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Review article

THE GENETIC BASIS OF AUTISM SPECTRUM DISORDERS

Hesat ALIU[1], Qëndresa LUMA[1], Elmedina ADEMI[2]

[1*]*Department of Biology, Faculty of Natural Sciences and Mathematics, MK*
[2] *Professional Medical School, Gostivar, Mk*
[*]*Corresponding author: email: hesat.aliu@unite.edu.mk*

Abstract

Autism Spectrum Disorder (ASD) is a long term used to describe people who have a special neurodevelopmental condition, that causes hardships in their social abilities, communication, and behaviors. Since 1977 when it was first discovered that genes contribute to the manifestation of this heterogeneous condition, the epicenter of a lot of research has been and still is the discovery of that basis that contributes to the manifestation of Autism. Over the past decade, genomic technologies have enabled rapid progress in the identification of risk genes for ASD. In our country, there is still indecision as to what the causes that affect Autism, and the purpose of this paper is to document that, Autism Spectrum Disorder (ASD) has a strong and complex genetic component, with multiple familial inheritance patterns and an estimated of up to 100 genes potentially implicated. The realization of this research is based on the quantitative method, through questionnaires made for the parents of children diagnosed with ASD, and the literature survey method through which we've used topic, scientific and professional research in the genetics field.

Keywords: : Autism spectrum disorders, genetics, genes, heritability.

1. Introduction

Autism spectrum disorders (ASD) are among the most common developmental disabilities. Since its first description, autism has been redefined multiple times. In the early 20th century, autism was classified as a psychotic disorder, grouped with schizophrenia by professionals. In the latter decades of the 20th century, the diagnosis was completely revised in the third revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-3) and redefined as a pervasive developmental disorder. At the outset of the 21st century, autism was re-conceptualized as a spectrum of neurobiological developmental disorders. [1]

"Spectrum" refers to the wide range of characteristics and abilities that different people with autism have. No two people are affected by autism in the same way. People with ASD have a broad range of phenotypes and commonly also have intellectual disability (35%), language delay (50%), or epilepsy (5–15%).ASD is consistently reported to be more prevalent in boys than in girls. [2]

Given the complexity of the disorder and the fact that symptoms and severity vary, there are probably many causes. Due to the progress of autism in recent decades, a wide range of studies have been done to identify the etiological factors of autism. It has been found that genetic and environmental factors are both involved in autism pathogenesis.

Over the last 40 years, the understanding of autism has evolved enormously. We have moved from a time when the role of genetics was unknown to an era when the first twin and family studies showed autism to be one of the most highly heritable disorders (Rutter 2011).[3]

Through this research we have tried to describe the genetic basis of autism spectrum disorders; through the family method, we collected data from the parents of children diagnosed with ASD, while using adequate

literature from Google Scholar, PubMed, Research Gate, etc., we collected data from various types of research that were carried out using the twin method and the cytogenetic method. All these data will guide us to better understand the complicated architecture of this state.

Materials and Methods

Extensive literature from PubMed, Google Scholar, and Research Gate was used to describe the characteristics of autism, the history of the first genetic research the methods from the earliest to the most modern ones by which the heterogeneity and causes of autism have been determined.
Method: by our conditions and possibilities, we chose to use the family method, as a method through which we think we will reach the expected results. Through questionnaires prepared by Psychology Tools, we interviewed the parents of children with ASD.

Results from literature survey

Twin studies

The twin method serves to determine the participation of hereditary factors, on the one hand, and environmental factors, on the other hand, in the development of a feature in a person. Twins can be monozygotic (identical), which develop from one fertilized egg cell (zygote), and have the same genotype as well as the same sex. While dizygotic (non-identical) twins are created from two egg cells fertilized at the same time by two different spermatozoa, and in terms of genetic structure, they are like other sisters and brothers. If monozygotic twins live separately from each other (in different environments), for all features that remain the same, we say that hereditary factors play a more important role in determining them; while all the changes that appear among their features are exclusively attributed to the influence of external environmental factors. In this direction, the comparisons in the similarities of features between monozygotic and dizygotic twins are also important.
Twin studies were the first to demonstrate the heritability of autism. In 1977, the first twin-heritability estimate was published, based on a study of 10 dizygotic (DZ) and 11 monozygotic (MZ) pairs (Folstein & Rutter, 1977). Four out of the 11 MZ pairs (36%) but none of the DZ pairs were concordant for autism. Subsequently, over 30 twin studies have been published, further supporting the high heritability of autism (Ronald & Hoekstra, 2011). More recent diagnostic concordance studies have confirmed high monozygotic concordance for ASD (>88%), but also higher than previously appreciated dizygotic (>30%) and sibling (>15%) concordance rates (Ozonoff et al. 2011; Rosenberg et al. 2009; Taniai et al. 2008). Observations of high dizygotic concordance have raised the prospect of non-trivial environmental contributions to ASD. A recent study by Hallmayer and colleagues (Hallmayer et al. 2011), using a large, carefully ascertained ASD-affected twin sample, identified a substantial environmental contribution to ASD diagnosis (~58%), although other studies have found minimal shared environmental effects (Bailey et al. 1995; Lichtenstein et al. 2010).[4]

Family studies are fundamental tools in the discipline of behavioral genetics (Turner, Cardon, & Hewitt, 1995) and can provide information of great interest in Behavioral Medicine. They permit assessments of degrees of familial resemblance, or aggregation, of physical, psychological, and behavioral characteristics.

The risk of a child having ASD was found to be proportional to the percentage of the genome they shared with an affected sibling or parent (Constantino et al., 2010; Risch et al., 2014; Sandin et al., 2014). Like many hereditary conditions, your genes give you a certain likelihood that you will have autism.

Results and Discussion from our research using the family method

This research aimed to know and identify the origin of autism in a family, and who among the parents have the big contributions to the passing of the genes that carry autism.
Also, in cases where the child with ASD has other siblings, we wanted to prove if they are also with similar symptoms.
To collect information about the wider family circle that may have had a family history of autism.

Table1.1 The results obtained from the questionnaires filled in by the children's parents
*CAST- Childhood Autism Spectrum Test [5]
*AQ -The Autism-Spectrum Quotient Test [6]

Family no.	CAST diagnosed children (6-12y)	Gender	AQ Mother	AQ Father	only child/with other siblings
1.	social communication difficulties	M	Few autistic trait	Few autistic trait	Only child in family
2.	social communication difficulties	M	Indicated significant autistic trait	No autistic rait	Firstborn/one brother ADHD
3.	social communication difficulties	M	Indicated significant autistic trait	No autistic trait	Only child in family
4.	social communication difficulties	M	No autistic trait	No autistic trait	3 other siblings/1w Down Syndrome
5.	strong autism symptoms	M	Few autistic trait	No autistic trait	Only child in family
6.	strong autism symptoms(Epilepsy)	M	No autistic trait	No autistic trait	Middle child/2 other siblings without autistic trait

7.	strong autism symptoms	M	language delay	No autistic trait	Firstborn/sister ADHD
8.	social communication difficulties	M	No autistic trait	No autistic trait	Only child in family
9.	strong autism symptoms(Epilepsy)	M	No autistic trait	No autistic trait	Only child in family
10.	social communication difficulties	M	No autistic trait	No autistic trait	Only child in family
11.	social communication difficulties	M	No autistic trait	Indicated significant autistic trait	Firstborn/unaffectet2 siblings
12.	social communication difficulties	M	No autistic trait	No autistic trait	Only child in family

12 families with children diagnosed with ASD participated. The average age of the selected children is 6-12 years old, they attend the two primary schools in Tetovo, "Liria" and "Istikbal". To classify the severity of symptoms, we used the Childhood Autism Spectrum Test or CAST (formerly the "Childhood Asperger's Syndrome Test") is a 39-item yes or no assessment that parents completed.

Based on the answers of the parents who completed the CAST, we have:

- 8 cases (67%) were characterized by social communication difficulties and
- 4 cases (33%) with strong autism symptoms including 2 cases (16%) also with Epilepsy (self-reported by parents).

Regarding the prevalence between girls and boys, all our cases belonged to the male gender

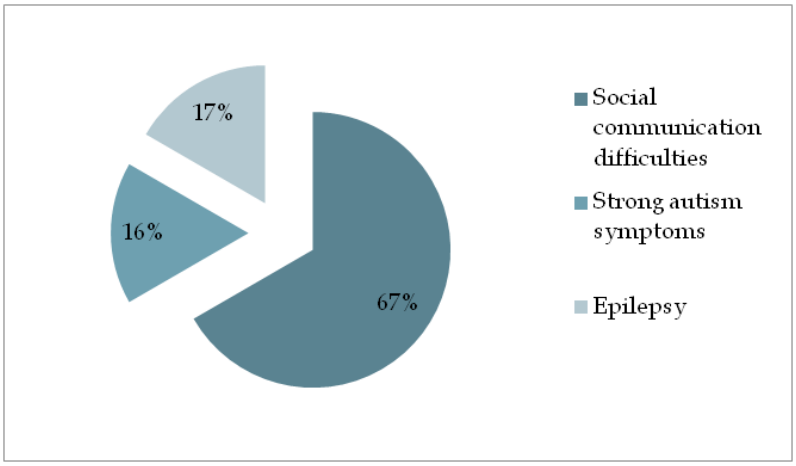

Figure 1. *Severity of autism spectrum symptoms in children with %*

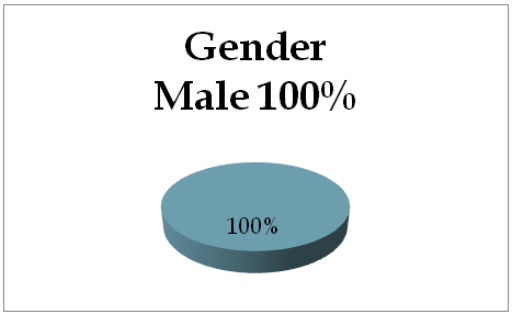

Figure2. *Gender percentage of children diagnosed with ASD*

To see in which parent the traits are present, we used the Autism Spectrum Quotient Test (abbreviated AQ), which is a diagnostic questionnaire designed to measure the expression of the Autism Spectrum traits in an individual, with his/her self-assessment/subjective. Based on the answers we received from both parents for each family, we obtained the following results:

- in four families some features of autism were present in the mother,
- in one family the father,
- in one family both parents had few traits, while in six families neither parent had any features that can be compared with those of their child.

For an individual, the risk of autism is increased 10-fold if a full sibling has the diagnosis and about 2-fold if a cousin has the diagnosis. [7]

Parents (one per family, usually the mother) were asked to provide quantitative characterizations of autistic symptomatology in each of the 4-18- 18-year-old children in their families. In our case, 5 children also had other sisters/brothers, while the other 7 were the only children in the family.

From these 5 families, the results were like this:

- Family n.2 one other child with ADHD (attention deficit hyperactivity disorder)
- Family n.4 one other child with Down Syndrome and two other unaffected children
- Family n.6 three other children, without autistic traits.
- Family n.7 One other child with ADHD (attention deficit hyperactivity disorder)
- Family n.11 two other children without autistic traits.

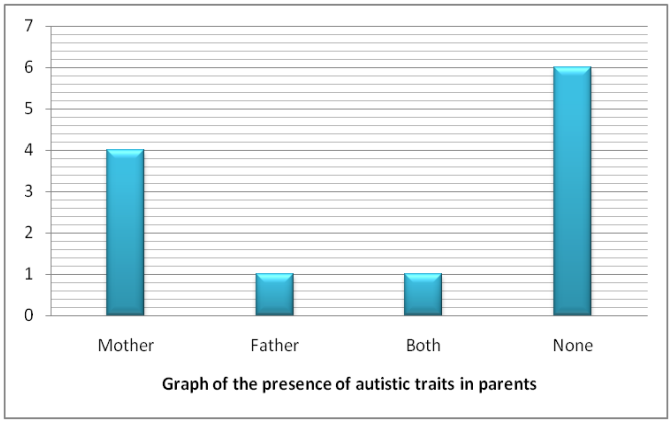

Figure 3. Presence of autictic traits in parents

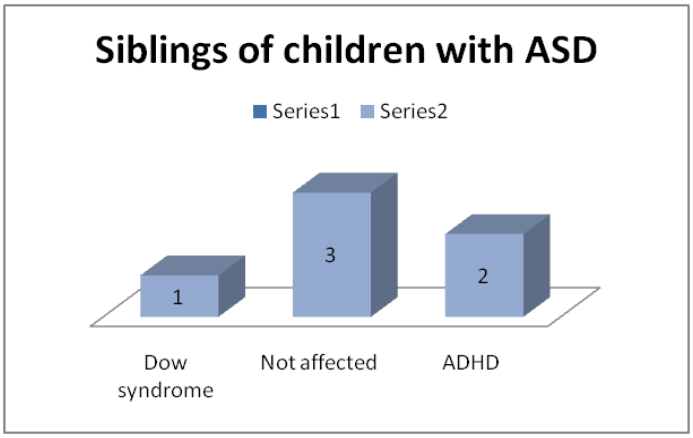

Figure 4. Siblings of children with ASD

From the interview with the mothers, they were also asked if they have known cases in their family, or from their husband's side.
59% refuse to answer,25% have admitted that they have no affected family members, and 16% indicated that they have a relative with Down Syndrome and Hyperactivity.

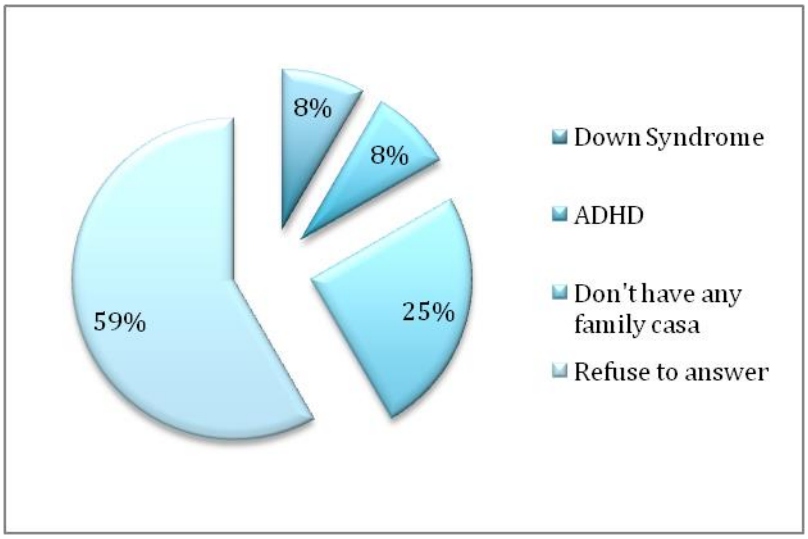

Figure 5. *Results from the wider family circle*

Important from these data is the fact that for 75% of cases, we can say that some autistic features are also present in the mother, father, siblings, and relatives of children diagnosed with ASD; in 25% of the cases the child does not share the same similarities with parents or other family members.

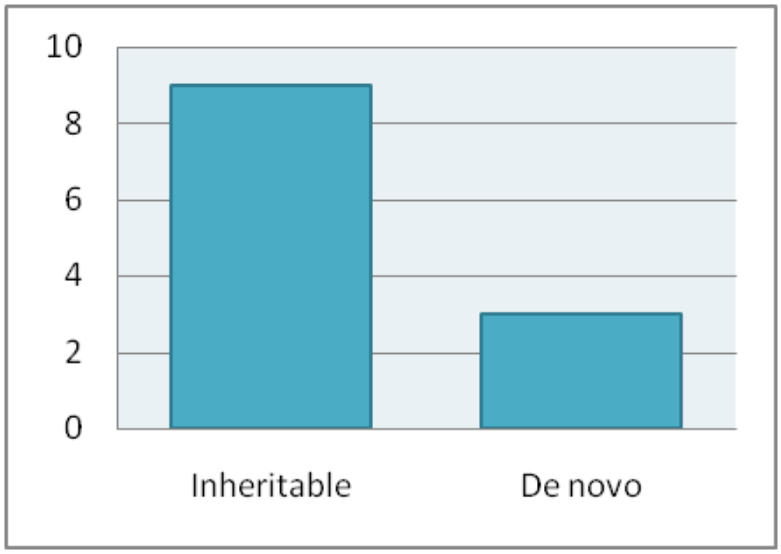

Figure 6. *The relation between inheritable and de novo cases*

Cytogenetic contribution to uncovering regions of the genome involved in autism

Early karyotype studies documenting chromosomal abnormalities began to shed light on which regions of the genome were involved (Gillberg and Wahlström, 1985). Additional susceptibility loci screen implicated regions on chromosome 7q, 1p, 3q, 16p, and 15q. [8]

The major genome-wide and candidate gene association studies, which were used to test for common variants contributing to risk, did not identify consistent genomic areas of interest. The greatest progress toward identifying genetic causes of autism has come from identifying known genetic mutations and disorders that can predispose to the development of autism. [9]

Identified genetic causes of autism can be classified as cytogenetically visible chromosomal abnormalities (~5%), copy number variants (CNVs) (i.e., submicroscopic deletions and duplications) (10–20%), and single-gene disorders (~5%). [10]

Many surveys revealed cytogenetically visible chromosomal anomalies in 7.4% of autistic patients, among the most consistent cytogenetic findings are Fragile-X and duplication of maternal chromosome 15q11–13. [11]

In 1999, Rett Syndrome became the first ASD with a defined genetic cause. Although the majority of people with RTT have mutations in the X-linked transcriptional regulator Methyl-CpG-binding Protein 2 (MECP2),4 up to 5% of people with RTT do not have mutations in MECP2. [12]

5% of cases are the result of mutations in the genes CDKL5 (cyclin-dependent kinase 5) or FOXG1. (Ariani et al. 2008, Russo et al. 2009).

With chromosome abnormalities as the initial step to identify ASD candidate loci, mutations have most convincingly been reported in SHANK3 on chromosome 22q13, two neuroligin (NLGN3 and NLGN4) genes on the X chromosome,10 and the neurexin 1 gene on chromosome 2p16. [13]

Table1.2 ***Chromosomal Defects Implicated in ASD*** [14]

Syndromic ASD			**Non-syndromic ASD**	
Syndrome	**Gene**	**Function**	**Gene**	**Function**
Fragile X	*FMR1*	RNA binding	*NLGN3*	Ligand for neurexins
Rett	MeCP2	Methyl-DNA binding	*NLGN4*	Ligand for neurexins
Angelman	*UBE3A*	Ubiquitin ligase	*SHANK2*	Post-synaptic density protein
Timothy	*CACNA1C*	Ca^{2+} channel	*SHANK3*	Post-synaptic density protein
Tuberous sclerosis	*TSC1/TSC2*	Cell cycle	*PCDH10*	Cell adhesion
Sotos	*NSD1*	Histone modification	*NRXN1*	Synaptic receptor
PTEN-macrocephaly	*PTEN*	Protein phosphatase	*CNTN3*	Synaptic receptor
Cortical dysplasia[a]	*CNTNAP2*	Synaptic protein	*CNTN4*	Synaptic receptor
Phenylketonuria	*PAH*	Phenylalanine metabolism	*NHE9*	Na^+/H^+ exchanger
Creatine transporter	*GAMT/AGAT/SLC6A8*	Creatine metabolism		
Adenylosuccinate lyase deficiency	*ADSL*	Purine metabolism		
Smith–Lemli–Opitz	*DHCR7*	Cholesterol metabolism		
Syndrome	***Chromosome***		***Chromosome***	
Phelan–McDermid	22q13.3 deletion		16p11.2 deletion	
Angelman	15q11–q13 maternal deletion		15q11–q13 maternal duplication	
Prader–Willi	15q11–q13 paternal deletion		7q11.3 duplication	
Smith–Magenis	17q11.2 deletion		2q37 deletion	
Potocki–Lupski	17q11.2 duplication		1q21.1 deletion and duplication	

Syndromic ASD			Non-syndromic ASD	
Syndrome	**Gene**	**Function**	**Gene**	**Function**
VCFS	22q11.2 deletion		15q13.3 deletion/duplication	

Over the last five years, technological advances have facilitated the identification of causal DNA variants associated with ASD. Advances in next-generation sequencing (NGS), whole-exome sequencing (WES), and whole-genome sequencing (WGS) have enabled the identification of large numbers of rare single nucleotide variants (SNVs), including small insertion/deletion mutations (indels) that are associated with ASD[15]
Rare variations can be found as small insertions and deletions (indels), CNVs, or SNVs. Moreover, these can be inherited from a paternal and/or maternal origin or they may appear de novo in the affected subject (De Rubeis et al., 2014).
The most common autism-related CNVs are the 15q11.2-11.3 duplications, similar to duplications revealed by FISH, and reciprocal 16p11.2 microdeletions and duplications. The 16p11.2 microdeletions and microduplications of approximately 555 kb are located at a hotspot of genomic instability caused by duplicated blocks of DNA, which lead to unequal crossing over during meiosis. The 7q11.23 duplication of the Williams syndrome region is also found. Taken together, these CNVs seem to confer susceptibility to ASD in up to 1% of patients with ASD. [16]
Furthermore, family-based sequencing (trio and sibling families) has helped to disentangle the causal relationship of de novo and inherited variants (Ku et al., 2013, Stein et al., 2013), such that, we now understand hundreds of genetic variations affect a wide range of molecular functions associated with ASD (Betancur, 2011b, Buxbaum et al., 2012, Stein et al., 2013). Individuals affected by ASD, particularly in severe cases, exhibit a higher burden of de novo mutations (DNMs) in an expanding list of genes (Coe et al., 2019; Fischbach and Lord, 2010; Iossifov et al., 2014).

Conclusions

Autism as a condition is very heterogeneous genetically and can be caused by both hereditary and de novo gene variations.
Genetic causes of autism can be classified as chromosomal abnormalities, copy number variants (CNVs) (i.e., submicroscopic deletions and duplications), and single-gene disorders.
Depending on whether the origin of ASD is known or not, the Autism spectrum is classified into two subgroups: syndromic ASD and non-syndromic or Idiopathic ASD.

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