Research in Autism Spectrum Disorders 50 (2018) 43–50

Contents lists available at ScienceDirect

Research in Autism Spectrum Disorders

journal homepage: www.elsevier.com/locate/rasd

Contribution of chromosomal abnormalities at 10q and 22q to autism

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ARTICLE INFO

Number of reviews completed is 2

Keywords:
Autism
Chromosomal abnormalities
Chromosome 10q
Chromosome 22q

ABSTRACT

Autism's etiology is heterogeneous. It derives generically from a complex of interactions between genetic, epigenetic and environmental factors. Chromosomal rearrangements at almost all chromosomes have been reported among individuals with autism spectrum disorders (ASD). In this report, we represent three autistic patients with chromosomal abnormalities at 10q and 22q with an interesting case of 10q duplication rather than deletion. This report explores the contribution of the affected genomic regions to ASD. It may contribute to the field of research categorizing candidate loci for ASD, which would be useful in genotype– phenotype analyses for ASD.

1. Introduction

Autism Spectrum Disorder (ASD) is a group of individuals having complex neurodevelopmental disorders with great genetic/genomic components (Yu, Wu, & Wu, 2015). ASD individuals are known to have an impaired social interaction and communication skills, in addition to restricted, repetitive and stereotyped behavior patterns. ASD prevalence is relatively high. It affects 1–3% of children mostly among males that present about 4 times more frequently than females. About two thirds of ASD patients may suffer from other clinical problems. These include epilepsy (25–30%), different gastrointestinal conditions (9–70%), attention deficit and hyperactivity disorder (ADHD) (~30%) and sleep disorders (~50%) (Novarino et al., 2012; Dickerson, Pearson, Loveland, Rahbar, & Filipek, 2014; Moreira et al., 2014; Mosca-Boidron et al., 2016).

In the latter decades, genetic influences have obviously emerged as the most important etiology for ASD. In spite of the several case reports of cytogenetic abnormalities and the associations with specific Mendelian disorders, most of the ASD cases are idiopathic and apparently due to complex inheritance patterns. This had made the identification of susceptibility genes difficult (Folstein & Rosen-Sheidley, 2001). However, the present concept embraces that ASD derives generically from a complex interaction between genetic, epigenetic and environmental factors. Many genes/loci and possibly gene–gene interactions are involved. The genetic factor for ASD etiology has been reported in about 20% of ASD individuals. (Ivanov, Stoyanova, Popov, & Vachev, 2015; Mosca-Boidron et al., 2016).

Different chromosomal anomalies involving most of the chromosomes have been described in individuals with ASD. The prevalence of chromosomal abnormalities in autism has a wide range (5–48%) depending on the participant intelligence quotient (IQ) level and/or physical anomalies. Chromosomal abnormalities, which are visible microscopically, account for ~5% of ASD cases. The

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https://doi.org/10.1016/j.rasd.2018.03.003
Received 15 September 2017; Received in revised form 12 March 2018; Accepted 15 March 2018

submicroscopic deletions and duplications (copy number variants, CNVs) present in 10–20% of ASD cases. While, single gene disorder present in ~5% of ASD cases (Haldeman-Englert et al., 2010; Ivanov et al., 2015).

The genetic involvement in ASD is complex. There is an evidence suggesting that the risk genes eventually target a relatively small set of molecular pathways. It includes those crucial for synaptic development and plasticity, such as the ***SHANK3*** (SH3 and multiple ankyrin repeat domains 3) gene. ***SHANK3*** gene lies in the telomeric portion of 22q13.33 and its protein product acts as a scaffolding protein in its interactions with various synaptic molecules (Sarasua et al., 2014; Oberman, Boccuto, Cascio, Sarasua, & Kaufmann, 2015). Screening for ***SHANK3*** mutations in 3833 individuals with ASD and Intellectual disability (ID) showed mutation in >2% (Baio, 2012). However, the incidence of ASD in patients with abnormalities in the region of the ***SHANK3*** gene, such as patients with 22q13 deletion syndrome or Phelan-McDermid Syndrome (PMS), is conflicting. It ranges at 0–94%, depending on how the information was obtained (Fombonne, 2001; Engel & Daniels, 2011; Eapen, 2011).

Moreover, Children with microdeletions at 22q11 have a higher prevalence of ASD. ASD represents up to 15–50% of 22q11 microdeletion cases. Diagnosis of ASD in these children is not predictive of developing a psychotic disorder or persistent psychotic symptoms later in life, as some have hypothesized. Several encoded genes in this deleted region are highly expressed in the brain. They were known to affect early neuronal migration and cortical development. Moreover, it was proposed that alterations of a distinct set of multiple noncontiguous genes encoded in the chromosomal region 22q11.2 have impacts on the developmental of neuropsychiatric disorders (Hiroi et al., 2013; Jonas, Montojo, & Bearden, 2014; Fiksinski et al., 2017; Ousley et al., 2017).

Several recurrent rearrangements have been added to the growing list of genomic disorders. These includes 10q22.3q23.2 region comprising a complex set of low-copy repeats (LCRs) that may lead to various genomic alteration through non-allelic homologous recombination (NAHR) (Lupski & Stankiewicz, 2005; van Bon et al., 2011). Cognitive and behavioral abnormalities are features of recurrent deletions of 10q22.3q23.2. The breakpoints of this deletion are flanked by LCRs. LCR3 flanks the proximal breakpoint and it harbors two large (4300 kb) highly homologous (99.8% identity) segmental duplications. LCR4 flanks the distal breakpoint and it contains ~170 kb of sequence homologous to LCR3 and 4100 kb of sequence homologous to LCRs located near the chromosome 10 centromere (Balciuniene et al., 2007; van Bon et al., 2011). The recurrent 10q22.3–q23.3 deletions with breakpoints within LCR3 and LCR4 have been described to be associated with a wide range of cognitive and behavioral phenotypes, including learning difficulties, speech and language delay, ADHD, dysmorphic features, cardiac defects, cerebellar anomalies, macrocephaly and autism (Balciuniene et al., 2007; van Bon et al., 2011).

Duplications involving 10q22–q23 region are known to be rare. Only four cases with an overlapping at this region have been reported (Goss, Voullaire, & Gardner, 1998; Han et al., 2004; Dufke et al., 2006; Erdogan et al., 2008). The precise genotype–-phenotype correlations are hindered because these aberrations have often been detected by conventional cytogenetic techniques. With the exception of the only case that has been reported by Dufke et al. (2006), these duplications were found to be much larger in size.

Accordingly, the aim of the present report is to describe three autistic patients with chromosomal abnormalities, at 10q and/or 22q and to explore the contribution of the affected genomic regions to ASD as well.

2. Clinical reports

The present report includes three children; two males and one female. Fully informed written consent was obtained from the parents. Positive consanguinity of parents was documented in the all three cases.

2.1. Patient one

The first patient was male. He was six years old when his parents requested medical assistance. He presented with delayed language development and other autistic features. At 34 weeks of gestation, the mother experienced preeclampsia, when termination of pregnancy by Caesarian section was indicated. Minor dysmorphic features could be noticed, in the form of brushy eye brows, thick lips and synophris of eye brows. Bilateral mild back pressure effect on kidneys and mild splenomegaly was discovered by Pelvi-abdominal Ultrasonography (US). Electroencephalography (EEG) was performed and it revealed no abnormalities. Hearing assessment testing the auditory brain stem response (ABR) was also performed. It was done by means of objective audiometry. It revealed normal hearing thresholds at 2.4 kHz.

The child was diagnosed with severe autism. Clinical diagnosis of autism was based on the criteria of autistic disorder as defined in DSM-V. In addition, ADI-R, CARS (40) and ADOS were carried out by interviewing the parents. He suffered from pica. The cognitive capability of the proband was evaluated by using the Stanford Binet scale. He had ID with an IQ of 39. MRI showed dilated ventricles and delayed myelination of white matter of the brain. EEG was normal.

Chromosomal analysis; for the proband and the parents, was done according to the standard protocols (Verma & Babu, 1995) and was karyotyped according to the ISCN (2016). The karyotype of the proband showed 46,XY,r(22)(:p11-q?:) in all analyzed metaphases (Fig. 1), whereas the parents had normal karyotype. aCGH was done by using a Cytochip ISCA array (BlueGenome-version 1.0) with oligos. It revealed a male profile with terminal deletion of approximately 6.27Mb in size on the long arm (q-arm) of chromosome 22 at chromosomal band 22q13.31 extending to 22q13.33, which overlaps with deletion syndrome (Phelan-McDermid Syndrome), [location: 44,945,868–51,218,979 using build GRCh37 (hg19)]. The deletion confirmed the karyotype results and it further delineated the breakpoints. The deleted region contains many RefSeq/OMIM genes including the ***SHANK3*** gene.