



## Parental age and assisted reproductive technology in autism spectrum disorders, attention deficit hyperactivity disorder, and Tourette syndrome in a Japanese population

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### ABSTRACT

We investigated whether advanced parental age and assisted reproductive technology (ART) are risk factors in autism spectrum disorders (ASDs), attention deficit hyperactivity disorder (ADHD), and Tourette syndrome (TS). Clinical charts of Japanese outpatients with ASD ( $n = 552$ ), ADHD ( $n = 87$ ), and TS ( $n = 123$ ) were reviewed. Parental age of individuals with ASD, ADHD, or TS was compared with parental age in the general population (GP) of Tokyo after adjusting for year of birth. Paternal and maternal ages were significantly higher in persons with ASD and ADHD, but not those with TS. In final steps of stepwise logistic regression analysis, both maternal and paternal age were associated with ASD after controlling for the other parent's age, gender, and birth order. In cases where the presence or absence of ART could be ascertained (ASD  $n = 467$ ; ADHD  $n = 64$ ; TS  $n = 83$ ), the rate of ART in cases of persons with ASD (4.5%) was 1.8 times the frequency expected in the GP, while ART was not present in cases of persons with ADHD and TS. These preliminary results remain tentative pending replication with larger, community-based samples.

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### 1. Introduction

The etiology of autism spectrum disorders (ASDs) is not well understood. Recent studies suggest that *de novo* mutations (Marshall et al., 2008; O'Roak et al., 2011; Pinto et al., 2010; Sebat et al., 2007) and epimutations (Grafodatskaya, Chung, Szatmari, & Weksberg, 2010) in the genome play a role in ASD. Advanced parental age at delivery and assisted reproductive technology (ART) may be mediating factors in this process (Bonduelle et al., 2002; Manipalviratn, DeCherney, & Segars, 2009; Rivera et al., 2008). An association between advanced parental age and ASD has been reported mainly in studies from the United

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States (Croen, Najjar, Fireman, & Grether, 2007; Durkin et al., 2008; Grether, Anderson, Croen, Smith, & Windham, 2009; King, Fountain, Dakhlallah, & Bearman, 2009; Shelton, Tancredi, & Hertz-Picciotto, 2010), Europe (Hultman, Sandin, Levine, Lichtenstein, & Reichenberg, *in press*), and Israel (Reichenberg et al., 2006). Many studies (Croen et al., 2007; Durkin et al., 2008; Grether et al., 2009; Hultman et al., *in press*; King et al., 2009; Reichenberg et al., 2006; Shelton et al., 2010) have reported similar significant associations between the occurrence of ASD and advanced parental age. However, several questions remain.

The first question is whether advanced parental age directly affects the development of ASD symptoms (i.e., difficulties with social situations and/or reciprocal communication with people), or whether it affects intellectual or general aspects of child development that could be associated with the risk of an ASD. A previous study reported an association between advanced paternal age and lowered intelligence quotient (IQ) in the general population (Saha et al., 2009), but it also found an association between advanced maternal age and higher IQ. Most previous studies have not separately investigated parental age and ASD according to whether or not the child displayed some degree of mental retardation (MR). One exception may be Tsuchiya et al. (2008), who identified advanced paternal age in individuals with ASD and  $IQ > 70$ , but the use of a control group unmatched for sex and age means that caution must be used when interpreting results: mean parental age in cases where ASD was present was five years less than mean parental age in the control group. These results could be affected by the fact that parental age in Japan has increased over the last few decades. Thus, the issue remains to be clarified.

If advanced parental age affects general brain development, it is reasonable to hypothesize that this impact might also be observed in other developmental disorders, such as attention deficit hyperactivity disorder (ADHD). Thus far, however, only one study has investigated this issue in relation to ADHD, and it found no association with parental age (Gabis, Raz, & Kesner-Baruch, 2010).

The second question is whether the association of advanced parental age with ASD is confined to cases of advanced paternal age, advanced maternal age, or both. Two recent large-scale population-based studies conducted in Europe and Israel reported an association between ASD and paternal age, but not maternal age (Hultman et al., *in press*; Reichenberg et al., 2006). In the United States, one study reported an association with maternal age (King et al., 2009), while four studies reported associations with both paternal and maternal ages (Croen et al., 2007; Durkin et al., 2008; Grether et al., 2009; Shelton et al., 2010). Thus, the issue remains to be clarified.

In Asian populations, in contrast to Western populations, few studies have investigated the association between ASD and parental age. Case-control studies in Japan and China found an association with paternal age (Tsuchiya et al., 2008; Zhang et al., 2010). Another study (Koyama, Miyake, & Kurita, 2007) found that both paternal and maternal ages were elevated in cases of persons with ASD, compared with place-matched general population data.

The present study also attempted to explore whether an association exists between assisted reproductive technology (ART) and ASD. ART includes in vitro fertilization with trans-cervical embryo transfer (IVF) and intracytoplasmic sperm injection (ICSI). The number of children born using ART has been sharply increasing in the past decades in Japan and other developed countries. The first IVF child was reported in the UK in 1978 (Stephoe & Edwards, 1978). The first ICSI child was born in Belgium in 1992 (Palermo, Joris, Devroey, & Van Steirteghem, 1992). In Japan, the first IVF child was reported in 1983, and the first ICSI child in 1994 (Yanagida et al., 1994); in 2006, 1.8% of all Japanese newborns were by ART (Japan Society of Obstetrics and Gynecology, 2008).

ART may have the potential to affect the genetic and/or epigenetic structure of the genome in gametes, fertilized eggs, and embryos through its procedures and unnatural selection of germ cells. However, a limited number of studies have explored the impact of ART on developmental disorders, including ASD. Using birth registry data from Finland, Klemetti, Sevon, Gissler, and Hemminki (2006) compared cases of 4500 children born via IVF and 27,000 born via natural conception (NC), and found that ART was associated with a broad range of psychiatric conditions, including disorders of psychological, behavioral and emotional development. Knoester et al. (2007) followed children born after ICSI, IVF, and NC. After diagnosing these children at the age of 5–8 years based on parental report, they identified ASDs in three of 87 children born via ICSI; none in 85 children born via IVF; and one in the 81 children born via NC. These results may be inconclusive due to the small sample size.

Using the Danish national registry (Maimburg & Vaeth, 2007) compared the frequency of assisted conception (AC) in persons with autism and age-, sex- and birth place-matched healthy controls. The frequency of AC was not higher in autism (2.3%;  $n = 461$ ) than in controls (5.4%;  $n = 461$ ). Another study using the Danish registry found the incidence of ASD to be 0.68% in children born via AC ( $n = 33,000$ ) and 0.61% in children born via NC ( $n = 556,000$ ) (Hvidtjorn et al., 2010). The effect of AC was not found to be significant after adjusting for confounders. These studies did not separately analyze ART and other AC (ovulation induction and/or intrauterine insemination). Thus, there are few studies of the impact of ART on developmental disorders, including ASD, and those that do exist tend to be inadequate.

In an attempt to explore these questions, we conducted a chart review study of persons diagnosed with ASD and other developmental disorders, including ADHD and Tourette syndrome (TS). Parental age and frequency of ART were investigated for each of these three disorders.

## 2. Methods

### 2.1. Setting and procedures

We conducted a retrospective chart review of persons diagnosed with ASD, ADHD, and TS who first visited the child psychiatry outpatient clinic of the University of Tokyo Hospital, from April 2006 to March 2009. These disorders were the

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