Unnoticed Genetic Predisposition Identified as Risk Factors among Intellectually Disabled Families in Tirunelveli District, Tamil Nadu, India

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Abstract:
Problem: Intellectual disability (ID) is a developmental disorder that includes both intellectual and adaptive functioning deficits. Genetic predisposition already found in the family can be identified as risk factors for the ease of implementing preventive strategies. This research aims to investigate selected genetic risk factors prevalent in families affected by ID, emphasizing the potential significance of early identification of the condition. **Approach**: A Cross-Sectional study was conducted in Tirunelveli District, Tamil Nadu, India, through special schools meant for Intellectually disabled people. A total of 203 ID samples were included in the study. Personal interviews were conducted over telephone among the biological mothers of the ID samples. **Findings**: Among the participating families, 31.5% had a history of parental consanguinity with first cousin marriages being the prevalent one followed by uncle-niece marriages and second cousin marriages. Familial ID was found in 31% of the participants. Sibling involvement was observed in 24.3% of the cases, with sibling recurrence accounting for 12.3% of the affected group. Analysis using odds ratio and chi-square tests demonstrated that affected siblings had a significant impact on the severity of ID. Maternal age at conception and history of miscarriage/stillbirth as risk factors were reported in fairly low numbers in the population and found not to be associated with severity of ID. **Conclusion**: This study is the first epidemiological investigation that provides essential data to inform the formulation of strategic policies and to improve public health outcomes.
Keywords: Genetic Risk factors, Consanguinity, Familial intellectual disability, Sibling recurrence, Genetic counselling, Maternal age.

1 Introduction: Intellectual Disability (ID) is an extremely heterogeneous condition involving environmental, genetic, and many other multifactorial causes. The various factors contributing to the genetic etiology of ID can be chromosomal abnormalities that include gross aneuploidies to partial aneuploidies, microdeletions, microduplications, and rearrangements; single-gene disorders that include autosomal and X-linked disorders and finally polygenic factors[1]. Various factors can be considered risk factors for a developing foetus to have a genetic cause for intellectual disability based on research and evidence all around the world. Consanguineous mating, familial presence of ID, increased maternal age, recurrent miscarriages/stillbirth and teratogen exposure are the risk factors for a family or a couple to opt for prenatal genetic counselling or other preventive strategies.

Consanguineous marriages pave way for imbalanced genetic conditions leading to many diseases and conditions. Consanguineous unions lead to increased expression of autosomal recessive disorders [2,3]. Couples who are distantly related could have a similar risk of birth defects in their offspring as first cousin couples in

highly inbred populations because in inbred populations, the actual relationship coefficient among two individuals is much higher than the one calculated based on the information given by the couple[4].

The contribution of Autosomal recessive forms of intellectual disabilities (ARID) is about 10% of cases in an outbred population. In consanguineous unions, the risk for ARID is about 2–3 times higher. Familial ID reported by previous studies was found to vary between 7% - 53% [5]. The finding of a positive family history strongly suggests a genetic etiology. Positive family history of ID especially with two or more affected members has been considered an indicator of a sub telomeric defect and possibly Fragile X[6]. However little data exists about the epidemiological relevance of familial ID. Foetal chromosomal abnormalities are a widely known cause of miscarriage and have been defined as the main cause of both single and recurrent miscarriage, particularly numerical alterations, with the majority occurring de novo rather than being inherited[7]. Older maternal age has been associated with an increased risk of ID, with a study reporting a 22% increase in offspring of mothers over the age of 40 compared to those under the age of 30 [8]. A retrospective cohort study also shows increased maternal age as a single risk factor can produce significant complications for the foetus which includes chromosomal abnormalities, congenital abnormalities, low birth weight and perinatal mortality [9].

Prevention should be given equal importance as the management of ID. By identifying pregnancies at risk, appropriate interventions and critical decisions can be made to eliminate or reduce the risk of having a child with ID. This studyinvestigated the genetic risk factors present in families of individuals affected by ID to emphasize that if these familial risk factors were identified as genetic predisposition earlier, there is a fair chance of mitigation or intervention which could have reduced the familial burden. This study also provides epidemiological data on risk factors which could be approached strategically through potential policiesat the right time in the future.

2. Methodology:

2.1Study Design: This cross-sectional descriptive study was carried out in Tirunelveli district, Tamil Nadu, India.

***2.2 Data Collection*:** The data collection process commenced after obtaining permission from the District Disability Welfare Department, which serves as the issuing authority for disability cards and other welfare schemes for disabled individuals. The utilization of telephone calls as the mode of data collection was necessitated by then prevailing circumstances of the COVID-19 lockdown, which led to the closure of schools. The study was conducted from March 2021 to December 2021

***2.3Ethical Considerations*:** Institutional Ethical Committee approval for the study was obtained from the Sarah Tucker College-Institutional Ethical Committee (STC-IEC) following the guidelines set forth by the Indian Council of Medical Research (ICMR). Prior to data collection, participants were informed about the study's objectives and assured that their information would be used solely for research purposes. Confidentiality was guaranteed, and participants were assured that their identities would not be revealed in any published findings. They were also made aware of the voluntary nature of their participation and were required to provide oral consent before proceeding with the interview.

***2.4Sample Selection*:** The study sample were the mothers of ID individuals registered in special schools. Out of the 401 children and individuals registered, 203 mothers participated in the study, yielding a response rate of approximately 50%. The inclusion criteria required the ID-affected individuals to have a proper disability card issued by the government, confirming the presence of ID as assessed by relevant medical professionals.ID-affected individuals living in homes without direct contact with their parents or in the care of relatives were excluded from the study to ensure the collection of primary data from respondents directly related to the affected individuals. According to sample science calculations considering the prevalence of the condition,

inclusion and exclusion criteria and population of Tirunelveli district, 181 samples would be sufficient to conduct the study, so the available 203 samples were included in the study.

***2.5Data Analysis*:** Descriptive statistics were employed to summarize the collected data, providing an overview of the study variables. Furthermore, a chi-square test was used to investigate potential correlations between the variables and the severity of ID, with a significance level of α=0.05. Odds ratio analysis was utilized to compare different severity statuses with the study variables. Data analysis was performed using Microsoft Excel.

3. Results:

***3.1Demographic and socioeconomic characteristics of the affected individuals and their families*:** The mean age of the affected sample was 18.73yrs. Majority of the affected individuals, approximately 56%, fell within the age range of 11 to 20 years. Moreover, the study observed a significant prevalence of males among the affected sample. The disabilities were categorized as moderate, severe, and profound, constituting approximately 50.74%, 47.29%, and 1.97% of the cases, respectively. The mothers of the participants primarily belonged to the age category of 41-50 years, accounting for 44% of the sample. The study also reported that 80% of the participants identified as Hindus. In terms of family size, around 52% of the families had two children, and 29% had three children. Furthermore, the participants were distributed between rural and urban backgrounds, with 59.1% coming from rural areas and 40.8% from urban settings. Regarding education, a substantial number of parents had attained a secondary school level of education, with 45.3% of mothers and 48.3% of fathers falling into this category. Additionally, the study found that approximately 42% of the participants worked for daily wages, while around 45% had regular employment. It was also noted that 64% of households had only one working member. In terms of income, 83% of families had an average monthly income below ₹10,000, and only 4.43% of families reported an income exceeding ₹30,000 per month.

3.2Prevalence of Genetic Risk Factors among the ID affected population of Tirunelveli District: Consanguineous mating- presence and pattern, family history of ID- Degree of relationship with the affected member, sibling status, maternal age, and miscarriage or stillbirth incidence were the genetic risk factors considered for this study. Consanguinity among parents was seen in 64 families among 203 families which constitute 31.5%. A total of 63 families which constitutes 31% have another affected member with ID. Table 1 shows the variables of genetic risk factors seen among the family members. There are few families with multiple affected members across generation. Out of 59 families with affected first-degree relatives, 50 families have affected siblings with/without other affected family members. The contribution of maternal age at the time of birth and history of miscarriage/ still birth as risk factors were also indicated in Table 1. Mothers above the age of 35 at the time of conception was reported to be very low. Almost 91% (n=185) has not reported any miscarriage or still birth history among the participants. Out of 50 families with siblings being affected, 25 families showed recurrence incidence and for the other 25 families, the first born was the affected one.

Table 2 shows the comparative status between the status of consanguinity with familial ID and sibling affected status. With consanguinity, the sibling affected status seems to be in higher percentage (42.6%) compared to families without consanguinity (195). Similarly with consanguinity, familial ID shows higher percentages (54.7%) when compared to families without consanguinity (38.8%). Figure 1 and 2 compares the status of consanguinity with siblings being affected and with the presence of familial ID respectively.

Figure 1: Status of consanguinity and siblings being affected.

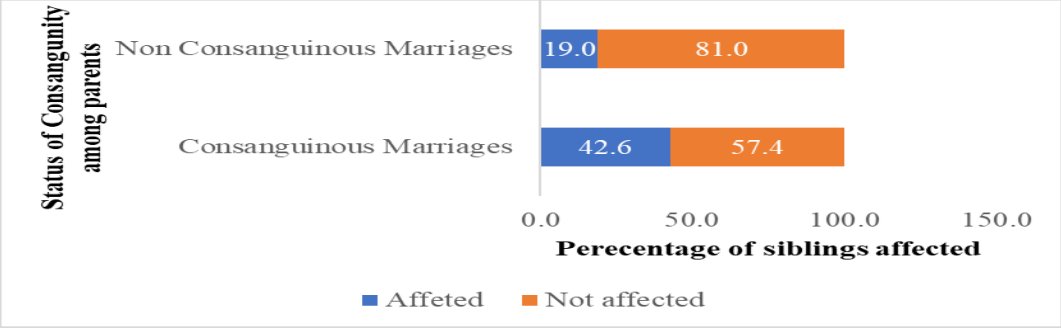
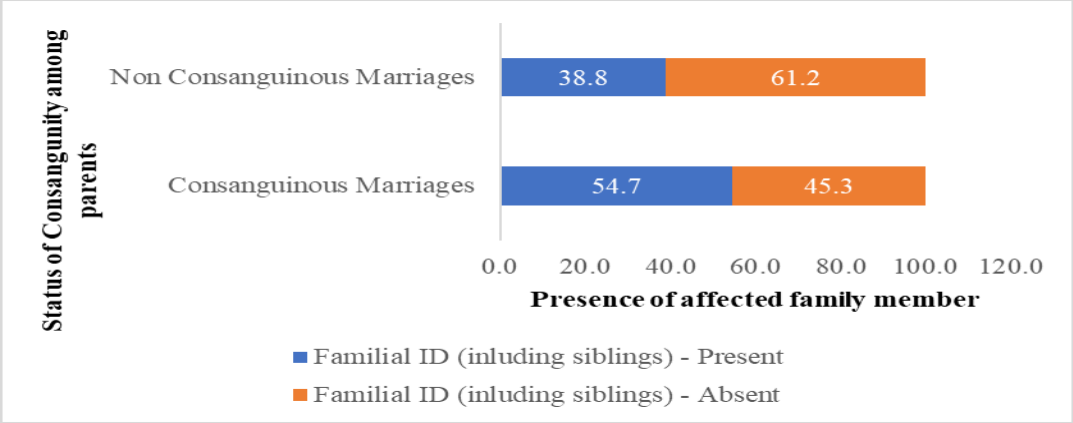


Figure 2: Status of consanguinity and familial ID



***3.3Association analysis between variables of genetic risk factors and severity of ID*:**
Table 3 shows the results of the odds ratio analysis where the variables of genetic risk factors were checked for its dependence on severity of ID. Only one variable- Siblings affected, has a significant relationship with the severity of ID with p value 0.04. All other variables do not show any significant relationship with the severity of ID. Odds ratio analysis also did not show greater odds as indicated in Table 3 except between subcategories for maternal age at the time of birth which all falls under risk free age category. The studied population did not report considerable number of mothers above the age of 35 or 40 as shown in the Table 3.

4. Discussion: Principal findings of this study reported that consanguinity among parents (31.5%) was found at a slightly higher rate than the population prevalence of consanguinity as 28% in Tirunelveli District [10]. Familial ID was found in 31% of families with affected first-degree relatives in the first place and sibling occurrence in familial ID has an impact on the severity of ID with statistical significance.
In a large cross-sectional study, which comprises 68,681 people with ID conducted in the Republic of Ecuador, 6.35% reported consanguinity in parents and 23.78% had a family history of ID[11]. A South Jordan study reported males and females being equally affected and consanguinity was seen among 54.6% of parents [12,13]. A similar study in the Israeli Arab community and Iran reported that 68% and 77% of consanguineous marriages resulted in ID children [13,14]. Higher consanguineous marriages were between first-cousin marriages of almost 50% according to the reports from Iran whereas this study reports almost 55% of consanguineous marriages were between first cousins. In some communities, the highest inbreeding coefficients were reached with unions between double first cousins practiced among Arabs and uncle-niece marriages practiced in South India where

(F) reaches 0.125 [15]. There are studies which shows that premarital genetic counselling is of great use in the detection of genetic disorders and is an essential step in changing attitudes towards premarital testing and reducing consanguineous marriage [16].

Lakhan, 2015 has seen an association between a history of familial ID with severe ID but not with mild ID [17]. A family study from Barwani, India showed 37.02% of parental consanguinity, 17.5% have had a family history of ID and 5.35% have had other mental illnesses [18]. A population-based family cohort study of 4,165,785 individuals born 1973–2013 in Sweden, which includes 37,787 ID individuals and their relatives reported that the relatives of ID individuals were at increased risk of ID (14.2-fold increase) compared to individuals with unaffected relatives [19].

In clinical genetics, sibling recurrence is the measure of family aggregation in an adverse health condition. This measure is used in genetic epidemiological studies to provide evidence of gene conferring susceptibility to a particular disease [20]. A study conducted at the University of Helsinki among Finnish families using exome sequencing reports that 64% of the study participants had defective variants in known ID genes. Most of the variants (75%) occurred during foetal development as the variants were not seen in the parental genome. Inherited variants were found only in less than a quarter of the pathogenic gene which concluded that the risk of recurrence of ID is usually low [21]. A study from southern California reported that the recurrence rate in full siblings was found to be approximately 12%. The recurrence rate was significantly higher if the proband was male and the severity of ID significantly influenced the recurrence rate [22]. An Australian study found lower recurrence rates of 10% in siblings of male and 8% in siblings of female probands [23]. A study of probands with non-syndromic ID in British Columbia also found lower recurrence rates of 4% in subsequent siblings [24]. Similar rates of ID among all siblings of male (14%) and female (15%) probands were found among Israeli families [25]. The present study showed a recurrence rate of 12.3% among the total affected population and 50% among the families where the siblings are affected. When there was consanguinity in parents, both familial ID and sibling occurrence can be seen in a higher trend depicting the empirical effect of consanguinity which should be further analysed in future research.

The maternal age at the time of birth of ID child was found between 21-25yrs for almost 43% of mothers and between 26-30 yrs. for other 25% of mothers. The maternal age above 35yrs was reported for only about 6% of mothers. The odds ratio also showed no influence on maternal age towards the severity of ID as per the present study in Tirunelveli. An established risk factor for Down syndrome (trisomy 21), the most prevalent genetic cause of mental impairment, is an older maternal age [26].

Furthermore, several reports have shown that children of mothers aged 40 years or older at delivery have somewhat lower mental test scores than children of women in their thirties. The issue of whether central nervous system-related congenital defects may be connected to older maternal age had been well studied [27,28]. Conceivably, less commonly detected or more subtle maternal age-dependent aberrations in genetic recombination events may exist and may adversely affect embryogenesis.

The present epidemiological study had reported almost no mothers above the age of 40 and very less numbers of about 6% above the age of 35 unlike many other studies all over the world. The present scenario may be due to the rural social structure which prevails in Tirunelveli where most of the marriages were arranged in early 20s which may extend to 26 or 27 and very rarely around 30 years of age.

The history of miscarriage/still-birth was found only among 18% of the participants compared to 82% who does not have the history of miscarriage/still birth. Odds ratio also showed no influence on the severity of ID. Previous studies suggest that history of miscarriage/still birth is highly associated with known trisomies and gross aneuploidies which may lead to early deaths, but not highly associated with idiopathic ID [29].

Like any other epidemiological study, this study also has limitations with the fact that there was no access to the identity card of other family members with ID except siblings, but the information by the respondentwas solely considered, as she is dealing with a similar kind of condition in her day-to-day life. There were no

people with mild ID (<40%) enrolled in the special schools through which the study was conducted, which made the study void of thisparticular group of ID.

5. Conclusion: This study aimed to evaluate risk factors that are commonly considered for prenatal genetic counselling which provide empirical evidence towards genetic etiology of ID and have provided valuable data on the prevalence of genetic risk factors in Tirunelveli District, Tamil Nadu, India. This epidemiological data can have significant implications for formulating preventive strategies and healthcare policies in a developing nation like India.

Further studies investigating the epidemiological prevalence of genetic defects or mutations among the affected population can contribute to broader screening efforts and can facilitate targeted genetic diagnostics and screening. Similar advancements have already been achieved in the screening and diagnosis of certain trisomies but targeting a group of population with increased risk factors will efficiently help in addressing the condition more systematically considering a wide range of genetic abnormalities. Increased awareness of both genetic and environmental risk factors is crucial, as they can profoundly impact the overall public health and well-being of families.

6. Conflict of interest statement: The Authors had reported no conflict of interest.

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Table 1: Genetic risk factors present among the participant families.

Particulars	Numbers	%
Consanguinity in Parents(n=203)		
Yes	64	31.5
No	139	68.4
Pattern of consanguinity(n=64)		
Uncle-niece	17	26.5
First cousin	35	54.6
Second cousin	12	18.75
Familial ID (n=203)		
Yes	63	31
No	140	69
Degree of relationship with the affectedmember(n=63)		
1st degree	59	93.6
2nd degree	17	26.9
3rd degree	25	39.6
4th degree and higher	18	28.5
Sibling status		
Affected	50	24.6
- Male	35	17.24
- female	15	7.39
Not affected	137	67.4
No siblings	16	7.88
Sibling recurrence status- among the affected siblings		
Yes	25	50
- Male	18	36
- Female	7	14
No	25	50
Sibling recurrence status		
Yes	25	12.3
- Male	18	8.8
- Female	7	3.4
Maternal age at the time of birth		
<20	31	15.27
21-25	86	42.36
26-30	51	25.12
31-35	22	10.84
36-40	12	5.91
>41	1	0.49
History of miscarriage/ still birth		
Yes	18	8.87
No	185	91.13

Note: 1. *Some families had more than one affected member and some families had multiple affected members. 2. First cousins once removed and double first cousins were included under the broader category of first cousins. 3. Recurrence- An older child is already affected in the family, ID- Intellectual disability*

Table 2: Comparative status between consanguinity and other variables

Particulars	Numbers	In%
Comparative status of consanguinity with familial ID		
+ve for consanguinity and familial ID	35	54.7
-ve for consanguinity and familial ID	85	61.2
+ve for consanguinity and -ve for familial ID	29	45.3
-ve for consanguinity and +ve for familial ID	54	38.8
Comparative status between consanguinity and siblings affected.		
+ve for consanguinity and siblings affected.	26	42.2
-ve for consanguinity and siblings affected.	102	81
+ve for consanguinity and -ve for siblings affected.	35	57.4
-ve for consanguinity and +ve for siblings affected.	24	19

***Note**: +ve is Yes for consanguinity and siblings affected.*
-ve is No for consanguinity and siblings affected.

Table 3: Odds ratio and Chi Square analysis between variables of genetic risk factors and severity of ID:

No	Variable	Severe / Profound ID		Moderate ID		OR	95% CI		Chi-Square p-value
		Number	%	Number	%		Lower	Upper	
1	**Consanguinity In parents**								
	Yes	30	46.88	34	53.13	0.87	0.48	1.57	0.64
	No	70	50.36	69	49.64				
2	**Any other affected member in the family (Familial ID)**								
	Yes	38	42.7	51	57.3	0.62	0.36	1.09	0.1
	No	62	54.39	52	45.61				
3	**Siblings Affected**								
	Yes	17	34	33	66	0.49	0.25	0.97	0.04
	No	70	51.09	67	48.91				
4	**Maternal age at the time of birth**								
	<20	14	45.2	17	54.8	1.36	0.55	3.34	0.49
	21-25	45	52.3	41	47.7	1.02	0.51	2.05	0.94
	31 - 35	11	50	11	50	1.12	0.41	3.06	0.82
	36-41	7	53.8	6	46.2	1.31	0.38	4.45	0.66
	26-30	27	52.9	24	47.1				
5	**History of miscarriage /still birth**								
	Yes	5	27.8	13	72.2	0.36	0.12	1.06	0.06
	No	94	51.4	89	48.6				

Note:*OR- Odds Ratio, odds above 1 represents association between the compared variables. Chi- square analysis of significance level, $\alpha=0.05$ where $p<0.05$ indicates that the variables of study and severity of ID are dependent on each other and $p>0.05$ indicates that the variables of study and severity of ID are independent on each other.*