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Review

Genome-wide expression studies in Autism spectrum disorder, Rett syndrome, and Down syndrome

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ABSTRACT

Though different in their aetiology, autism spectrum disorder (ASD), Rett syndrome (RTT) and Down syndrome (DS) are three neurodevelopmental disorders sharing significant clinical and neuropathological overlaps. Genome-wide expression studies are reviewed and available datasets from post-mortem brains reanalyzed to identify genes and gene pathways dysregulated in all three disorders. Our results surprisingly converge upon immune, and not neurodevelopmental genes, as the most consistently shared abnormality in genome-wide expression patterns. A dysregulated immune response, accompanied by enhanced oxidative stress and abnormal mitochondrial metabolism seemingly represents the common molecular underpinning of these neurodevelopmental disorders. This conclusion may be important for the definition of pharmacological therapies able to ameliorate clinical symptoms across these disorders.

Contents

Introduction

Autism Spectrum Disorder (ASD), Rett Syndrome (RTT) and Down Syndrome (DS) are three developmental disorders affecting mainly, though by no means exclusively, the central nervous system (CNS). The incidence of ASD and DS is as high as 60–70/10,000 (Fombonne, 2009; Rutter, 2005), and 14–25/10,000 (Antonarakis et al., 2004),

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respectively. RTT is a relatively rare disease, affecting approximately 1/10,000–15,000 females (Leonard et al., 1997). The male:female gender ratio is 4:1 for ASD, whereas DS shows only a slight male excess (Kovaleva, 2002), and RTT, being an X-linked dominant disorder, affects only females (Weaving et al., 2005).

The causes of DS and RTT are genomic/genetic in nature, and have been elucidated for the vast majority of cases: DS is caused by a complete, or occasionally partial, triplication of chr. 21 (Lejeune et al., 1959), whereas approximately 80% of RTT patients carry de novo mutations inactivating the X-linked gene MECP2, which encodes the methyl-CpG binding transcriptional repressor MeCP2 (Amir et al., 1999; Chahrour and Zoghbi, 2007; Colvin et al., 2004). Unlike these two diseases, only approximately 10% of ASD cases have been associated with a known genetic or cytogenetic cause, though heritability estimates are the highest among psychiatric disorders (i.e., >90%, as estimated by twin studies) (Persico and Bourgeron, 2006). Syndromic forms of ASD have been associated with (a) *de novo* chromosomal rearrangements (duplications of maternal 15q11–13; deletions of chr. 2q37, 7q31, 22q11; microdeletions of chr. 22q11.2 and 16p11.2); (b) other well-known genetic or genomic disorders, including neurofibromatosis, tuberous sclerosis, Angelman syndrome, Cornelia de Lange syndrome, and DS; (c) mitochondrial disorders; (d) copy number variants (CNVs) and/or mutations affecting neuroligins (NLGN3 and NLGN4), the SH3 and multiple ankyrin repeat domains gene (SHANK3), neurexin 1 (NRXN1), methyl-CpG-binding protein 2 (MECP2), homeobox A1 (HOXA1), and the phosphatase and tensin homologue gene (PTEN), among others (for review see Cohen et al., 2005; Lintas and Persico, 2009; Palmieri and Persico, 2010; Weiss, 2009; Zafeiriou et al., 2007). Hence, the cause of ASD is known only in a small minority of cases, although increasing attention is being placed on rare genetic variants and CNVs affecting "synaptic" and neurodevelopmental genes (Betancur et al., 2009; Buxbaum, 2009), as well as on immune abnormalities (see below).

Clinical and neuropathological overlap between autism spectrum disorder, Rett Syndrome and Down syndrome

Although different in origin, these three developmental disorders show significant clinical and neuropathological overlaps. Autistic traits are always present in RTT females and approximately 8% of DS patients are autistic (Cohen et al., 2005; Zafeiriou et al., 2007). Mild to severe mental retardation (MR) is present in approximately 70% of ASD cases (Fombonne, 2005), and in virtually all cases of RTT and DS. Seizures, a hallmark of RTT, also occur in approximately 30% and 37% of ASD and DS patients, respectively (Tuchman and Rapin, 2002). Other neurological features shared by ASD and RTT include stereotypies (typically hand movements in RTT girls), and language regression, which occurs in several ASD children and in the vast majority of RTT girls. Evidence of aetiological and pathophysiological overlaps comes from the *MECP2* mutations occasionally found in non-syndromic autistic girls (reviewed by Lintas and Persico, 2009). Interestingly, the clinical phenotype associated with ASD-causing *MECP2* mutations often includes MR, but not microcephaly, nor epilepsy or regression, which are typical features of RTT. In addition, ASD shares many non-neurological features with DS, including anomalies of the immune and gastrointestinal systems. Many DS patients show decreased lymphocyte peripheral counts, increased liability to infections, presence of autoimmune diseases, and anomalies of the innate immune system similarly to ASD patients, who also display familiality for autoimmune diseases, asthma and allergies (Bloemers et al., 2010; Comi et al., 1999; Croen et al., 2005; De Hingh et al., 2005; Enstrom et al., 2009a; Jyonouchi et al., 2005; Mouridsen et al., 2007). Gastrointestinal symptoms, such as gastroesophageal reflux, are frequently encountered both in DS and ASD (Buie et al., 2010).

One of the most prominent signatures of these three disorders consists in impaired neural development, which is well documented by neuropathological studies:

(a) In RTT, synaptogenesis appears strongly impaired, with disrupted axodendritic connections pointing toward a postnatal onset for deranged neurodevelopment (Kaufmann et al., 1998). This timing is consistent with normal head size at birth and slower-than-normal head growth starting approximately at 1 year of age in RTT. Decreased brain size in grown-up RTT girls has been attributed on one hand to reduced numbers of synapses and decreased dendritic arborizations, also resulting in increased cell density, and on the other hand to decreased neuronal cell numbers and body size (Bauman et al., 1995; Engerstrom and Kerr, 1998). The shortening and thickening of dendritic branches is localized to the same brain regions showing decreased total volume, such as layers III and V of the frontal, motor and inferior temporal cortices; by contrast, dendrites of other brain regions, such as the occipital cortex, are less affected (Armstrong et al., 1995).

(b) Post-mortem studies on ASD brains have shown heterogeneous and patchy microscopic abnormalities, including areas of increased cell density and reduced neuronal size, cytoarchitectonic disruptions with ectopic neurons and/or poor lamination, increased frontal and/or temporal cortical thickness, decreased cerebellar Purkinje cell number (for review see DiCicco-Bloom et al., 2006; Persico and Bourgeron, 2006). These abnormalities involve neurodevelopmental processes physiologically occurring during the first and second trimester of pregnancy (Rice and Barone, 2000), namely reduced apoptosis and/or increased cell proliferation, altered cell migration, and abnormal cell differentiation with reduced neuronal size and abnormal wiring (Bauman and Kemper, 2005). Hence ASD and RTT do differ in pre- vs. post-natal timing of neurodevelopmental derangement, but significantly overlap in the endpoint result, yielding unbalanced local vs. long-distance and excitatory vs. inhibitory connectivity underlying disrupted sensory integration, altered social information processing, and frequent comorbidity with epilepsy (for review see Courchesne and Pierce, 2005; Geschwind and Levitt, 2007; Rubenstein and Merzenich, 2003). Additionally, many ASD brains show signs of neuroinflammation, including hyperproliferation and activation of astroglial cells, increased expression of immune genes, and overproduction of pro-inflammatory cytokines, such as IL-1, IL-6, IL-12, MCP-1, IFN-γ, and TNF-α (Garbett et al., 2008; Vargas et al., 2005).

(c) Post-mortem brains of DS patients are characterized by decreased brain size and weight, with disproportionate reductions of the superior temporal gyrus, cerebellum, and brainstem (Mrak and Griffin, 2004). In addition to decreased neuronal counts, dendritic trees fail to progressively grow in size, complexity, and connectivity after birth, despite their normal appearance during prenatal life (Takashima et al., 1981, 1994). Brains of adult DS patients typically display variable degrees of premature Alzheimer-type neuropathology, including beta amyloid deposition, dystrophic neurites, apoptotic cell death, and neuroinflammation (Mrak and Griffin, 2004).

Genome-wide expression studies

The advent of microarray technologies allows the design and implementation of genome-wide expression profiling, which is helping to unravel the molecular basis of phenotypic variation in many disease states. The partial, yet significant overlap between ASD, RTT and DS briefly discussed above, points toward the possible