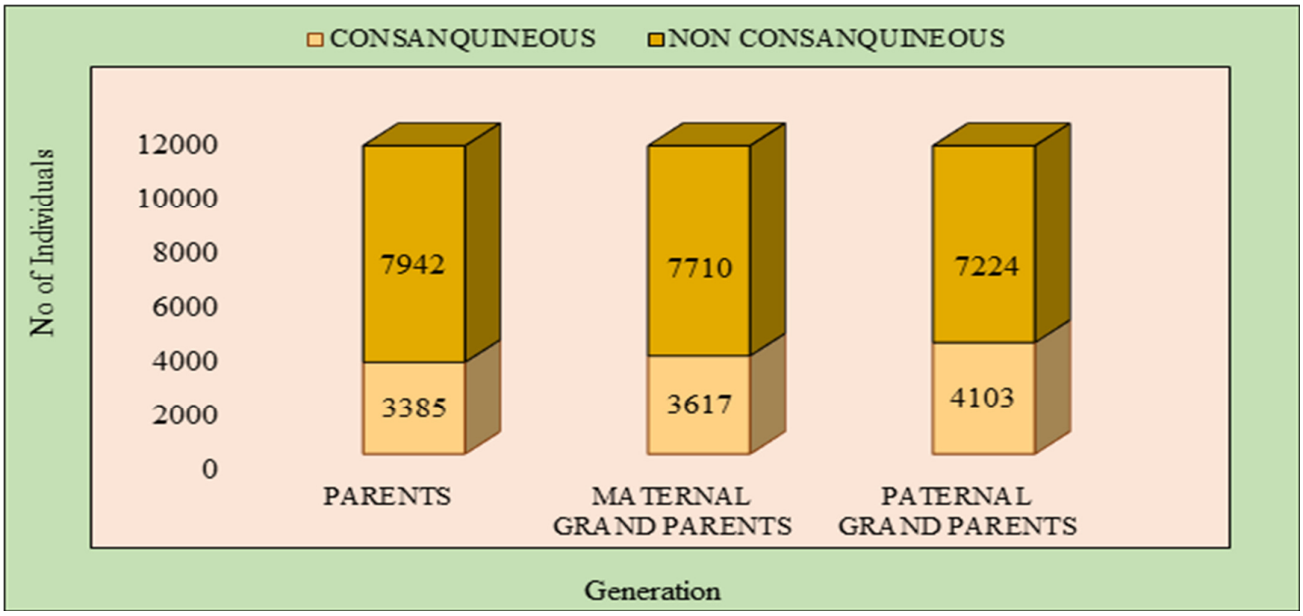
The present study is a population-based cross-sectional study. The prevalence of Consanguinity and degrees of endogamy has been estimated with the standard methods of Abdulbari Bener *et al.,* 2006. The genetic survey on the consanguinity has been carried out between January 2021 and December 2023. All information was gathered based on structured face-to-face interviews in the local language. Furthermore, content validity, face validity and reliability of the questionnaire were tested in a sample of 11327 subjects and self-reported diseases were confirmed in medical charts. The relationship between the spouses was recorded as whether their parents were consanguineous. Marriages between relatives were classified into 6 groups: double first cousins; first cousins; first cousin once removed, second cousin, less than second cousin (third cousin), and Non-consanguineous marriage.(Abdulbari Bener *et al.,* 2007) Late-onset diseases of heart diseases, diabetes, hypertension, blood disorders, kidney problems, hearing defects, asthma, etc. were recorded. Odds ratios were computed for the likelihood of disease by consanguinity status in the current generation as well as the respondent's children. For the current generation, cases were defined as respondents who were offspring of consanguineous (disease report limited to either self or siblings having the disease), and controls were defined as respondents who were offspring of non-consanguineous unions (disease report limited to either themselves or siblings having the disease). Similarly, definitions were adopted for the respondent's offspring. The tests were used to ascertain the association between two or more categorical variables.

Result

Among the selected population (11327), 3385 were found to be a consanguineous couple and 7942 non-consanguineous couple in the parental

generation. In the total population, 29.88 % of couples were recorded as consanguineous and 70.11 % as non-consanguineous. The difference was statistically significant (P<00001). In the maternal grandparents' population, the consanguineous and non-consanguineous were 3617 and 7710 respectively. The percentage of Consanguinity and non-consanguineous were 31.93% and 68.07% respectively. In the paternal grandparents' generation, 4103 were consanguineous couples and 7224 were non-consanguineous generations and the percentage was 36.22% and 63.78% respectively. In the total grandparents' population, 34.08% of the couples were consanguineous and 65.92% were non-consanguineous. The difference was statistically significant (P<.00001).

Figure 2 Rate of Consanguinity.



The percentage of consanguinity and non-consanguineous were 32.68% and 67.32% respectively. In the current study, the 3rd degree of consanguinity was recorded at a maximum of 48.5% when compared to the other degrees. Among the consanguineous couples, 48.5% had married their first cousin, 19.4% had married their maternal uncle, 18.9% had married their second cousin and 13.2% had married their first cousin once removed. The risk ratio was calculated to determine the ratio of the probability of the consequence in the late-onset diseases of kinship parents to the chance of an outcome in the late-onset diseases of non-consanguineous parents. The odds ratio for late-onset diseases of the current generation in consanguineous (250) and non-consanguineous (191) was 2.5320 and the risk ratio was 2.4840. At 95% confidence level, the CI recorded was 2.0931 to 3.0629. The association between late-onset diseases and

kinship was significant ($\chi 2=9.566$, $p < 0.0001$). The odds ratio for late-onset diseases of offspring in consanguineous (46) and non-consanguineous (30) was 3.5976 and the risk ratio was 3.5627. At 95% confidence level, the CI recorded was 2.2672 to 5.7086. The association between late-onset diseases and kinship was significant ($\chi 2=5.435$, $p < 0.0001$).

Figure 3 Patterns of Consanguineous Marriages.

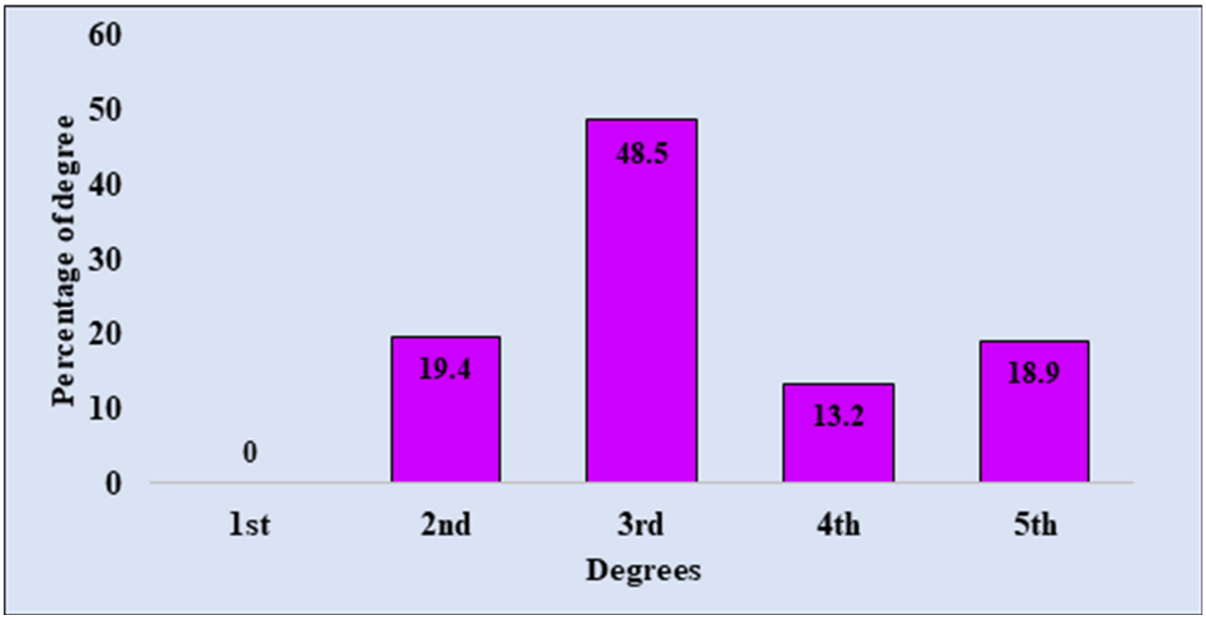
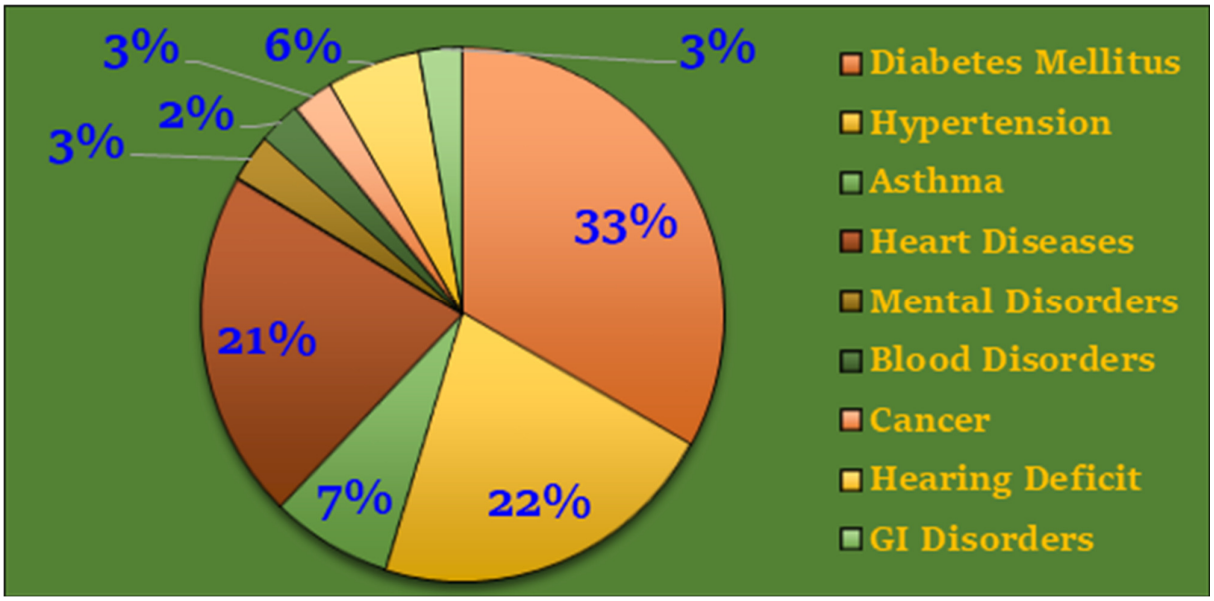


Figure 4 Percentage of diseases among the Sivagangai population.



The prevalence of hereditary late-onset diseases of the current generation versus consanguineous

and non-consanguineous in Sivagangai is presented in Tables 1 and 2. among parents, current generation and offspring.

Table Prevalence of hereditary late-onset diseases among the current generation versus consanguineous and non-consanguineous population.

Diseases	C	NC	Odd Ratio	Risk Ratio	95%Cl	X^2	P-Value
Diabetes Mellitus	**87**	**69**	**2.4391**	**2.4074**	**1.7741 to 3.3534**	**5.490**	**<0.0001**
Hypertension	**63**	**43**	**2.8342**	**2.8047**	**1.9196 to 1846**	**5.240**	**<0.0001**
Asthma	**19**	**11**	**3.3413**	**3.3299**	**1.5885 to 7.0284**	**3.180**	**=0.0015**
Heart Diseases	**58**	**39**	**2.8769**	**2.8491**	**1.9136 to 4.3251**	**5.080**	**<0.0001**
Mental Disorders	**04**	**05**	**1.5476**	**1.5470**	**0.4153 to 5.7665**	**0.651**	**=0.5153**
Blood Disorders	**04**	**05**	**1.5476**	**1.5470**	**0.4153 to 5.7665**	**0.651**	**=0.5153**
Cancer	**04**	**04**	**1.9345**	**1.9335**	**0.4835 to 7.7392**	**0.933**	**=0.3509**
Hearing Deficit	**05**	**08**	**1.2090**	**1.2088**	**0.3953 to 3.6983**	**0.333**	**=0.7393**
GI Disorders	**06**	**07**	**1.6581**	**1.6571**	**0.5568 to 9373**	**0.908**	**=0.3637**

Table Prevalence of common late-onset diseases among the offspring versus consanguineous and non-consanguineous unions.

Diseases	C	NC	Odd ratio	Risk Ratio	95% CI	X^2	p-value
Diabetes Mellitus	**09**	**02**	**10.5581**	**10.5327**	**2.2800 to 48.8923**	**3.014**	**=0.0026**
Hypertension	**02**	**01**	**4.6925**	**4.6903**	**0.4253 to 51.7692**	**1.262**	**=0.2069**
Asthma	**06**	**07**	**2.0111**	**2.0093**	**10.6753 to 5.9885**	**1.255**	**=0.2095**
Heart Diseases	**07**	**04**	**4.1059**	**4.0995**	**1.2011 to 14.0354**	**2.252**	**=0.0243**
Mental Disorders	**02**	**04**	**1.1731**	**1.1730**	**0.2148 to 6.4080**	**0.184**	**=0.8538**
Blood Disorders	**03**	**01**	**7.0387**	**7.0334**	**0.7319 to 67.6938**	**1.690**	**=0.0911**
Cancer	**03**	**02**	**3.5194**	**3.5171**	**0.5878 to 21.0722**	**1.378**	**=0.1682**
Hearing Deficit	**11**	**05**	**5.1617**	**5.1482**	**1.7920 to 14.8675**	**3.041**	**=0.0024**
GI Disorders	**03**	**04**	**1.7597**	**1.7590**	**0.3936 to 7.8667**	**0.740**	**=0.4595**

The Data showed that the parents and current generation against the late-onset diseases was statistically significant. Moreover, the current generation of consanguineous parents had a significantly higher risk than the non-consanguineous parents of fatal diseases such as cancer, mental disorders, heart diseases, blood disorders, hypertension, hearing deficit and diabetes mellitus. The effect of Endogamy on late-onset diseases among the total affected individuals was 57.25% of product of consanguinity and 42.75 % of product of non-consanguineous. All reported diseases were more frequent in consanguineous marriages.

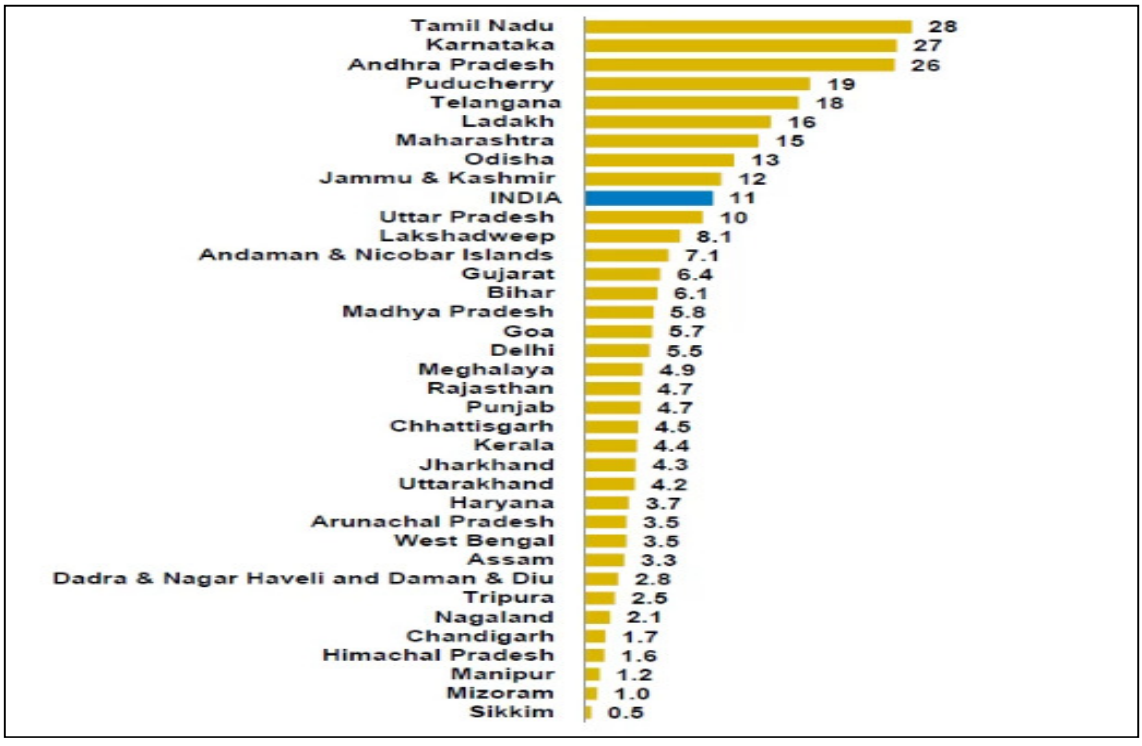
Discussion

Tamil Nadu has a heterogeneous population of diverse cultures and traditional practices. A greater part of the findings on consanguinity in India focuses mostly on the southern states of India. Results revealed that the occurrence of consanguineous unions was higher in Tamil Nadu (38%) followed by Andhra Pradesh (30%), Karnataka 29% and Maharashtra 28%,. On the contrary, another state such as Himachal Pradesh has the lowest proportion (1%) of blood-related marriages. Overall, the South Indian states displayed the greatest incidence of consanguineous marriages than the other parts of India (Shrikant *et al.,* 2013). This implies that almost 1 in 4 women in these states marry a blood relative of a first cousin or second cousin. Some endogamous communities prefer a custom of practising marriage between cousins while other communities put into practice marriage between niece and maternal uncle. Among the inbreeding relationships, cross-cousin marriages are more preferential than marrying uncles. The incidence of consanguinity is much higher in developing countries than in developed countries. Abdulbari *et al.*, 2007 estimated the proportion of consanguinity in the Qatar population was 51% (95% confidence interval = 47.7– 54.4). Beck (1972) plotted the distribution of the first choice for consanguineous nuptials and their customs in four south Indian states including Andhra Pradesh, Karnataka, Kerala, and Tamil Nadu. In the populations of South India, consanguineous marriages are ethnically and communally favoured, and constitute about 20-50% of all marriages. Consanguinity toll in a variety of societies was found to be dependent on numerous factors such as religion, educational level, native traditions socio-economic status, and demography (Fuster, 2003; Assaf *et al.,* 2009). The intra-familial marriage preference is associated with deeply embedded cultural beliefs, societal life, and customs. Such marriages are considered to be added stable, due to nearby similarities in communal and cultural values between the pair and the monetary benefits of maintaining wealth within the families (Baner *et al.,* 1996; Mokhtar *et al.,* 2001; Khoury and Massad 1992; Sueyoshi and Ohtsuka 2003; El-Hazmi *et al.,* 1995; Bener and Ali 2006; Bener and

Hussain 2006). Moreover, intra-familial marriage is considered beneficial to maintain family fortunes within the identical family structure. Anthropologists have approved that the main success of consanguineous marriages is the birthright of family structure and assets (Granguist 1931; Resonfeld 1957 and Schull et al., 1972). In the present study, the percentage of consanguineous in the parental was 28.26% and the total consanguinity of maternal and paternal grandparents was 40.18%. The P-value calculated was <0.00001 which shows they are statistically significant. In Tamil Nadu, as per the National Family Health Survey, India (1995) and Kuntla *et al.,* (2013), the estimated prevalence of consanguineous marriage was 38.2%. Verma *et al.,* (1992) estimated that in Pondicherry the prevalence of consanguineous marriage was 30%. The rate of recurrence of consanguineous nuptials is thought to be falling in the majority populations as an effect of better female education, resettlement to urban areas, and decrease in the number of eligible relatives, improved socio-economic status, and a decline in parental decisions in marriages. In the present study, the first cousin union was the most predominant one than others which accounts for 51.4 % of total consanguineous marriages. First cousins kinship are accounting for about one-third of all marriages (Bittles 2011; Tadmouri et al., 2009). By comparison, uncle-niece marriage and first-cousin unions had long practice in South India (Sastri 1992). According to the study of Roychoudhury (1976) and Kuntla *et al.,* (2013) the frequency of first-cousin marriages in different parts of South India varied from 5 to 57%. The degree of consanguinity in the present study is 51.4% for the third-degree, 19.6% for the second-degree, 12.3% for the fourth-degree, and 16.7% for fifth-degree relatives. Subalakshmi and Jepa (2018) found that the third degree of endogamy is higher in Tamil Nadu. The majority of the widespread form of consanguineous marriage throughout the world is among first cousins, who on average have co-inherited 1/8 of their genes from one or more common ancestors. First-cousin progeny will consequently be homozygous at 1/16 of all loci, which is predictably expressed as a coefficient of endogamy (F) of 0.0625 (Bittles *et al.,* 2009). Consanguineous marriage has a significant societal function and hereditary consequences. In several consanguineous families, the circumstances are made more problematic by the co-existence of unusual mutations. According to WHO, an elevated proportion of abnormal children were the descendants of consanguineous parents. On the other hand, a consanguineous marriage distributes the threat of bearing offspring with recessively inborn diseases. In this respect, exact and accountable articles should be published in the mass media, schools and colleges on the impact of endogamy on traditional endogamy. This investigation is one of the openings attempts to

explore the endogamy coefficients and detailed information to look at the effects of inbreeding on neonatal impairments among the native populations of Sivagangai. This study serves as an underpinning platform for further studies. The prevalence of intra-familial relationships among the Middle East countries, North Africa and South Asia account for 20-50% of all marriages. First cousin (F = 0,0625) unions are more frequent comprising 20-30% of all marriages (Bittle and Black, 2010 and Bittle 2010). This social custom is practised mainly for religious and economic reasons. In some religions marriages between first cousins and uncle-niece are permitted, but not between brothers and sisters. Among the Hindu population of South India, about 30% of marriages are consanguineous, with 20+% between uncle-niece unions (F = 0.125) (Bittle *et al.,* 1991). However, studies from South India where inbreeding has been practised for more than 2,000 years showed that there has been no appreciable elimination of recessive lethal and sub-lethal genes in the gene pool (Devi ARR *et al.,* 1987). It has been reported that several genetic disorders, congenital malformations and reproductive wastage.

Figure:5 Consanguineous marriages by states



Source: National Family Health Survey (NFHS) – 5, Ministry of Health & Family Welfare, Government of India.

Are more frequent in consanguineous marriages (Bittles *et al.,* 1991)Some previous research work in Tamilnadu pointed out the high risk of intra-familial relationships on

pregnancy outcome and other autosomal anomalies in Sivagangai. This amplified risk is because closely associated individuals are more likely to share genetic material, including risky mutations. As a result, the chances of recessive heritable disorders occurring in offspring of intra-familial unions are significantly higher. In some populations, consanguinity has been practised for generations, which means that certain genetic impairments can be more predominant in these populations. The communities of Middle Eastern and South Asian communities have high rates of recessive hereditary disorders such as diabetics, thalassemia, epilepsy and sickle cell anaemia, which are caused by point mutation (Subalakshmi and Japa, 2020) The hereditary disorder among Sivagangai populations was higher among consanguineous communities.(T.Subalakshmi and Jepa Chandra Mohan 2018). Consanguineous marriages increase the likelihood of homozygosity for autosomal recessive disorders. This means that both parents are more likely to carry the same deleterious recessive gene, which can lead to a higher incidence of genetic disorders such as cystic fibrosis, sickle cell anaemia, and thalassemia in their offspring (Bittles, 2012). The highest prevalence of congenital heart diseases in the populations of Qatar was found to be higher among consanguinity families (Bener *et al.,* 2007). Consanguinity has also been linked to an increased risk of type 2 diabetes this is possibly due to the aggregation of genetic factors that predispose individuals to diabetes within families practising consanguineous marriages (Alharbi et al., 2014). Obesity is known to be a risk factor for many different diseases including cardiovascular disease, insulin resistance, and type 2 diabetes mellitus. Polymorphisms in the ACE gene have been implicated in different metabolic disorders, including obesity. A recent study investigated genetic associations in the offspring of first cousins and found an association of the ACE II polymorphism with obesity in the Saudi population (Alshammary and Khan 2021). This effect of consanguineous study shows a higher incidence of certain diseases in consanguineous couples and that, in a population with a high rate of consanguinity, there is a significant increase in the prevalence of common adult diseases cancer, mental disorders, heart diseases, gastro-intestinal disorders, hypertension, hearing deficit and diabetes mellitus. The genetic impact of cognate marriages can lead to an increased risk of passing on deleterious or harmful genes to offspring due to the limited genetic diversity within the closely related individuals. This can potentially lead to a higher prevalence of genetic disorders and inherited diseases within the offspring of consanguineous couples. It is important to understand and address these genetic implications when considering

consanguineous marriages and their potential effects on future generations' health and well-being. It is important to increase knowledge and public awareness regarding the risks of consanguinity and worldwide education programs may help with this. Patients, families, and their physicians should actively engage in research on the relationship between consanguinity and disease through a multidisciplinary approach.

Conclusion

Based on the information provided, intra-familial marriage, also known as consanguineous marriage, refers to the union between two individuals who share a common ancestor. This practice is prevalent in many communities, particularly in South India. The impact of consanguineous marriage on the prevalence of late-onset genetic diseases, such as diabetes mellitus, hypertension, asthma, heart diseases, cancer, blood disorders, gastrointestinal diseases, and hearing impairment, among the population of Sivagangai was studied, revealing that 29.88% of couples were recorded as consanguineous and 70.11% were non-consanguineous. The study indicated a statistically significant difference between the two groups, with a higher prevalence of genetic disorders in families with a history of consanguinity. Overall, the study emphasizes the need for awareness and action to address the prevalence of genetic disorders related to consanguineous marriages through education and counselling to ensure the well-being of future generations.

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