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Contribution of advanced parental age in case of autism spectrum disorder

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Abstract:

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that is commonly diagnosed by certain symptoms such as deficits in language, social communication at time of 2 or 3 years in children. The prevalence of ASD in male is higher than female as well as the rate is increasing in such a mark that about 12 %autistic individuals in year 2000 have been increased to 50% in 2012. Advanced paternal age and advanced maternal age have been identified as risk factors for ASD independently by means of several studies. Mutations as well as copy number variations are at increased rate with increasing parental age that are inherited in offspring although mothers remain unaffected. The age of parents is a significant factor during the childbirth. Increased risk of adverse birth outcomes in teenage fathers and mothers can also be considered. In the current study, contribution and relation of parental age including heritage history have been explored and reviewed.

Key words: Paternal age, maternal age, socioeconomic status, chromosomal abnormalities & child birth

1 INTRODUCTION:

Socioeconomic status (Bray, Gunnell, & Davey Smith, 2006) , higher education (Cantalini, 2017) have led to both male and female starting their families later. Modern patterns of

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education , employment , as well as marriage indicates that the average age of childbearing for women is increasing , resulting in greater risks of adverse reproductive outcomes (Bewley, Davies, & Braude, 2005; Qureshi, Ahmad, Qureshi, Memon, & Qazi, 2010). Progression in reproductive technologies are also contributing to this tendency (Blickstein, 2003). Chromosomal abnormality due to advanced maternal age (Gaulden, 1992) , many autosomal dominant diseases in case of advanced paternal age (Kühnert & Nieschlag, 2004a) as well as the risk of autism spectrum disorder(ASD) increased monotonically , rising from 10 to 107 per 10,000 births when paternal ages were tested by means of five increasing categories (Cantor, Yoon, Furr, & Lajonchere, 2007).

Autism spectrum disorders (ASDs) represent a heterogeneous group of neurodevelopmental disorders including autism , Asperger syndrome , childhood disintegrative disorder , pervasive developmental disorder – not otherwise specified (PDD-NOS) which is among the most devastating disorders in childhood (DiCicco-Bloom et al., 2006) . Autism is a highly heritable syndrome that is lifelong defined by deprivation in three core domains: social interaction, language and range of interests (Abrahams & Geschwind, 2008). Macrocephaly is observed in autistic individuals of 15 to 35 percent cases whereas autism is 10 times more common in children with Down syndrome (Caglayan, 2010). Abnormal brain growth have been observed in autistic children at the time of early childhood after several studies such as head circumference measurements, magnetic resonance imaging studies that is called macrocephaly (Redcay & Courchesne, 2005).

The genetic basis can be well established for the first behavioral disorder called autism (Miles, 2011) . A significant genetic basis for ASD susceptibility is indicated by some family studies (Devlin & Scherer, 2012). Mutation rates in humans are extreme in males compared with females as well as associated

with increased paternal age (Goriely, McVean, Röjmyr, Ingemarsson, & Wilkie, 2003).

In several studies, after controlling for several factors such as maternal age and other documented risk factors for autism , there were 2.2 times more likely to have autism in offspring of men aged >50 years compared with offspring of men aged <29 years (C. M. Hultman, Sandin, Levine, Lichtenstein, & Reichenberg, 2010). De novo aberration as well as mutations or epigenetic alterations associated with aging are possible biological mechanisms (Marshall et al., 2008). Several studies have discovered an extreme prevalence of de novo copy number variants along with other forms of genomic alterations in autistic children (Sebat et al., 2007).

1.1 Objectives

- To know the association of autism spectrum disorder with advanced parental age by means of previous studies
- Is advanced maternal age is greater risk than advanced paternal age for ASD?

2 What is ASDs:

ASD is highly heritable , biologically based neurodevelopmental disorder that involves multiple genes (Bailey, Phillips, & Rutter, 1996). Autistic disorder, Asperger syndrome, and pervasive developmental disorder - not otherwise specified (PDD-NOS) comprise a heterogeneous group of neurodevelopmental disorder known as autism spectrum disorders (ASD) (Anitha et al., 2012). ASD is a genetically heterogenous disorder with variation ranging from simple copy number variants(CNV), to mutations in genes involved in complex synaptic and neurodevelopmental pathways (Bhat et al., 2016). Whereas ASDs are known to be highly heritable

(~90%) , the fundamental genetic determinants are still largely not known (Pinto et al., 2010).

Autism, a complex neurodevelopmental brain disorder characterized by deficiencies in social interaction and communication, and repetitive and stereotyped behaviors as well as an onset earlier on the age of 3 (Cantor et al., 2007). Asperger syndrome with individuals are commonly diagnosed through noncompliant , aggressive behavior (Armstrong & Kimonis, 2013) but no significant retardation either in language development or cognitive development (Dewrang & Sandberg, 2010) in late childhood or are rarely diagnosed before the age of 7 years (Haglund & Källén, 2011). The prevalence of autistic disorder and PDD-NOS are much higher than Asperger disorder (Fombonne, 2009) that are diagnosed in early childhood through the co-occurrence of various forms of psychopathology as well as challenging behaviors (Matson, Hess, & Boisjoli, 2010).

2.1 Several other factors are related to ASDs:

Mitochondrial dysfunction (MtD) has been observed in five percent of children with ASD as it contributes to autism by impairing highly energy –dependent processes such as neurodevelopment (Anitha et al., 2012). Mitochondrial dysfunction is the root cause of many diseases which is characterized by a loss of efficiency in the electron transport chain and reductions in the synthesis of high –energy molecules such as adenosine -5'- triphosphate (ATP) (Nicolson, 2014).

Maternal diabetes developed before and during pregnancy may increase the risk of ASD (Xu, Jing, Bowers, Liu, & Bao, 2014). Maternal hyperglycemia during pregnancy can result in hypoxia in the fetus (Eidelman & Samueloff, 2002) and a depleted oxygen supply to the fetus may impair neurodevelopment and thus contribute to a greater risk of ASD (Burstyn, Wang, Yasui, Sithole, & Zwaigenbaum, 2011; Alexander Kolevzon, Raz Gross, & Abraham Reichenberg,

2007). Hypoxia means deficiency in the amount of oxygen reaching the tissues.

Fragile-X syndrome, Rett syndrome, tuberous sclerosis, and recently certain rare de novo mutations and certain copy number variations are monogenetic causes of autism (Henningsson et al., 2009). Rare mutations have been identified in synaptic genes including *NLGN3, NLGN4X* and *SHANK3* and microarray studies have expressed copy number variations (CNVs) include *de novo* events as risk factors for 5-10% ASD cases (Pinto et al., 2010).

Genome-wide association studies using single nucleotide polymorphisms(SNPs) have highlighted two potent ASD risk loci at 5p14.1 and 5p15.2 (Pinto et al., 2010). The age of the father at the conception of the child dominates the diversity in mutation rate of single nucleotide polymorphisms (Kong, Frigge, Masson, Besenbacher, Sulem, Magnusson, Gudjonsson, Sigurdsson, Jonasdottir, Jonasdottir, et al., 2012).

The biological functions of gastrin releasing peptide receptor (GRPR) gene are consistent with a role in the pathophysiology of autism (Ishikawa-Brush et al., 1997). Dysfunctions in the cerebellum as well as possibly the temporal lobe occur in autistic symptoms that is pointed out from neuroimaging studies (Trottier, Srivastava, & Walker, 1999). Animal models of fetal alcohol syndrome (FAS) showing cerebellar abnormalities are a key finding in the neuropathology of autism (Trottier et al., 1999).

Gene expression modifying mechanism called DNA methylation increase and decrease with aging depending on the tissue and gene (Richardson, 2003).

2.2 Prevalence of ASDs:

Currently, 1 in 88 children in the United States have an ASD diagnosis in which boys being affected at a ratio of 5:1 compared to girls (Ramos, Sajuthi, Langefeld, & Walker, 2012). It is reported by several studies that ASD is 4 times more likely

to be occurred in girls than in boys implying an involvement of X-chromosome and / or imprinting mechanisms (Lintas & Persico, 2009).

Two potential genetic involvements have been consistently observed for ASDs:

- 25-fold greater risk of recurrence of ASDs in siblings than in general populations (Fassio et al., 2011).
- High consistency rate (70-90%) of monozygotic twins than in dizygotic twins(0-10%) (Fassio et al., 2011; Sebat et al., 2007).

2.3 Syndromes of ASDs:

ASDs develop prior the time of 3 years (Miles, 2011) . Infants may avoid as well as fail to make eye contact or stare into space (Miles, 2011) . Children with ASD show early signs but fail to make medical attention until after the second year when language delays are obvious (Miles, 2011) . The onset of ASD symptoms is gradual for most children and these children start to speak as well as then gradually lose language ,fail to make eye contact , do not respond to his or her name (Miles, 2011). On an average 25% of children fit the diagnostic criteria for ASD at the age of 2 or 3 years subsequently start to speak and communicate as well as at 6 or 7years of age blend to varying degrees into the regular school population (Miles, 2011). Some improvements with age of the remaining 75% continue to require parent ,school and social support (Miles, 2011). They treat their parents like objects as well as may climb on them to get a desired object , pull the parent by hand or place the parent's hand on the object (Miles, 2011). They refuse to make friendships with peers and siblings. They observe other children from a distance in school (Miles, 2011). Autistic children show extreme hypersensitivity to specific sounds like vacuum cleaner may make great discomfort causing the child to hold his hands over his ears (Miles, 2011). Insomnia as well as

abnormal sleep patterns are observed in about 60% of autistic children (Miles, 2011).

3 Epidemiological data of ASDs as a result of parental age

The etiology of autism is complex consisting of unknown genetic factors (Baxter et al., 2007). Although paternal and maternal age are non-genetic factors but can be a great concern and etiologically important also. Parent may influence the characteristics of offspring by many means such as intelligence, longevity, health outcomes and other characteristics (Y. Liu, M. Zhi, & X. Li, 2011). Delayed reproduction trend in many countries worldwide illustrated that in Spain in 1980 proportion of births from mothers above the age of 35 years was approximately 14% but increased to nearly 25% by 2007 and proportion of births from fathers aged 35-54 years was 25% in 1993,increasing 40% after ten years (Brian K Lee & John J McGrath, 2015). Nearly 40 epidemiologic studies across North America, Asia, Australia, Europe found evidence linking advancing maternal age and advancing paternal age with increased risk of autism in the offspring (Brian K Lee & John J McGrath, 2015). Births of child to mothers and fathers aged 35 years or over increased 14.9 % and 11.5% respectively between 1994 and 2001 in New York City (Quinlan, McVeigh, Driver, Govind, & Karpati, 2015). There is no interaction between mother's and father's age. Maternal age 25 years or over and paternal age 35 years or over were independently associated with increased risk of ASD in children (Quinlan et al., 2015).

Older parents having children tend to be more intelligent than the younger parents that has been demonstrated by many researchers, although there are some negative results also (Y. Liu et al., 2011). The risk of birth and health outcomes in offspring are almost associated with either

teenage (Levine, Emery, & Pollack, 2007) or advanced parental age (Y. Liu et al., 2011).

A study identified total 593 ASD children (277 were classified as autistic disorder and 316 as PDD-NOS or Asperger disorder cases) according to *International Classification Of Diseases, Ninth Revision, Clinical Modification, code 299.0 or 299.8* recorded two or more times at Kaiser Parmanente (KP) hospital in Northern California outpatient databases before May 2005 (Croen, Najjar, Fireman, & Grether, 2007). These ASD children were compared with all 132251 remaining singleton KP births and all singleton children born at KP from January 1,1995 to December 31,1999 (Croen et al., 2007). These findings showed that advanced maternal and paternal ages are independently associated with ASD risk (Croen et al., 2007). Maternal age ranged from 12 to 53 years (mean, 28.8+5.9 years) and paternal age ranged from 13 to 70 years (mean, 31.5+6.9 years) were considered in this study (Croen et al., 2007). The correlation between maternal and paternal age was 0.74 ($P< 0.001$) and children with ASDs were more likely to be male (Croen et al., 2007).

In 2005, Lauritsen et al. used categorical maternal and paternal age effects for autism (childhood autism or atypical autism) with reference 25-29 years category and reported significant increased adjusted relative risks for autism for highest paternal age categories: 35-39years, 40-44years, >40 years and lowest 12-19 years maternal age category (Janie F. Shelton, Tancredi, & Hertz-Picciotto, 2010). Larsson et al. in 2005 , a Danish study used the similar method and reported a preliminary data set of adjusted odds ratios where he found the simple of autism in children of mothers aged <20 years as well as fathers aged >39 years after adjusting perinatal risk factors (Janie F Shelton, Tancredi, & Hertz-Picciotto, 2010). However , these adjusted odds-ratios were no longer statistically significant (Janie F Shelton et al., 2010).

Parental age was stratified into five categories:<25, 25-29, 30-34, 35-39 and >40 years for categorical specifications where cohort median age for mothers was 27 years and fathers was 27 years as well as 25-29 years large age groups were as reference (Janie F Shelton et al., 2010). Advanced paternal age (39-49 years) was associated with childhood autism in offspring, whereas advanced maternal age (30-40 years) was associated with both Asperger syndrome and pervasive developmental disorder in offspring (Lampi et al., 2013) respectively was observed using conditional logistic regressional model in a study (Geier, Hooker, Kern, Sykes, & Geier, 2014).

Autosomal dominant disorders are greatly associated with advanced parental age (Yongsheng Liu, Mingxing Zhi, & Xiuju Li, 2011). A population based cohort study from five countries (Denmark, Israel ,Norway, Sweden, Western Australia) comprising 5766794 children born 1985-2004 and followed up to the end of 2004-2009 estimated the relative risk of autism using logistic regression and concluded that increases in ASD was not only depend on advancing maternal and paternal age alone but also depend on similarly aged parents (younger or older) as well as when there is 10 years or more age difference between father and mother (S. Sandin et al., 2015).

3.1 Maternal age, as a risk factor of ASDs by means of several studies:

Of 26 studies reviewed that vary in design, sample size and demographics of the study populations,10 showed a relationship of advanced maternal age and autism, while 16 did not (Baxter et al., 2007). There is no association between severity of autism and maternal age that was concluded in a study (Baxter et al., 2007).

It was found that ASDs risk increased significantly with each 10-year increase in maternal age (Lauritsen, Pedersen, & Mortensen, 2005) considering maternal and paternal age modeled as continuous variables (Croen et al., 2007). The effect

of maternal age was stronger for pervasive developmental disorder not otherwise specified (PDD-NOS) and Asperger's disorder than AD whereas paternal age effect for AD was higher than PDD-NOS and Asperger's disorder (Croen et al., 2007).

Mothers aged about 45-50 years showed an estimated 18.63 ASD cases per 1000 births whereas fathers aged 55-59 years had 16.35 ASD cases per 1000 births (Idring et al., 2014). This findings indicated the greater risk of having ASD children for older mothers (Glasson et al., 2004) than older fathers (Idring et al., 2014). In a 2012 meta-analysis focused on advancing maternal age using data from over 25000 ASD cases and eight million controls aggregated from ten studies, investigators found that mothers>35 years of age had 1.5 fold increased possibility of having a child with ASD compared to mothers aged 25-29 years (Brian K Lee & John J McGrath, 2015).

An Australian study by Glasson et al. 2004 reported statistically significant increased adjusted risks for ASD and advancing maternal age, but not for paternal age (Janie F. Shelton et al., 2010). Maternal age modeled as a continuous variable showed an approximate eighteen percent increased risk of autism for five years increment in age as well as when modeled categorically a stepwise increase risk for autism per 5-year interval of age (Janie F. Shelton et al., 2010). Mothers aged over 40 years compared with 25-29 years had 51 percent higher odds of having a child with autism after adjusting the model (Janie F. Shelton et al., 2010).

Very old and very young mothers have the risk of miscarriage , infant mortality than the intermediate group (Yongsheng Liu et al., 2011). The intermediate age range of mothers is between 25-35 years according to this study (Yongsheng Liu et al., 2011). Lowest mortality rates for infants of 32 years aged mothers was found by a national U.S. study (Yongsheng Liu et al., 2011). It is documented in a study that

the infants of teenage mothers have low birth weight (Yongsheng Liu et al., 2011). Downs syndrome , the most common genetic disorders in human was found to be associated with advanced maternal age (Yongsheng Liu et al., 2011). For instance , 1 in 2300 at age 20 and 1 in 45 at age 45 , have been shown in this study (Yongsheng Liu et al., 2011).

3.2 Paternal age, as a risk factor of ASDs by means of several studies:

It was found that increased paternal not maternal age was associated with an elevated risk of high –functioning autistic spectrum disorder results from a case-control study , was conducted in Japan considering eighty-four individuals with autistic spectrum disorder without intellectual disability and 208 healthy controls (Tsuchiya et al., 2008). In 2006 ,a historical study of Israeli military conscription records of a birth cohort of Jewish children from 6 consecutive years in the 1980, Reichenberg et.al found the association of increased risk of ASD for increased paternal age, but not for maternal age although there being a large fraction of sample missed (Janie F Shelton et al., 2010).

Genetic mutations accumulate with advancing paternal age are consistently associated with autism and ASDs (B. K. Lee & J. J. McGrath, 2015) whereas in some studies advancing maternal age is not consistent (A. Kolevzon, R. Gross, & A. Reichenberg, 2007). Data regarding a large 2010 meta analysis of advancing paternal age from 11 studies found that fathers aged 40-49 had 1.8 fold risk of a child with ASD than fathers <29 years where samples consisted of over 25000 ASD cases and eight million controls (B. K. Lee & J. J. McGrath, 2015).

Continuous modeling showed each five year increase in father age resulted in the 11% increase in the odds for autism (Janie F. Shelton et al., 2010). Categorical model showed 36% increased odds of having a child with autism when fathers aged >40 years compared to 25-29 years (Janie F. Shelton et al.,

2010). As a result the study demonstrated that advancing maternal age increased the risk of autism independent of father's age while advancing paternal age increased the risk of autism primarily for mothers under 30 (Janie F. Shelton et al., 2010).

Increased paternal age is significantly combined with instinctive abortion, independent of maternal age and multiple other factors (Yongsheng Liu et al., 2011). An increased risk of adverse birth outcomes of teenage fathers had been found by this study also (Yongsheng Liu et al., 2011).

Malaspina et.al (2001) conducted a large population based study and showed that the incidence of schizophrenia increased progressively with increasing paternal age, the risk being 2-fold or 3-fold for offspring of fathers aged 45-50 years or more compared to 25 years (Y. Liu et al., 2011).

There is 5.75 times risk of autism of offspring of fathers aged 40 years or more compared to younger than 30 years after controlling the socioeconomoic status and mothers age according to Reichenberg et.al (2006) (Y. Liu et al., 2011). Chromosomal aberrations and mutations accumulation during the maturation of germ cells are responsible for increasing risk of genetic diseases with advancing paternal age has been proposed in a study, conducted by Hemminkiet al.1999 , Bray et al.2006 (Y. Liu et al., 2011).

In a Jamaican study using Multivariate General Linear Model (MGLM) approach found that the parental ages are jointly associated with having a child with ASD (Rahbar et al., 2012). The MGLM approach treats parental ages as a vector of outcome variables (Rahbar et al., 2012). In addition, they reported that the paternal age may have a weaker association of having a ASD child than maternal ages (Rahbar et al., 2012).

Very large and diverse contemporary North American population study showed increasing maternal age and increasing paternal age were independently associated with

increased risk of autism (J. K. Grether, M. C. Anderson, L. A. Croen, D. Smith, & G. C. Windham, 2009).

For instance, each 10 year increment in age, odds ratio for autism associated with maternal age increased by 38% and that paternal age by 22% (J. K. Grether et al., 2009). Analyzation of the influence of parental age on offspring may be of great significance when is the best time to be a mother or father (Y. Liu et al., 2011).

3.3 Another diseases are associated with advanced maternal age:

It is said that Trisomy 21 or Down Syndrome is the most conventional genetic cause of human mental retardation as well as the main reason of premature pregnancy failure (Hobbs et al., 2000). Maternal age is the solely well-established hazard cause for Down Syndrome as well as the related risk increases exponentially at age greater than 30 years ,because the extra chromosome is derived from the mother in 93% cases (Hobbs et al., 2000).

In addition, women are facing an age-dependent increase of miscarriages, obstetric morbidities as well as chromosomal anomalies of the fetus (Kühnert & Nieschlag, 2004b) . Mothers aged >50 years practically can not give birth children in human (Kühnert & Nieschlag, 2004b).

3.4 Others are related to increased paternal age:

In industrialized countries, late childbearing is a casual event (Kühnert & Nieschlag, 2004b). Reduced fertility as well as fecundity of a couple are contributed by men aged >40 years, especially when the female partner is also of advanced age (Kühnert & Nieschlag, 2004b). There is a few statistical evidence that supports an association of genetic diseases with advancing paternal age (Kühnert & Nieschlag, 2004b). Yet autosomal dominant diseases as well as schizophrenia are related with advancing paternal age. For example, two

autosomal dominant diseases, achondroplasia and Apert's syndrome are caused by single point mutations in sperm that is increased with age (Kühnert & Nieschlag, 2004b). DNA damage involves hypomethylation of key genes , though it is poorly characterized (Aitken & De Iuliis, 2007). DNA hypomethylation refers to the loss of methyl group in the 5-methylcytosine nucleotide. The occurrence of dominant genetic mutations such as Apert syndrome or achondroplasia increases exponentially in the offspring in relation to the paternal age concerning the increase in DNA damage (Crow, 1997). Men over the age of 37 exhibit an average level of DNA damage in their spermatozoa that is three times greater than that observed in younger men (Singh, Muller, & Berger, 2003). Methylation is a heretidable epigenetic modifications , which is erased and reset during male and female gametogenesis when differential marking of imprinted genes is postulated to occur (Aitken & De Iuliis, 2007) . Increased rates of spontaneous abortion (Slama et al., 2005) and fetal death (Nybo Andersen, Hansen, Andersen, & Davey Smith, 2004) is known to be associated with paternal age .

3.5 Autism risk is increased with advancing grandpaternal age:

Men who fathered a daughter at the age of 50 or more were 1.79 times more likely to have a grandchild with autism and men who fathered at age 50 or older were 1.67 times more likely to have a autistic grandchild (Frans, Sandin, Reichenberg, & et al., 2013). Grandfather's age is associated with risk of autism in grandchild independent of maternal and paternal age.

3.6 Parental psychiatric disorders are associated with autism spectrum disorders in the offspring:

A population based case-control study was carried within a Swedish cohort of children born between 1977 and 2003 who

had a hospitalization record indicating autism earlier on 10 years of age (n=1227) and their parents , were matched with 30693 control subjects from the Swedish Medical Birth Register by gender , year of birth and hospital (Daniels et al., 2008) . Parents of autistic children were more likely have been hospitalized for a mental disorder than parents of control subjects (Daniels et al., 2008) . Psychiatric disorders like Schizophrenia was more common in case mothers and fathers than control parents but the positive association between childhood autism and psychiatric disorders was found only for depression and personality disorders in mothers , not for fathers (Daniels et al., 2008) .

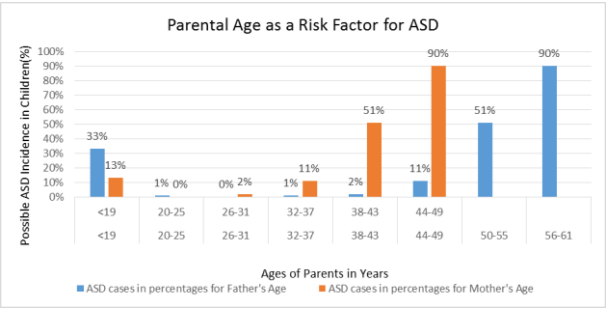

Figure 1 : Comparative analysis of ASD cases for father's age and mother's age independently , without considering other risk factors.

In figure 1, Mother's age is divided into six categories and father's age into eight categories. The showing possibility of ASD incidence in children will be considered only after controlling other factors such as age of their male or female partner during childbirth. The figure is generated using previously discussed epidemiological data (Judith K Grether, Meredith C Anderson, Lisa A Croen, Daniel Smith, & Gayle C Windham, 2009; Brian K Lee & John J McGrath, 2015).

In a 2012 meta-analysis, a special attention is given on advancing maternal age using information from over 25,000 ASD cases as well as eight million control from ten studies, it is found that mothers of >35 years age had 1.5 fold increased odds

of having ASD child compared with mothers of 25-29 years (Sven Sandin et al., 2012). A similarly large 2010 meta-analysis reported advancing paternal age from 11 studies that fathers of 40-49 years old had a 1.8 fold of increased risk of having ASD child than fathers aged <29 years (C. Hultman, Sandin, Levine, Lichtenstein, & Reichenberg, 2011).

4. Discussion:

The hypothesis of advancing parental age is supported by converging evidence from epidemiological , genetic , animal studies that the risk of autism spectrum disorder in offspring increases with age of both father and mother independently (Brian K Lee & John J McGrath, 2015). The mechanism of advanced maternal age and the risk of ASD in offspring is different from father as well as chromosomal abnormality is of special interest in this case. There are several congenital disorders that have been associated with older parental age at childbirth (C. M. Hultman et al., 2010).

The evidence of correlation between advancing paternal age or/and advancing maternal age as well as the risk of autism in offspring has been found from about 40 epidemiological studies across North America , Europe , Asia , Australia (Brian K Lee & John J McGrath, 2015). Several studies had been searched out the linking of advancing parental age and the increased risk of ASD in offspring (Idring et al., 2014) , some studies found evidence that the risk of ASD increases with increasing paternal age nor with older maternal age (Reichenberg et al., 2006) , some found risk factor as advanced maternal age nor advanced paternal age (Glasson et al., 2004) , others reported no correlation with increased parental age and the risk of ASD in offspring (Hehir-Kwa et al., 2011).

Several recent evidences have added a conclusion that autism is associated with de novo and inherited mutations (Iossifov et al., 2012; Kong, Frigge, Masson, Besenbacher,

Sulem, Magnusson, Gudjonsson, Sigurdsson, Jonasdottir, & Jonasdottir, 2012; Levy, Ronemus, Yamrom, Lee, Leotta, Kendall, Marks, Lakshmi, Pai, & Ye, 2011; Neale et al., 2012; O'Roak et al., 2011; O'Roak et al., 2012; Sanders et al., 2011; Sanders et al., 2012) . It is speculated that paternal age- related mutagenesis is associated with an increased risk of autism (Frans et al., 2013) considering the association between the advanced paternal age and de novo copy number variants in an animal model (Flatscher-Bader et al., 2011). Offspring of older fathers are at increased risk of accumulating de novo mutations and in some cases proportion of age – related de novo mutations are phenotypically silent in the offspring but can influence the risk of autism in futher generations via interaction with other susceptible factors (Frans et al., 2013).

The various studies claimed that the most widely accepted etiological model is one of multiple genes of small to moderate effect with both gene-gene and gene-environment interactions (Baxter et al., 2007). Increased rate of de novo mutations observed by some studies in older fathers makes advanced paternal age as a factor in autism spectrum disorder pathogenesis (Geier et al., 2014). Screening for copy number variations is easier than sequencing the entire genome to discover point mutations (Beaudet, 2007).

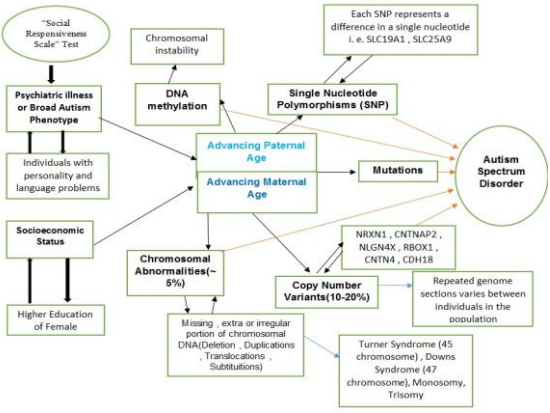

Figure 2 : The underlying factors of autism spectrum disorder and advancing parental age .

Subclinical (donating a disease which is not severe enough to present readily observable symptoms) personality traits similar to the defining features of autism have been found to be more common among family members of some individuals with autism , have become known as the broader autism phenotype (Bolton et al., 1994; Hurley, Losh, Parlier, Reznick, & Piven, 2007; Piven, Palmer, Jacobi, & Childress, 1997) .

The target genes loci of ASDs may be selective in some cases or uncertain and it is likely to be appropriate for recurrent loci also. Mutations in these loci are not always predictable. Several range of mutations (missense or truncation) have been found to be frequent in autism spectrum disorder. Most events overset dozen of genes instead of one gene (Levy, Ronemus, Yamrom, Lee, Leotta, Kendall, Marks, Lakshmi, Pai, Ye, et al., 2011). As the causes of autism spectrum disorder are diverse, it appears difficult to find out the actual etiology in affected individuals whether it is due to advanced parental age or not. In some cases, this lifelong brain disorder can be manageable in individuals depending on the type of disorder and its etiology. For example, an autistic child learns to do work himself / herself with ongoing training from childhood to adulthood.

5. Conclusion:

This study provides information regarding the relationship between parental age and autism spectrum disorders in offspring specially the autistic disorder. The rate of occurrence of ASD is higher in boys than girls. Higher rates of de novo mutations in some genes of older fathers. De novo mutations remain phenotypically silent in the offspring of older fathers but can influence the risk of autism in further generations via interaction with other susceptible factors. Chromosomal abnormality is of special interest in case of maternal age. Autism is associated with de novo and inherited mutations. The

hypothesis of advancing parental age is supported by converging evidence from epidemiological studies. There should be available information in the National Birth Registry, Bangladesh about parent's age along with others like date of birth of children , name of mother and father , health condition of parents etc. This will help to recognize the actual reason of disorders in offspring that they will meet in their lifecycle.

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