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Review Article

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Prevalence of Autism Spectrum Disorder (ASD) in Offspring's of Consanguineous Marriages

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Abstract

The Autism Spectrum Disorder (ASD) is a neurological disorder that can be characterized by repetitive behaviours, language delay, varying communication limitations (Lobe, 2006). Individuals on the spectrum are also more likely to be accompanied with ADHD (attention deficit hyperactivity disorder), found most frequently (Caron and Rutter 1991); depression (Angold et al. 1999), specific phobias (Love et al.1990), obsessive–compulsive disorder (OCD; Charlop-Christy and Haymes 1996), and anxiety (Woodward et al. 2005). Although there are no medical tests available, a diagnostic tool, DSM-V can be used to assess and form a reliable diagnosis by 2 years of age. The fact that this disorder isheterogeneous reflects the drastic differences between individuals with autism only, making diagnostic procedures more difficult. The disorder is more prevalent in boys than girls. Etiology is not definitely known, but research has indicated possible involvement of genetic, epigenetic, and environmental factors (Faras et al, 2010). Genetic investigation includes twin, family studies through cytogenetic analysis association and linkage analysis studies, copy number variation (CNV), DNA microarray analysis, as wellas whole-exome sequencing analysis and transcriptomic analysis (Li et al, 2012). Environmental factors such as parental age, medication use during pregnancy, maternal smoking and alcohol consumption and vaccination have also been explored.

With several indications of genetic contribution to etiology of autism spectrum disorder, the research aims to explore prevalence of ASD in offspring of consanguineous marriages. Consanguinity is commonly practiced in several cultures across South Asia, the Middle East, and Africa. These also include communities of these cultures who have migrated to other countries and continue to exercise this as per custom.

Keywords: autism spectrum; thalassaemias; cystic fibrosis; downs syndrome; infantile cerebral palsy; genetic heterogeneity; age; consanguineous marriage

Introduction

Statement of Problem: Research has displayed evidence of congenital conditions such as mental retardation (Ullah et al. 2018), thalassaemias, cystic fibrosis, Down's syndrome, infantile cerebral palsy, and hearing and visual disabilities (Corry 2014) resulted from consanguineous marriages. This exploratory research aims to identify how prevalent the autism spectrum disorder is in offspring of consanguineous marriages in the Pakistani population. This can assist future researches, if needed, to use scientific tools to discover genetic involvement in such occurrences.

The study will involve a survey form to be filled by parents of children on the Autism Spectrum. It will be distributed in several institutions providing services to these children.

Purpose of the study

The purpose of the study is to study the relationship between offspring of consanguineous marriages and prevalence of the autism spectrum disorder.

Research question: Do offsprings of consanguineous marriages have an increased risk of ASD (autism spectrum disorder)?

Research objectives: The research aims to identify the prevalence of autism spectrum disorder in offsprings of consanguineous marriages, and if identified, increase awareness amongst consanguineous union culture in the Pakistani population.

Significance of study: This study will identify evidential information on the possible effects of consanguinity on the offspring and its predisposition

to the autism spectrum disorder (ASD). Such findings can be helpful inspreading awareness amongst couples who may opt for consanguineous marriages and/or educate them of accompanying risks in addition to existing, proven disabilities.

Operation definition: The Autism Spectrum Disorder: The Autism Spectrum Disorder (ASD) is a heterogeneous neurological disorder (Matson et al. 2008). Language delay, social interaction and communication impairment, and repetitive actions or interests are three main, common characteristics found amongst them (Lobe, 2006). Most individuals on the spectrum may also exhibit comorbid conditions such as intellectual disability, gastrointestinal disorders, epilepsy, immune disorders, and sleeplessness (Almandil et al, 2019).

Consanguinity is "a union between a couple related as second cousins or closer" (Bittles, 2001). This is a common cultural concept embraced in several Asian and Middle Eastern countries as well as North Africa. This practice continues despite evidence suggesting increasing recessive gene expression and therefore autosomal recessive disorders by unmasking hidden traits.

The Autism Spectrum Disorder is a developmental disorder with both social and communication deficits, in addition to stereotyped, ritualistic, and/or repetitive behaviors (Ghaziuddin, 2012). Although ASD remains a widely heterogenetic disorder with no identified biological markers, studies have confirmed its heritability, suspecting an autosomal recessive transmission (Chaste, 2012). Autosomal recessive intellectual disorders are very common in populations with frequent parental consanguinity.

One billion people worldwide live-in countries where marriage among relatives is common. Of this billion, one in three is married to a second cousin or closer relative or is the progeny of such a marriage. The frequency of genetic disorders among such children is around twice that in children of non-related parents (Bradford Safeguarding Children Board Annual Report, 2017). Studies have shown that in Pakistan consanguinity was present in 60% of marriages out of which 80% were first cousins (Ullah et al., 2018). Factors that promote practices of consanguinity include restricted interaction with the opposite gender (even amongst cousins), difficulty finding marriage partners of same status and caste, security of knowing the spouses' family, and strengthening inter-family ties. It is also prevailingly common in rural and less educated areas where culture of dowry is common. Negotiating such expensive affairs is more convenient with blood relatives/cousins (Ullah et al., 2018). Recently a team of Pakistani scientists concluded that the prevalence of mental retardation in the Pakistani population is due to cousin marriage. They also discovered 30 new genes in these children that were responsible for this abnormality ((Ullah et al., 2018). Other common genetic disorders include thalassaemias, cystic fibrosis, Down's syndrome, infantile cerebral palsy, and hearing and visual disabilities (Corry, 2014).

Research in the past has concluded the risk of ASD to increase in offspring of consanguineous marriages. One conducted in the 2014 over a large population in India presented this increase in risk with an odds ratio of 3.22 (Mamidala et al., 2014). Homozygosity mapping in consanguineous autism pedigrees suggested considerable genetic heterogeneity, implicating several genetic loci in one study conducted on the Arab population. In the same study, it was also discovered several consanguineous pedigrees showed large, rare, inherited homozygous deletions within linked regions, some of which are very likely causative mutations (Morrow et al., 2008). In those with inherited ASD, researchers have also found there was no difference in the number of sporadic de novo mutations (i.e., new mutation), but the consanguineous subjects did have an increase in number of inherited CNVs (copy number variants) from one or both parents (Geschwind, 2008 and Morrow et al., 2008). This transmission of CNVs makesautism believed to be one of the most heritable mental health disorders, with estimates of heritability as high as 90% (Rastam et al. 2010 and Sandin et al., 2017).

This explanatory research aims to acquire information on the relationship between ASD and offsprings of consanguineous marriages in the Pakistani population. This study will be conducted via surveys to collect a sample size of 50 families, minimum. An anticipated restriction of this investigation will be the absence of formal ASD diagnoses due to financial limitations of families from lower socio-economic backgrounds.

Literature Review

The following review will discuss existing research findings that observe presence of autism spectrum disorder (ASD) in the offsprings of a resultant

consanguineous marriage. Introductory information on ASD, the nature of the disorder, diagnostic procedures, and present-day findings of plausible etiological factors will be briefly discussed to gain thorough understanding of the review, effectively. Following that, current research findings that have been conducted over the past few years on different cohorts and ethnicities, will also be explored. Some of these examined groups include regions in the Sub-Continent, the Middle East and several North African tribes, where consanguinity is commonly practiced.

The Autism Spectrum Disorder: The Autism Spectrum Disorder (ASD) is a heterogeneous neurological disorder (Matson et al. 2008). Language delay, social interaction and communication impairment, and repetitive actions or interests are three main, common characteristics found amongst them (Lobe, 2006). Most individuals on the spectrum may also exhibit comorbid conditions such as intellectual disability, gastrointestinal disorders, epilepsy, immune disorders, and sleeplessness (Almandil et al, 2019). Some co-occurring behaviours that may coexist include abnormal sleep patterns, atypical eating, and self-injurious behavior (Dominick et al. 2007). Besides such accompanying conditions, individuals on the autism spectrum are also more likely to present with psychopathological disorders (NebelSchwalm et al. 2007). This occurrence includes ADHD (attention deficit hyperactivity disorder), found most frequently (Caron andRutter 1991); depression (Angold et al. 1999), specific phobias (Love et al.1990), obsessive–compulsive disorder (OCD; Charlop-Christy and Haymes 1996), and anxiety (Woodward et al. 2005).

Diagnosis: Since there is no medical test for the diagnosis of autism, it can be challenging to diagnose ASD without having comprehensive information about the developmental history and behavior of the child. DSM-V is the current manual with the guidelines required to assess and diagnose autism A diagnosis for ASD can now happen at 18 months or younger and by the age of 2 years old a diagnosis made by professionals can often be relied upon. However, since severity of the disorder varies significantly amongst children with ASD, Asperger's is often There are three major steps involved in screening and diagnosis. These steps include:

Developmental monitoring: This observes your child's growth and changes over time and assesses whether or not the child meets the typical developmental milestones in different areas (cognition, behavior, receptive and expressive language and motor milestones); Developmental screening: This is a systematic process of looking for or monitoring signs that may indicate that a child is delayed in one or more areas of development. This is not the same as a diagnosis and is just important to determine whethera further assessment is warranted; Comprehensive Developmental evaluation: Developmental evaluationshelp identify the unique strengths and concerns of the child and family. The evaluations results determine whether a child is eligible for services or not. It will also help the team plan appropriate service and support. (Boyle CA et al, 2011).

Although risk for ASD is high among children with specific or global developmental delays (Wiggins et al. 2015), differential diagnoses of ASD are often missed or delayed once referred to EI (Early intervention). Given that recommended and reimbursable pediatric visits for young children occur periodically with lags ranging from 3 to 12 months (King et al. 2010), pediatric providers are not always able to fully monitor the emergence of ASD diagnoses that can occur during this phase of development (Ozonoff et al. 2015).

The results of a recent study showed that few of the important drivers for detection and diagnosis of ASD are the parents' concerns, provider's clinical judgment and shared decision making between the two parties. Parent and providers concerns proved to be more predictive in terms of referral completion as compared to evidence-based screening protocols. (Sheldrick et al. 2019), Any individual who screens positive for autism should be referred for treatment or evaluation.

Prevalence: A study done in 2016 showed that across the 11 tested sites, ASD prevalence was 18.5 per 1,000 (1 in 54) for children aged 8 years. ASD was 4.3 times more prevalent in boys as compared to girls. It was also seen that although prevalence varied from region to region in North America – they were approximately identical for non-Hispanic (white)(18.5), non-Hispanic (black)(18.3) and Asian/Pacific Islander children(17.9) but relatively

lower for Hispanic children (15.4). The age of initial evaluation also varied amongst races. (Maenner et al, 2020)

Data collected in South Asia reported prevalence ranged from 0.09% in India to 1.07% in Sri Lanka that indicates that up to 1 in 93 children have ASD in this region. Dhaka city had a high prevalence of up to 3%. Study sample sizes varied; where they were 374 in Srilanka and 18,480 in India. Ae also varied between 1 and 30 years. No studies or valid data was found for Pakistan, Nepal, Bhutan, Maldives and Afghanistan. (Hossain et al, 2017). It must be noted that in these regions most cases of autism are undiagnosed due to lack of public health services and poverty.

Current Findings Etiology: The heterogeneity of the Autism Spectrum Disorder has been unfavourable to the aims and objectivity of discovering unambiguous, specific etiological factors. Although no definite research has been able to conclude confirmed etiology, there are primarily three areas that have shown maximum possibility as a form of cause. These are genetic, epigenetic, and environmental factors (Faras et al, 2010).

Existing research has shown that 10% of ASD individuals will also present some other form of genetic or neurological disorder (Caglayon, 2010). These, predominantly, include Fragile X Syndrome, Tuberous Sclerosis and Congenital Infections. This brings to attention the nature of the autism spectrum disorders and its sharing of underlying causes - genetics. Another family study concluded that parents of an autistic child are 25% more likely than the rest of the population, to conceive another child on the spectrum (Abrahams et al. 2008). A British twin study, conducted in 1995 suggested following probabilities: a 60–90% concordance rate of having autism exists in monozygotic twins and a 0–24% decreased risk in dizygotic twins.

Despite the limited expertise to point exactly where the cause lies, scrutiny in this research area has established the number of risk factors that genetically influence the child's neural structures. Health lifestyle due to socioeconomic factors, drug and alcohol abuse have exhibited evidence in predisposing to this influence (Morales at al. 2018). Several methods have been used for genetic exploration, all with limitations. Some of these include: cytogenetic analysis association and linkage analysis studies, copy number variation (CNV), DNA microarray analysis, as well as whole-exome sequencing analysis and transcriptomic analysis (Li et al, 2012). All of these will be briefly discussed for a condensed understanding, necessary for the review.

The cytogenetic studies aim to observe chromosomal anomalies and deviations that may contribute to neurological disorders. Two research findings suggested that autism is a consequence of rare de novo or sporadic mutations (Li et al. 2012) (Hoffman, 2010). De novo/sporadic mutations are random mutations that have occurred instead of being inherited. However, they do become inheritable to the offsprings to follow, once this random mutation has occurred. Other researches (Vorstman et al. 2006, Bakkaloglu et al. 2008, Reddy 2005, Martin et al. 2007, Lukusa et al. 2004) have displayed findings indicating an active relationship between ASD and chromosomal anomalies.

The Copy Number Variation (CNV) analysis aims to discover indels (insertions and deletions of genomes) in the DNA making. Several loci showed influence on disruption in ubiquitin pathways. Ubiquitin pathways are made up of polypeptides that function to protect genes by discarding dysfunctional ones. In conclusion, numerous researches (Pigot et al. 2009, Pinto et al. 2010, Glessner et al. 2009, Levvy et al. 2011, Sebat et al. 2007, Girirajan et al. 2013, Maestrini et al. 2010) implied this genetic role in DNA formation.

Microarray Analysis can identify de novo mutations through its ability to distinguish abnormal chromosomal formations. Although most studies have aimed to discover potential biomarkers of ASD through their gene expression, not many have been successful. However, study research brought to light some new findings from 57 Saudi families, via whole exome sequencing. 47 rare variants discovered in 51 subjects. 38 of these variants had never been found before. These variants were discovered to be linked to ASD, some neurological conditions and were observed in 15 candidates on the spectrum (Al Mubarak et al. 2017).

Although earlier research claimed otherwise, recent ones have discovered a 40-50% factorial dependency on environmental conditions (Lyall et al. 2017). These include parental age, medication use during pregnancy, maternal smoking and alcohol consumption and vaccination. These are discussed briefly as follows:

A study, along with 27 more discovered 18% risk in a 10-year maternal age increase and 21% in paternal (Lyall et al. 2017). A strong relationship between Valproate (medication used for bipolar disorderand epilepsy) and ASD was discovered (Gentile, 2014). However, the relationship between risk of autism and antidepressants is yet uncertain. Studies conducted to investigate the relationship between SSRIs - selective serotonin reuptake inhibitors - (a primary anti-depressant component) revealed a 50% increase in the risk. However, another study showed a mother of psychiatric condition not exposed to SSRIs showed similar risks (Kobayashi et al. 2016). Although smoking and consuming alcohol has proven several birth abnormalities, Modabbernia et al. discuss 15 studies that show no linkage between these factors and ASD (Modabbernia et al. 2017). When in the 90s, researchers began exploring a connection between ASD and MMR (measles, mumps and rubella) vaccinations, no such association was found (Madson et al. 2002, Taylor et al. 2014).

Individuals with ASD are reported to have some genetic abnormalities with mutations in synaptic genes such as postsynaptic cell adhesion molecules neuroligins (*NLGN4X* and *NLGN3*) and postsynaptic scaffolding proteins (*SHANK2* and *SHANK3*) and presynaptic cell adhesion molecule neurexin 1 (*NRXN1*). (Almandil et al, 2019). Mutations in SHANK genes are a potential monogenic cause for autism spectrum disorder. (Monteiro et al, 2017). Results from STRING showed the presence of protein–protein interactions between *NLGN*, *SHANK*, and *NRXN* synaptic genes, and functional annotation clustering from DAVID indicated the possibility of ASD due to dysfunction in synaptic plasticity (Guilmatre et al, 2014). consequently, studies conducted on families have proven that autism is both familial and heritable. Recurrence rate of autism in the sibling of an autistic child is 2% to 8% which is higher than the general population (Faras et al, 2010). The most significant evidence for a genetic contribution to ASD comes from twin studies, which show 31% concordance rates for dizygotic twins and 88% for monozygotic twins. ASDs are clinically heterogeneous, with symptom severity ranging from mild social deficits with normal cognitive abilities to severe mental impairment and absence of language skill (HU VW et al, 2019).

Consanguinity across different cultures:

Consanguinity is "a union between a couple related as second cousins or closer" (Bittles 2001). Regions including North Africa, West and South Asia, are found to have 20-50% of consanguineous marriages. Pondicherry, South India exhibits 54.9% consanguinity in their marriages, 77.1% in Pakistan. 62.5% amongst the inbreeding population of Pakistan were first cousin marriages (Bittles 2008). Regions of Iberian Peninsula, Japan and South America showed prevalence of 1-10%. There are quite a few countries where marriage amongst relatives is common with a population of around one billion, out of which one in three is married to a second cousin or closer relative or is the descendant or offspring of such a marriage.

Consanguinity is discouraged in a number of faiths including: Judaism, Buddhism, and Zoroastrianism (Bittles, 2001). There have been no religious findings have revealed such encouragement in Islam either (Husain, 1999). Such findings bring attention to socio economic factors that have endorsed these practices. These factors, eventually, became tradition for families to follow. Social factors that promote practices of consanguinity include restricted interaction with the opposite gender (even amongst Cousins), difficulty finding marriage partners of similar status and caste, and security of knowing the spouses' family is some of the reasons for the popularity of consanguineous marriages in certain regions. It is also prevailingly common in rural and less educated areas where culture of dowry is common. However, it is not only restricted to such determinants. Other constituents include economic reasons such as strengthening inter-family ties, maintaining or building business relationships amongst the family men. Financial costs of marital ceremonies are also easy to negotiate amongst blood relatives and bring marriage and dowry expenses down to minimal (Ullah et al. 2018).

The frequency of genetic disorders among children who are a progeny of these marriages is around twice that of children of non-related parents. Studies have shown that in Pakistan consanguinity was present in 60% of marriages out of which 80% were first cousins (Ullah et al. 2018). Recently a team of Pakistani scientists concluded that the prevalence of mental retardation in the Pakistani population is due to cousin marriage. They also discovered 30 new genes in these children that were responsible for

this abnormality (Ullah et al. 2018). Other common genetic disorders include thalassaemias, cystic fibrosis, Down's syndrome, infantile cerebral palsy, and hearing and visual disabilities (Corry 2014).

Current Research Findings on the Relationship between ASD and Consanguineous Offsprings

Research in the past has concluded the risk of ASD to increase in offspring of consanguineous marriages. One conducted in 2014 over a population size of 500, in India, presented with an increase in risk for ASD with an odds ratio of 3.22... The cohort examined included 395 boys and 105 girls in a non-control group, and 397 boys and 103 girls in the control group (boys to girls ratio was 4:1), parental consanguinity was divided into 4 groups: first cousins, second cousins, and uncle-niece and double first cousins. (Mamidala et al.2014).

Another case- control study was done in Lebanon on the association of autism with maternal infections, perinatal and other Risk factors, where consanguinity was considered one of the risk factors for ASD during birth/pregnancy. This study remains relevant due to the high prevalence of consanguinity in Lebanon (35%) (Barbour et al. 2009), Another study conducted in Lebanon in 2016 also identified ASD susceptibility genes in certain families as well as specific copy number variations (Soueid et al. 2016) that provide evidence of the genetic predisposition and impact of consanguinity on the pathophysiology of the disorder. Along with the other risk factors assessed in this research, it was shown that consanguinity and family history of psychiatric disorders are indeed a risk factor for ASD, hence also supporting the genetic component in ASD (Barbour et al. 2009). A similar study on Turkish individuals with autism spectrum disorder showed that family recurrence rate of ASD is higher in consanguineous families. (Kiykim et al, 2016), Homozygosity mapping in consanguineous autism pedigrees suggested considerable genetic heterogeneity, implicating several genetic loci in one study conducted on the Arab population. This is because inbreeding causes mapping of loci from a smaller number of families. In the same study, it was also discovered that several consanguineous pedigrees showed large, rare, inherited homozygous deletions within linked regions, some of which are very likely causative mutations (Morrow et al. 2008).

Other researches bring light to genetic inheritance: in those with inherited ASD, it was also foundthere was no difference in the number of sporadic de novo mutations (i.e., new mutation), but the consanguineous subjects did have an increase in number of inherited CNVs (copy number variants) from One or both parents (Geschwind 2008, Morrow et al. 2008). The latter may show implication on disruption of ubiquitin pathways. This transmission of CNVs makes autism believed to be one of the mostheritable mental health disorders, with estimates of heritability as high as 90% (Lichtenstein et al. 2010, Sandin et al. 2017).

Conclusion

The review discussed several scientific implications that may indicate the biological and physiological etiology of the autism spectrum disorder. The genetic studies shed light on the gene involvement causing anomalies and deviations in gene expression, neurological organizations and possible heritability. Environmental circumstances still require more significant research findings for conclusive data. Such biological markers would bring about advances in early intervention and possible prevention, for those who wish to prevent or intervene.

While etiological studies, concentrating on the physiological and biological causes of the autism spectrumdisorder, continue to explore the realm of DNA structure, familial heritage, environment and neurological formations, it is equally essential to analyze individual factors at a time. The review discussed several existing investigations testing the relationship between offsprings of consanguineous marriages and autism. Studies conducted in India (Mamidala et al. 2014), Lebanon (Barbour et al. 2009, Soueid et al. 2016), Turkey (Kiykim et al, 2016) - 3 regions where consanguinity is commonly practiced as custom - revealed a higher prevalence of ASD in their offspring, and an increased risk of susceptibility. Studies in Pakistan revealed influenced genetic disorders such as thalassaemias, cystic fibrosis, Down's syndrome, infantile cerebral palsy, and hearing and visual disabilities (Corry 2014), but ASD was not explored.

Further cohort studies can assist in evaluating this correlation for a more thorough understanding. This will also allow a more substantiate and supportive theoretical analysis.

Research Methodology

Setting: The data was obtained by collecting data from parents of children with ASD from the

following institutes: Clinic of Speech, Language and hearing sciences, Ziauddin University Hospital.

Picture Autism: Social media platforms

Target Population: The population targeted for this study was Pakistani families with a child (or children) who were diagnosed with Autism or exhibited similar behaviors. There was no age limit for the age of the parents orage of the child and there was no control group either as the research was simply intended to measure the relationship between two variables.

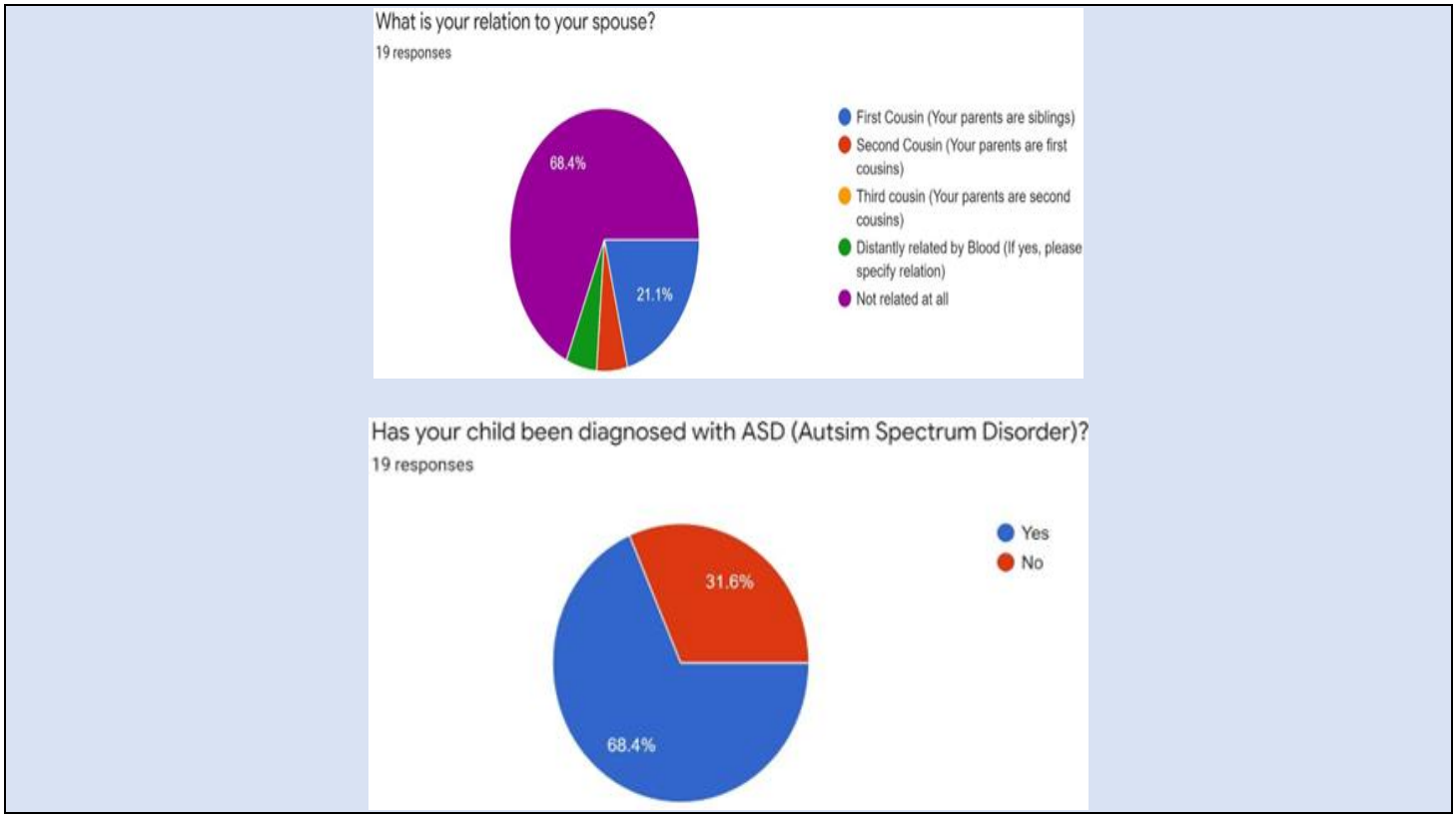
Study Design: This study is exploratory research that has been designed to be a cross-sectional study targeting the Pakistani population, specifically those with off-springs who have been diagnosed with ASD or show symptoms similar to those seen in ASD. The research was designed to be cross-sectional because it was intended to collect data at a specific point in time. It does not benefit from measuring changes over a period of time as the sole purpose of the study is to explore the correlation between consanguinity and prevalence of autism in their offspring.

Duration of Study: The survey was distributed in above mentioned platforms and institutions and data was collected over a span of 34 days.

Sampling Size and Technique: The intended sample size was 50 families; however, the findings in this study are based on data collected from 20 Pakistani families because of limited resources. Systematic sampling was used to collect data from a set group of families that had offspring who were diagnosed with ASD or exhibited symptoms similar to those shown in ASD.

Data Collection Procedure: The data was collected by using a short and precise online survey which was sent to parents via speech therapists or posted on social media groups catering to parents of children with ASD or behaviours similar to those found in ASD. The survey form mostly included closed ended questions and asked for descriptive answers only where details were required. The google doc survey converted all the data into graphs from which important information was extracted.

Data Analysis, Interpretation and Presentation: Statistical Analysis is being used as it is a quantitative research, correlation analysis and probability analysis applied to the data to extract results. Data has been represented using pie chartsand frequency graphs as follows:



Ethical considerations and declaration

No data has been obtained without consent or been forged. Parents were informed about the purpose of

the survey and what the research topic was. The children were not named and data was provided anonymously. The researchers vow to keep the provided information confidential and do not intend to make any monetary benefits through this research.

Research findings

The research aimed to explore the correlation between consanguineous marriages and risk of ASD. The data collected at present showed a negative relationship between the two variables indicating that consanguinity does not significantly increase the risk for ASD in offsprings. The data shows that out of the 19 responses given, 68.4% of the children had been diagnosed with Autism while the remaining 31.6% had not been diagnosed with Autism but showed symptoms similar to those found in children with ASD such as limited speech (77.8%), lack of eye contact (61.1%), hand flapping (50%), echolalia and inability to comprehend verbal instructions (44.4%). Other exhibited symptoms have been shown in the chart below. Data findings show that only 21.1% of children were a result of consanguineous unions between first cousins, 10.6% between second cousins or distantly related family members. 68.4% of the couples were not related at all. The parental age for the mothers at time of birth spanned between 19 years and 45 years while the age range for the fathers spanned between the ages of 23 to 46 years.

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