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Consanguinity

The innocent culprit in autism severity

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Abstract

Objective: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition with genetic and environmental factors. Although consanguinity is a common practice in the Middle Eastern population, the association between consanguinity and ASD severity is not clear. ***Methods:*** This retrospective study analyzed the records of 139 children (1.5-14 years) diagnosed with ASD from June 2011 to May 2024. The study analyzed the correlation between consanguinity, homozygosity, and ASD severity. ***Results:*** Of 139 cases, 74.1% were male, with an average age of diagnosis of 4.5 years (SD+- 2). Most ASD cases were at severity levels 2 (63.3%) and 3 (35.3%). Consanguinity was reported in 59% of cases, with a mean homozygosity rate of 4.6%. No significant correlation was found between consanguinity or homozygosity rates and ASD severity. ***Conclusion:*** No

significant association was found between consanguinity or homozygosity rates and ASD severity. Further research is needed to explore the genetic mechanisms of ASD in consanguineous populations.
Keywords: Consanguinity; Homozygosity; Severity; Autism Spectrum Disorder.

Advances in Knowledge:

- The study found that 59% of children diagnosed with Autism Spectrum Disorder in Oman came from consanguineous marriages, with an average homozygosity rate of 4.6%.
- No significant correlation was observed between consanguinity or homozygosity rates and the severity of ASD.
- Most ASD cases were at severity levels 2 and 3, with no evidence suggesting that consanguinity exacerbates ASD severity.
- Future studies are needed before solidifying conclusions about the relationship between consanguinity and ASD.

Application to Patient Care:

- The findings suggest that consanguinity does not significantly influence the severity of Autism Spectrum Disorder (ASD), which can inform genetic counselling practices in consanguineous populations.
- Policymakers and healthcare providers should consider these results when developing support systems for families affected by ASD, ensuring that resources are directed towards factors that more strongly influence ASD outcomes.

Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by challenges in social interaction, communication, and repetitive behaviors.[1] Global prevalence estimates for Autism Spectrum Disorder (ASD) exhibit substantial variability, with a median rate of 100 per 10,000 individuals (1%) and a range extending from 1.09 to 436 per 10,000.[2] In the Sultanate of Oman, the estimated prevalence of ASD was determined to be 20.35 per 10,000 children, with a 95% confidence interval (CI) of 19.39 to 21.32.[3] The aetiology of ASD is multifactorial,

including both genetic and environmental components. Recent developments in genetic research have underscored the importance of genetic contributions to ASD. A multitude of studies have identified distinct genetic variants and polymorphisms linked to ASD.[4–6] Consanguinity—the practice of getting married within a close family—is common in several areas, including the Middle East, South Asia, and North Africa.[7] Approximately 20% of the global population prefers consanguineous marriages due to their positive social impacts. Consanguinity rates can differ within groups due to various factors, such as geography, ethnicity, culture, and religion.[8] In Oman, an estimated 52% of marriages are consanguineous, involving couples who are second or third-degree relatives.[9]

Consanguineous marriage increases homozygosity within the population, as offspring of consanguineous unions are more likely to inherit identical alleles from both parents. Elevated homozygosity can result in a higher incidence of autosomal recessive disorders and may influence the expression and severity of complex traits.[10,11] On the other hand, the clarity of the association between consanguinity and ASD as a risk factor is somewhat obscured in the context of a polygenic multifactorial disorder such as ASD, with conflicting evidence in the current literature.[12,13]

Runs of homozygosity, an indicator of the genetic diversity within an individual's genome, is particularly relevant in consanguineous populations. The percentage of homozygosity (Froh) can be inferred from SNP microarray data and utilized to estimate the degree of parental consanguinity. This estimation is typically conducted by aggregating the total length of autosomal regions of homozygosity (ROH) that exceed a specified size threshold and dividing this sum by the total number of autosomal base pairs represented on the microarray platform.[14–16] Higher homozygosity rates can increase the likelihood of inheriting recessive genetic variants.[17] The association between consanguinity, homozygosity, and intellectual disability was investigated and revealed that the amount of homozygosity seems to modulate the degree of cognitive impairment despite the cause of intellectual disability.[18] However, the impact of homozygosity on the severity of ASD has yet to be fully understood.

Hereafter, we present our research findings on the correlation between homozygosity rates as a marker of consanguinity and the severity of (ASD). Our study underscores the significance of accounting for genetic diversity in the context of ASD, particularly within consanguineous populations.

Methods

The study was conducted at the Genetic & Developmental Medicine Clinic at Sultan Qaboos University Hospital (SQUH), Muscat, Oman, where a retrospective analysis of computerized records of patients diagnosed with (ASD) was performed between June 2011 and May 2024. Children who were 14 years of age or less, who had a homozygosity rate determined by (SNP and CGH) microarray testing, and who had a full clinical phenotype as assessed by developmental paediatricians and medical geneticists were eligible for inclusion in this study. A total of 710 children, aged 1.5 to 14, received Microarray CGH testing over the course of the study. Of those, 139 cases had comprehensive clinical information recorded in the electronic health record, including the homozygosity rate and degree of severity. To prevent any interference from substantial copy-number variations (CNVs) that could affect the accuracy of ROH measurements (i.e., genomic deletions that appear as a segment of homozygosity but actually reflect hemizygosity), cases with CNV were excluded from the dataset.

The study received ethical approval from the Medical Research and Ethics Committee associated with Sultan Qaboos University in Oman. The report adheres to the ethical guidelines set out in the World Medical Association's Declaration of Helsinki (1964-2008) regarding the privacy and confidentiality of participants and the handling of data.

Assessment of Cases

A multidisciplinary team led by a senior developmental paediatrician employed the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule, ADOS-2, to confirm the diagnosis of ASD in the cases. Abiding with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, ASD specifiers require clinicians to use their clinical judgement to delineate between three classifications: Level 1 ("Requiring support"), Level 2 ("Requiring substantial support"),

and Level 3 ("Requiring very substantial support"). Hence, the severity level was determined by diagnosticians trained in developmental paediatrics at the time of diagnosis.[1,19]

The consanguineous couple's data were incurred from electronic records where the consanguineous definition included 'first cousin, father's side' including father's brother's son (patrilateral parallel cousin) or father's sister's son (cross-cousin Type I). Similarly, the 'first cousin, mother side' includes the mother's brother's son (matrilateral parallel cousin), the mother's sister's son (cross-cousin type II), and second-degree cousins. Non-consanguineous marriages included non-relatives or distant relatives but with a lesser relatedness than second cousins.[9] The homozygosity rate was classified as follows: offspring of second cousins are expected to have children with (1.56%) 1/64 of their genome homozygous; offspring of first cousins, (6.25 %) 1/16; offspring of double–first cousins, (12.5%) 1/8; and offspring of an incestuous union, (25%) 1/4.[17]
The DNA samples from patients were collected to facilitate etiological diagnosis as part of the clinical protocol. The samples were outsourced to SISTEMAS GENÓMICOS S.L. This laboratory adopts the American College of Medical Genetics and Genomics (ACMG) guidelines for interpreting deletion, duplication, homozygosity and variants.[20,21]

Statistical analysis

A set of clinical phenotypic characteristics along with the parent's and child's demographic characteristics were evaluated. Data analysis involved the utilization of both descriptive and inferential statistical techniques. The data was analyzed using SPSS Statistics version 27. The characteristics of children with ASD were described using frequency distribution. The correlation between categorical factors was assessed using a chi-square test, while the significance of the association between a category and a numerical variable was examined using One-way ANOVA. Fisher's exact test was conducted when a cell's expected value is less than 5. A P-value of <0.05 was considered statistically significant. Furthermore, the parental report of consanguinity was correlated with the rate of homozygosity and tested against the severity level.

Results

The study included 139 cases. Out of the 139, males constituted the majority, or 74.1%. The average age at diagnosis was 4.5±2 years. Around 50% of the cases were from Muscat and Al Batinah. The average age of fathers was 38.7(SD±8.2) years, while the mean age of mothers was 34.4(SD±5.5) years. Most parents, 60%, had secondary school education. Table 1 summarises the sociodemographic characteristics of the study subjects. Around 15.8% of subjects had a family history of autism or developmental disorders in their siblings. Approximately 10.8% of subjects were preterm. Twenty-three percent of test subjects were born through caesarean section. Regarding ASD severity, 1.4% had level one ASD, 63.3% had level 2 ASD, and 35.3% had level 3 ASD. The proportion of reported consanguinity was 59%. The mean homozygosity rate was 4.6 (SD±4.8).

The distribution of homozygosity rates was as follows: 51 had a homozygosity rate equal to or less than *≤1.56%,* 50 were children with homozygosity rate between 1.57% and 6.25%, 31 were children with homozygosity between 6.26% and 12.5%, 6 were children with homozygosity rate between 12.6% and 24.9%, and one subject was homozygosity rate of 30%. This is illustrated in Figure 1.

Table 2 compares the homozygosity rate against the sociodemographic characteristics. There was a significant relationship between homozygosity and consanguinity. The mean homozygosity rate among subjects from consanguineous marriages was 6.9%, while the mean homozygosity rate among subjects from non-consanguineous marriages was 1.25%.

A comparative analysis of consanguinity status and ASD severity, as illustrated in Figure 2, revealed no statistically significant association. Similarly, the investigation into the relationship between homozygosity and ASD severity, depicted in Figure 3, indicated no significant correlation.

Discussion

Our cohort consisted of 74% males, highlighting the gender skewness toward males in the distribution of autism.[22] Additionally, the consanguinity rate was 59%, reflecting characteristics typical of the Middle Eastern Arab population.[8] The cases were dispersed widely across all parts of the country, with the majority of parents residing in the capital city. Additionally, the parents' educational attainment was predominantly at the secondary school level.

The distribution of severity levels within our cohort indicates a significant skew towards more severe cases of Autism Spectrum Disorder (ASD). Specifically, 63.3% of the cases were classified as level 2 ASD, with only a single case classified as level 1. This distribution contrasts the findings from the Autism Treatment Network (ATN) sites in the United States, where approximately 30% of cases were classified as level 1.[23] This discrepancy may be attributed to several factors, including limited community awareness about ASD and inadequately distributed diagnostic services in Oman. The constrained availability and accessibility of these services likely contribute to the presentation of more severe ASD phenotypes in the Omani population.[3,24,25]

The study demonstrated a statistically significant disparity between parental reports of consanguinity and observed homozygosity rates exceeding 1.56. This finding indicates potential discrepancies in estimating the theoretical inbreeding coefficient, which may be attributed to parental misconceptions regarding their relatedness or inaccuracies in calculating the homozygosity rate. Although the percentage of homozygosity is commonly employed to estimate consanguinity, and physicians managing families with known consanguinity may utilize an SNP microarray, emerging research indicates that data mining within regions of homozygosity (ROH) can substantially enhance the diagnosis of suspected autosomal recessive conditions.[26] Notably, the percentage of homozygosity may inaccurately represent the theoretical inbreeding coefficient due to various confounding factors. These include deviations from theoretical expectations, challenges in accounting for multiple generations of consanguinity, random crossover events during meiosis, variability in ROH size inclusion criteria, and differences in microarray platform coverage.[16] Consequently, a nuanced approach that integrates the

history of consanguinity with other genetic assessment tools is imperative for accurate diagnostic outcomes.

The association between the severity of ASD on one side and consanguinity or rate of homozygosity on the other side was not statistically significant in our cohort, suggesting that neither consanguinity nor rate of homozygosity influences ASD severity. These findings are consistent with those of Gamsiz et al., who observed a statistical relationship between runs of homozygosity and measures of intellectual functioning but not with measures of autism symptoms or severity.[27] On the other hand, recent data from Saudia Arabia reported that children of consanguineous parents had higher Autism Treatment Evaluation Checklist (ATEC) scores, indicating more severe symptoms, although this was not statistically significant in all analyses.[28] However, several scholars critique the reliance on parental reports for determining the degree of a child's disability, arguing that parents may misclassify the severity in comparison to clinical diagnoses.[29–31] Furthermore, it is crucial to acknowledge that the Autism Treatment Evaluation Checklist (ATEC) was specifically designed to assess treatment efficacy rather than to serve as a diagnostic tool. Consequently, the ATEC can only approximate ASD severity through total scores, which are further differentiated by age.[32,33]

In India, Mamidala et al.[33] found a significant association between consanguineous marriages and increased ASD risk, highlighting the genetic implications of such unions. Similarly, Bitar et al.[34] reported from Lebanon that children born to consanguineous parents had a higher prevalence of ASD, suggesting that consanguinity may contribute to the genetic load of autism-related mutations. In contrast, studies on the Arabian Peninsula provide a different perspective. Data originating from the Omani population,[3,34] and Qatar,[12,35,36] shows no significant increase in ASD prevalence among consanguineous populations.[3,12,34–36] These findings suggest that while consanguinity may be a risk factor in specific populations, its impact on ASD prevalence is not universally observed. The discrepancy in data may indicate that other genetic, environmental, or sociocultural factors might play a more significant role in these regions.

The limitations of this study stem from its retrospective design and its status as a single-centre study with a relatively small sample size. The low prevalence of ASD in the country - compared to the global estimates- may affect the variability of cases and the generalizability of results to other parts of the world. The summation of consanguinity in one category rather than having levels may possess a bias. The predominance of cases at levels 2 and 3 of ASD severity within the dataset may introduce another bias towards a more severe autism spectrum disorder population, thereby limiting the generalizability of the findings. This bias also hindered comprehensive intellectual abilities testing. Additionally, outsourcing genetic testing posed another limitation, as it restricted the ability to analyze the entire regions of homozygosity due to incomplete data availability.

Conclusion

Our study did not support the hypothesis that consanguinity increases the severity of Autism Spectrum Disorder (ASD). Further research is needed to understand the genetic mechanisms and the extent to which consanguinity influences the risk and severity of ASD.

Authors' Contribution

The authors confirm their contribution to the paper as follows: Study conception and design: Ahmed B. Idris & Watfa Al-Mamari. Data collection & cleansing: Najat Fadlallah Muna Aljabri and Ahmed B. Idris. Data analysis: Maha Mohammed and Ahmed B.Idris. Interpretation of results: Ahmed B. Idris, Maha Mohammed, Abeer Al-Saegh & Watfa Al-Mamari. Drafting initial manuscript: Ahmed B. Idris & Saquib Jalees. All authors reviewed the results and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interests.

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Table 1: Sociodemographic characteristics of children with ASD

Gender (n=139)	*Male*	103(74.1%)
	Female	36(25.9%)
Age at diagnosis, mean (S.D.)		4.475(±2)
Age of Father at diagnosis, mean (S.D.)		38.7(±8.2)
Age of Mother at diagnosis, mean (S.D.)		34.4(±5.5)
Father educational level	*Primary Education or Lower level*	15(10.8%)
	Secondary School level	61(43.9%)
	University or postgraduate level	61(43.9%)
Mother educational level	*Primary Education or Lower level*	7(5%)
	Secondary School level	13(9.4%)
	University or postgraduate level	113(81.3%)
Area of residence	*Muscat*	42(30.2%)
	Ad Dakhiliyah	23(16.5%)
	Al Batinah North	20(14.4%)
	Al Batinah South	19(13.7%)
	Ash Sharqiyah	20(14.4%)
	Dhofar	6(4.3%)
	Ad Dhahirah	7(5.0%)
	Musandam	2(1.4%)
Prematurity	*Full term*	124(89.2%)
	Preterm	15(10.7%)
Mode of delivery	*SVD*	103(74.1%)
	C/S	32(23.0%)

Consanguinity	*Yes*	82(59%)
	No	51(36.7%)
Homozygosity	*≤1.56*	51(36.7%)
	>1.56	88(63.3%)
Seizures	12(8.6%)	
Sleeping Problems	33(23.7%)	
Feeding Problems	42(30.2%)	
Others	17(12.2%)	

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Table. 2: Comparison of homozygosity and socio-demographics.

		Homozygosity		*Total*	
		≤1.56	*>1.56*		*P value*
Gender	*Male*	36(35%)	67(65.0%)	103(100%)	0.472
	Female	15(41.7%)	21(58.3%)	36(100%)	
Age at diagnosis Mean (SD)	*≤1.56*		4.14(±2.03)		0.138
	>1.57		4.67(±2.02)		
Father educational level	*Primary Education or Lower level*	7(46.7%)	8(53.3%)	15(100%)	0.475
	Secondary School level	24(39.3%)	37(60.7%)	61(100%)	
	University or postgraduate level	19(31.1%)	42(68.9%)	61(100%)	
Mother educational level	*Primary Education or Lower level*	1(14.3%)	6(85.7%)	7(100%)	0.465*
	Secondary School level	5(38.5%)	8(61.5%)	13(100%)	
	University or postgraduate level	42(37.2%)	71(62.8%)	113(100%)	
Family history of autism / developmental disorders in siblings	*Yes*	9(40.9%)	13(59.1%)	22(100%)	0.413
	No	42(35.9%)	75(64.1%)	117(%)	
Consanguinity	*Yes*	6(7.3%)	76(92.7%)	82(100%)	0.000**
	No	41(80.4%)	10(19.6%)	51(100%)	
Prematurity	*Full term*	46(37.1%)	78(62.9%)	124(100%)	0.507
	Preterm	5(33.3%)	10(66.7%)	15(100%)	
Mode of delivery	*SVD (spontaneous vaginal delivery)*	37(35.9%)	66(64.1%)	103(100%)	0.525
	C/S (caesarean sections)	11(34.4%)	21(65.6%)	32(100%)	
ASD Severity level	*Level 1*	1(50.0%)	1(50.0%)	2(100%)	0.925*
	Level 2	32(36.4%)	56(63.6%)	88(100%)	
	Level 3	18(36.7%)	31(63.3%)	49(100%)	

** Fisher's exact test was conducted when a cell's expected value is less than 5*

*** Statistically significant*

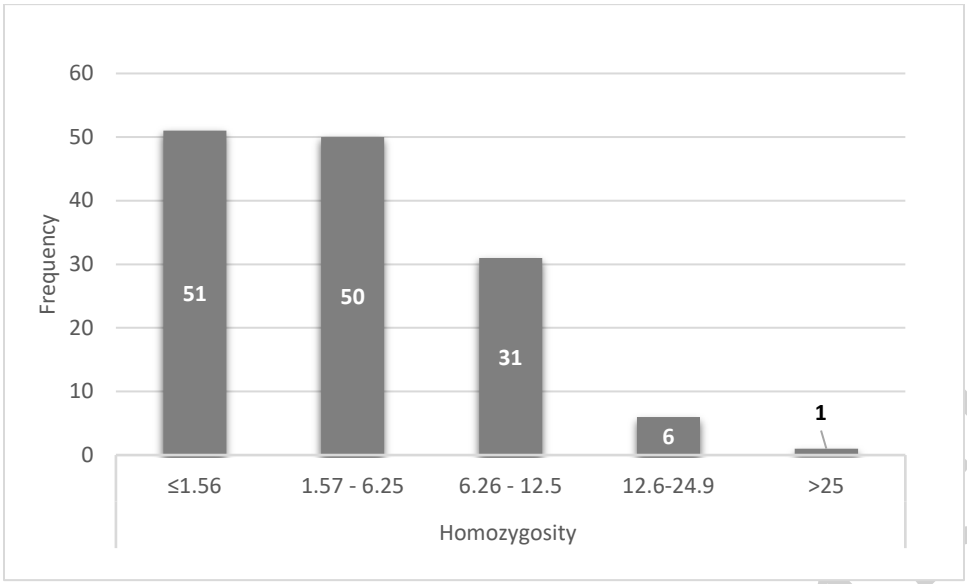


Figure 1: Distribution of homozygosity rate among children with ASD

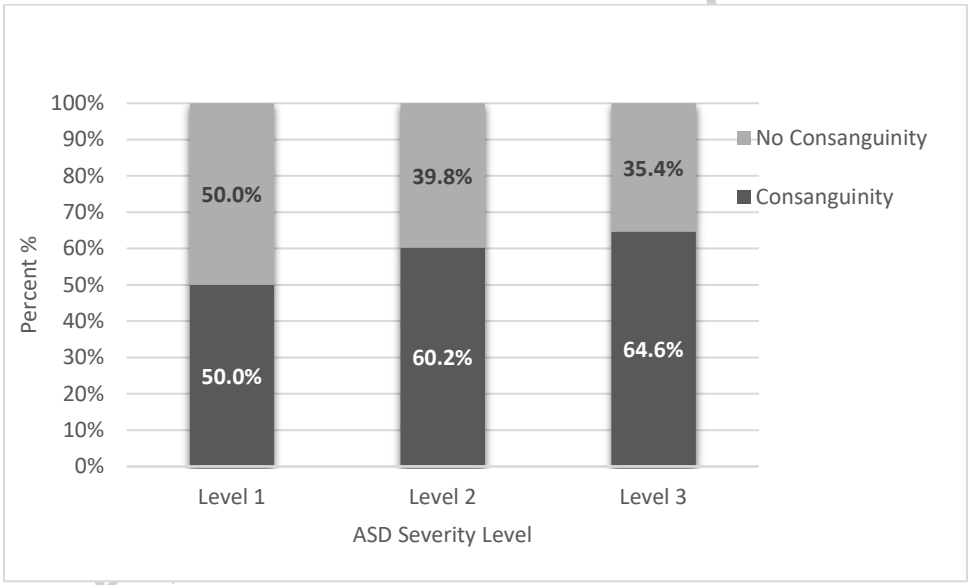
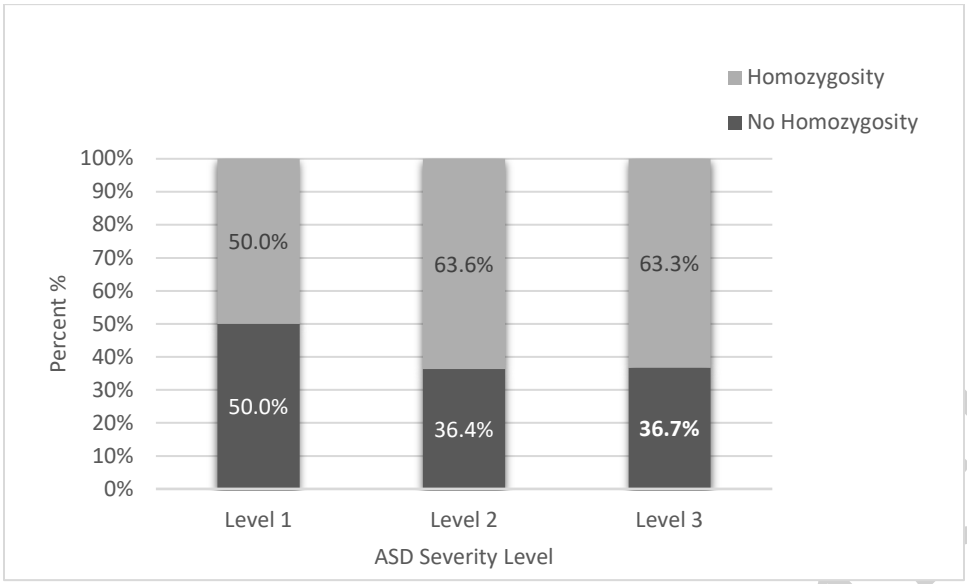


Figure 2: Comparison between consanguinity and ASD severity level. (P value=0.836)



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411 **Figure 3: Comparison between homozygosity rate and ASD severity level.**

412 **(P value=0.925)**

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