Autism and Cancer Risk

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A literature review was conducted on the genetic and developmental bases of autism in relation to genes and pathways associated with cancer risk. Convergent lines of evidence from four types of analysis: (1) recent theoretical studies on the causes of autism, (2) epidemiological studies, (3) genetic analyses linking autism with mutations in tumor suppressor genes and other cancer-associated genes and pathways, and (4) contrasts with schizophrenia, Parkinson's, and Alzheimer's disease indicate that autism may involve altered cancer risk. This evidence should motivate further epidemiological studies, and it provides useful insights into the nature of the genetic, epigenetic, and environmental factors underlying the etiologies of autism, other neurological conditions, and carcinogenesis. ***Autism Res** 2011,4:302–310.* © 2011 International Society for Autism Research, Wiley Periodicals, Inc.

Introduction

Pleiotropy, whereby genes exert effects jointly on multiple phenotypes, is a universal mechanism of gene action. Pleiotropic effects involved in disease risks can be recognized using data on comorbidities between diseases, patterns of phenotypes associated with genetically based syndromes, and evidence regarding the developmental and physiological pathways whereby genetic and epigenetic alterations, alone and through interactions with specific environmental factors, exert their phenotypic effects.

Phenotypic traits that have been associated with idiopathic and syndromic autism include, among others, larger head and brain size, higher birth weight, and enhanced early childhood growth [DiCicco-Bloom et al., 2006; Dissanayake, Bui, Huggins, & Loesch, 2006; Lainhart et al., 2006; Mills et al., 2007; Mraz, Dixon, Dumont-Mathieu, & Fein, 2009; Sugie, Sugie, Fukuda, & Ito, 2005; Vaccarino & Smith, 2009]. This set of growth-related phenotypes, and associations of autism with some genetic syndromes involving losses of function in tumor-suppressor genes, such as phosphatase and tensin homolog (PTEN) [Butler et al., 2005] and NF1 (neurofibromin 1) [Mbarek et al., 1999], suggest that pleiotropic genetic and epigenetic factors, and environmental effects, may jointly affect risk of autism and cancer. Such effects are important both in the management of health care for autistic individuals, and in the specification of genetic and environmental factors that underlie autism risk. The purpose of this short review is to draw together the evidence salient to cancer risk in autism, to evaluate the hypothesis that these two conditions are mediated by common etiological factors.

Methods

The PubMed and Web of Science databases were searched using the keywords autism, autistic, genetic, imprinted, testosterone, cancer, pathway, theory, neurodevelopment, epidemiology, schizophrenia, Alzheimer's, and Parkinson's, alone and in various combinations.

Results and Discussion

A suite of recent studies provides evidence for genetically mediated effects that jointly influence risk of cancer, autism, and other neurological conditions. The evidence comes from four lines of research: (1) recent developmental models for the types of genetic, epigenetic, and environmental perturbations that mediate the etiology of autism, (2) epidemiological studies of cancer risk in relation to autism, (3) genetic-association and molecular-genetic studies demonstrating that mutations in tumor suppressor genes, and in other negative regulators of growth-stimulating signal-transduction pathways, are associated with the development of syndromic and idiopathic autism, and (4) altered risk of cancer in other neurological disorders, including schizophrenia, Alzheimer's, and Parkinson's.

Models on the Etiology of Autism

Two developmental models of autism have been described; (1) the extreme male brain theory, which posits a role for high fetal testosterone in the etiology of autism [Baron-Cohen, 2002; Baron-Cohen, Knickmeyer, & Belmonte, 2005], and (2) the imprinted brain theory, which postulates that autism is associated with a bias in

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the expression of imprinted genes toward increased relative effects from paternally expressed genes [Badcock & Crespi, 2006; Crespi & Badcock, 2008]. These two models should be considered as nonexclusive and relevant in some subset of autism cases, given the high degree of genetic, clinical, and etiological heterogeneity found in this condition [Happé, Ronald, & Plomin, 2006].

The extreme male brain theory, and a role for elevated fetal testosterone in the development of autism, have been supported by diverse evidence from endocrinology, neurodevelopment, and psychology [Baron-Cohen et al., 2005; Knickmeyer & Baron-Cohen, 2006]. This theory predicts that cancer rates should be elevated in autism for cancers whose development is potentiated or mediated by testosterone and other sex steriods, such as cancers of the breast, ovary, and uterus [Chakrabarti et al., 2009; Ingudomnukul, Baron-Cohen, Wheelwright, & Knickmeyer, 2007; Mitrunen & Hirvonen, 2003].

In a study based on self-report questionnaires, Ingudomnukul et al. [2007] found that compared to controls, women with autistic spectrum disorders or an autistic child reported a significantly higher incidence of one or more close relatives with: (a) ovarian cancer, tumors, or growths, (b) uterine cancer, tumors, or growths, or (c) prostate cancer. Similarly, significantly more mothers of children with autism reported a family history of breast, ovarian, or uterine cancers or growths, compared to controls. These data provide preliminary support for the hypothesis that rates of testosterone-mediated cancer may be higher in individuals on the autism spectrum, given that autism is highly heritable. The mechanisms for such increased cancer risk may involve both prenatal effects on stem cell pools, which potentiate cancer risk [Baik et al., 2005], and direct effects of hormone levels on the development of cancers in later life.

The imprinted brain theory predicts that autism is mediated in part by imbalances in the expression of imprinted genes, toward higher relative paternal-gene expression [Badcock & Crespi, 2006; Crespi & Badcock, 2008]. Some paternally expressed imprinted genes also tend to promote the development of cancer via growth enhancement, whereas many maternally expressed imprinted genes act as tumor suppressors and reduce cancer risk [Hernandez, Kozlov, Piras, & Stewart, 2003; Tycko & Morison, 2002]. The development of cancer is thus characterized by increased expression (via loss of imprinting) for paternally expressed imprinted genes and reduced expression of maternally expressed imprinted genes whose products suppress growth and proliferation [Feinberg & Tycko, 2004; Jelinic & Shaw, 2007]. The imprinted brain theory thus predicts a higher incidence of cancer in autism, in part due to enhanced growth (which modulates cancer risk), and in part due to effects of imprinted-gene dysregulation on the somatic evolution of cancer.

Beckwith–Weidemann syndrome, which involves general body overgrowth due to increased expression of the paternally expressed gene IGF2 (insulin-like growth factor II) or reduced expression of the maternally expressed genes H19 or CDKN1C (cyclin-dependent kinase inhibitor 1C) [Eggermann, 2009], is associated with greatly increased childhood cancer risk [Rump, Zeegers, & Van Essen, 2005]. High rates of autism (6.8%) have also be reported among children with this syndrome [Kent, Bowdin, Kirby, Cooper, & Maher, 2008].

A pattern of overgrowth in a subset of idiopathic autism cases is suggested by findings of highly proliferative placentation [Anderson, Jacobs-Stannard, Chawarska, Volkmar, & Kliman, 2007], increased head size, brain size, and cortical thickness in some studies [DiCicco-Bloom et al., 2006; Dissanayake et al., 2006; Lainhart et al., 2006; Mraz et al., 2009], higher birth weight in males in one study [Sugie et al., 2005], faster body growth [Dissanayake et al., 2006], and increased expression of growth factors [Connolly et al., 2006; McCaffery & Deutsch, 2005; Miyazaki et al., 2004]. Mills et al. [2007] also report higher levels of IGF1 (insulin-like growth factor I) and IGF2 in autistic boys. Higher levels of IGF1 and IGF2 and larger birth size (weight, length, and/or head size) are also associated with increased risk of some adult-onset cancers such as breast cancer [Kurmasheva & Houghton, 2006; Maehle, Vatten, & Tretli, 2010; Silva et al., 2008; Tamimi et al., 2010].

Epidemiological Studies

Shavelle, Strauss, and Pickett [2001] analyzed the causes of death in autistic individuals between 1983 and 1997 in California, excluding cases of severe tuberous sclerosis. These authors reported a standardized mortality ratio of death from cancer of 1.9 for subjects with no or mild mental retardation, and a ratio of 2.9 in subjects whose mental retardation was moderate, severe, or profound. However, the absolute number of deaths was small in each of these two categories (6 and 15), and the population was relatively young, with over 80% under age 15. Additional studies are needed on an older population to evaluate the robustness and generality of these results.

A recent study [Kao, Buka, Kelsey, Gruber, & Porton, 2010] tested for epidemiological associations between the incidence of autism and rates of a suite of cancers, based on state-wide prevalence of these two conditions as reported in the U.S.A. They found highly significant correlations of autism rates with the incidence of in situ breast cancer, but not with rates of other cancers, across states, after controlling for among-state differences in methods of reporting. Such correlations may be due to environmental risk factors that jointly mediate the

development of autism and breast cancer, or to gene by environment interactions [e.g., D'Amelio et al., 2005].

Genetic Studies of Genes and Pathways Underlying Autism

Studies of the genetic basis of autism can provide insight into potential links between autism and cancer, given that these two conditions may share underlying genetic or epigenetic changes and developmental-metabolic pathway alterations. Several recent lines of evidence indicate that autism is associated with upregulation of the PI3K (phosphatidylinositol 3-kinase)-Akt-mTOR (mammalian target of rapamycin) growth-signaling pathway, via mutational loss of function or reduced function in genes which negatively regulate pathway activity [Belmonte & Bourgeron, 2006; Bourgeron, 2009; Hoeffer & Klann, 2010; Kelleher & Bear, 2008; Kwon et al., 2006; Neves-Pereira et al., 2009; Serajee, Nabi, Zhong, & Mahbubul Huq, 2003].

Genes in this pathway that influence autism risk are depicted in Figure 1, in the context of pathway structure and regulation. Upregulation of the PI3K-Akt-mTOR pathway is also closely associated with the development of many human cancers [Bunney & Katan, 2010; Ciuffreda, Di Sanza, Incani, & Milella, 2010; Engelman, Luo, & Cantley, 2006].

First, autism and macrocephaly have been associated with germline mutations in PTEN, a tumor suppressor gene that acts as a key negative regulator of PI3K-Akt-mTOR signaling [Butler et al., 2005; Greer & Wynshaw-Boris, 2006; Herman et al., 2007; McBride et al., 2010; Varga, Pastore, Prior, Herman, & Mcbride, 2009]. Deactivation of PTEN in a mouse model resulted in reduced social interaction, increased responsiveness to sensory stimulation, neuronal hypertrophy and macrocephaly, hyperactivity, resistance to handling, and impaired social learning, all phenotypes associated with autism [Kwon et al., 2006]. Germline and somatic PTEN loss of function

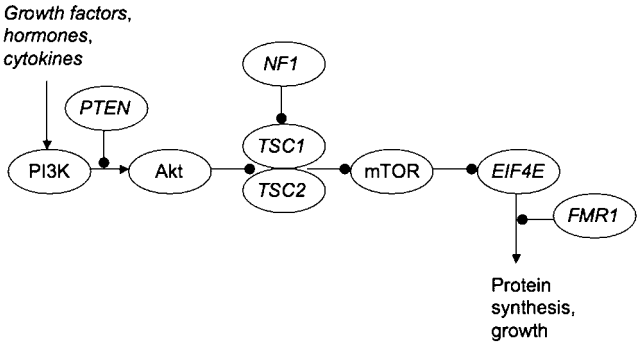

Figure 1. Simplified version of a component of the PI3K-Akt-mTOR pathway, showing positive (arrows) and negative (pegs) interactions, in relation to genes that have been associated with autism risk (shown in italics). NF1 interacts via the Ras pathway. Alterations of six genes, EIF4E, FMR1, NF1, PTEN, TSC1, and TSC2, that regulate this pathway have been associated with autism.

mutations have been associated with the incidence and development of early onset cancers, including cancers of the breast, kidney, prostate, and brain [Endersby & Baker, 2008; McBride et al., 2010].

Second, autism is found at a high frequency in the neurological-tumor syndrome tuberous sclerosis, a condition caused by mutations in the TSC1 (tuberous sclerosis 1) or TSC2 (tuberous sclerosis 2) genes, whose gene products form a heterodimer that acts as a tumor suppressor due to its negative effects on PI3K signaling [Curatolo, Napolioni, & Moavero, 2010; Kwon et al., 2006; McCall, Chin, Salzman, & Fults, 2006; Serajee et al., 2003]. TSC2 has also been linked with autism in a genetic-association study, as have two other genes in the PI3K pathway, inositol polyphosphate-1-phosphatase, and PIK3CG (phosphatidylinositol 3-kinase, catalytic, gamma) [Serajee et al., 2003]; all three of these genes are also in consensus areas for linkages to autism from genome-scan data.

Third, the neurofibromatosis gene NF1, which also acts as a tumor suppressor and negative regulator of the PI3K-Akt-mTOR pathway (via the Ras pathway), has been linked with autism in an association study [Marui et al., 2004]. Epidemiological studies indicate that autism involves a greater than 100-fold increase in risk for neurofibromatosis [Mbarek et al., 1999]; this conditions also involves macrocephaly and high rates of cancer [Szudek, Evans, & Friedman, 2003].

Fourth, a high proportion of males with Fragile X syndrome, due to mutations in the FMR1 (fragile X mental retardation 1) gene, exhibit autism [Hagerman, 2006; Hernandez et al., 2009], and head size is increased in this condition [Hagerman, 2006]. Fragile X syndrome is caused by loss of function of the FMRP protein, which leads, in a mouse model, to upregulation of the PI3K-Akt-mTOR pathway [Sharma et al., 2010]. One study demonstrated, however, that Fragile X syndrome appears to involve reduced cancer risk (with 4 of 223 subjects developing cancer; Schultz-Pedersen et al., 2001], a finding that may be related to reduced expression of the WNT7A (wingless-type MMTV integration site family member 7A) gene in this condition [Rosales-Reynoso et al., 2010].

Fifth, autism has been associated with mutations in the gene eIF4E (eukaryotic translation initiation factor 4E), which codes for a protein that functions in the rate-limiting step of eukaryotic translation initiation, downstream of the PI3K-Akt-mTOR pathway [Neves-Pereira et al., 2009]. Such mutations involve increased promotor activity, suggesting increased activity of the gene and pathway upregulation. High expression of eIF4E in many cancers has motivated the recent development of chemotherapeutic agents to reduce its activity [Fischer, 2009].

Altered regulation of the PI3k-Akt-mTor pathway may engender different physiological or developmental effects depending upon the tissue, developmental stage, and cell

type involved. Thus, pathway upregulation in mitotic cells (and in cancer) may lead to higher rates of growth, but in post-mitotic neurons, pathway upregulation may stimulate excessive translation that modulates synaptic plasticity and behavior, leading to increased risk of autism spectrum conditions [Costa-Mattioli, Sossin, Klann, & Sonenberg, 2009; Hoeffer & Klann, 2010; Richter & Klann, 2009; Rosner et al., 2008].

Additional genes associated with both cancer and autism, genetically or via altered expression (or both), include the tumor suppressor gene adenomatous polyposis coli (APC) [Zhou et al., 2007; see also Cui, Jiang, Jiang, Xu, & Yao, 2005], brain-derived neurotrophic factor (BDNF) [Connolly et al., 2006; Hu et al., 2006; Miyazaki et al., 2004; Tsai, 2005], the proto-oncogene MET [Burdick, DeRosse, Kane, Lencz, & Malhotra, 2010; Campbell et al., 2006], the imprinted gene UBE3A (ubiquitin protein ligase E3A) [Gao et al., 2005; Glessner et al., 2009; Jiang et al., 2004; Samaco, Hogart, & Lasalle, 2005], and the gene PARK2 (parkin 2) [Glessner et al., 2009; Morris, Veeriah, & Chan, 2010].

Growth and macrocephaly in idiopathic and syndromic autism may also be influenced by pathways more or less independent of the PI3K-Akt-mTOR pathway, as described by McCaffery and Deutsch [2005] for autism, fragile X syndrome, Sotos syndrome, and valproic acid teratogenicity. Indeed, McCaffery and Deutsch [2005] provide extensive evidence that autism may commonly involve overstimulation of nuclear receptor signaling, mediated by effects of androgens, estrogen, thyroid hormones, retinoic acid, and vitamin D in fetal and early post-natal development.

Comparisons with Other Neurological Conditions

A precedent for altered rates of carcinogenesis in neurodevelopmental conditions is provided by schizophrenia, which involves a well-replicated reduction in cancer risk among probands and first-order relatives [Barak, Achiron, Mandel, Mirecki, & Aizenberg, 2005; Cohen, Dembling, & Schorling, 2002; Dalton, Mellemkjaer, Thomassen, Mortensen, & Johansen, 2005; Goldacre, Kurina, Wotton, Yeates, & Seagroat, 2005; Levav et al., 2007; Lichtermann, Ekelund, Pukkala, Tanskanen, & Lonnqvist, 2001; meta-analysis by Catts, Catts, O'Toole, & Frost, 2008]. Several mechanisms may mediate such reductions in cancer risk.

First, evidence from genome scans, association studies, functional analyses, and pharmacology suggests that, in contrast to autism, reduced activation of the PI3K-Akt-mTOR pathway is an important risk factor for schizophrenia and bipolar disorder [Emamian, Hall, Birnbaum, Karayiorgou, & Gogos, 2004; Kalkman, 2006; Stopkova et al., 2004; see also Freyberg, Ferrando, & Javitch, 2010]. Reduced activation is also associated with lower cancer risk, by well-documented mechanisms [Agarwal, Carey, Hennessy, & Mills, 2010; Kalkman, 2006].

Second, schizophrenia also contrasts with autism in that it has been reported to involve reduced expression of growth factors [Durany & Thome, 2004; Gunnell & Holly, 2004; Kale et al., 2009; Moises, Zoega, & Gottesman, 2002; Weickert et al., 2003], including BDNF [Chen et al., 2009; Grillo et al., 2007].

Third, stem cell proliferation is decreased in schizophrenia [Eriksson, 2006; Reif et al., 2006], which may partially account for the notable olfactory and hippocampal dysfunctions in this disorder [e.g., Hanlon et al., 2006; Moberg et al., 2006] given that these are the only two brain regions that normally undergo adult neurogenesis [Sohur, Emsley, Mitchell, & Macklis, 2006]. Stem cell function has yet to be studied directly in autism. However, neurogenesis is stimulated by BDNF and serotonin [Sohur et al., 2006], both of which have been shown to be elevated in autism in some studies [Connolly et al., 2006; Hranilovic et al., 2007; Miyazaki et al., 2004], and Courchesne and Pierce [2005] suggest that autism involves increased neurogenesis in childhood, in association with accelerated brain growth Cancer is strongly linked with stem cell dysregulation and proliferation [e.g., Li, Tiede, Massague, & Kang, 2007].

Finally, schizophrenia involves reduced thresholds for apoptosis or cellular senescence, mediated by tumor suppressor genes [Catts et al., 2006; Glantz, Gilmore, Lieberman, & Jarskog, 2006; Ni et al., 2005], and increased expression of some tumor suppressor genes such as APC [Cui et al., 2005]. The APC gene has also recently been linked with autism risk [Zhou et al., 2007]; the same three SNPs were genotyped in this autism study as for the linkage of APC with schizophrenia [Cui et al., 2005] and showed a different pattern of disease-haplotype asssociation, T–G–A in autism, and C–A–T in schizophrenia. The APC gene was upregulated in schizophrenia, which is consistent with reduced cancer risk [Cui et al., 2005]. Whether this gene was up or downregulated in autism was not studied, but the authors [Zhou et al., 2007] reported a significantly higher frequency in autism for a different APC allelic variant, 8,636C>A, that may be associated with higher risk of colorectal cancer [Zhou et al., 2004]. APC is a component of the Wnt-dependent signaling pathway. Other components of the WNT pathway have been associated with cancer and schizophrenia [Cotter et al., 1998; Janssens, Janicot, & Perera, 2006, Table 1] as well as with autism [De Ferrari & Moon, 2006; Vaccarino & Smith 2009; Wassink et al., 2001].

Parkinson's disease also involves a decreased incidence of cancer [Bajaj, Driver, & Schernhammer, 2010; West, Dawson, & Dawson, 2005], in part as a result of dysregulation of PTEN and downregulation of the PI3K-Akt-mTOR pathway [Kim & Mak, 2006]. Reduced incidence of cancer has also been found among individuals with Alzheimer's disease, compared to controls [Roe,

Behrens, Xiong, Miller, & Morris, 2005; Roe et al., 2010; Ukraintseva et al., 2010, for females]. Taken together, this evidence from schizophrenia, Parkinson's and Alzheimer's suggests that neurological diseases involving some degree of neurodegeneration may engender relatively low risks of cancer, apparently due to decreased thresholds for apoptosis or reduced growth-signalling pathway activation [Behrens, Lendon, & Roe, 2009; Caricasole et al., 2005; Morris et al., 2010; Plun-Favreau, Lewis, Hardy, Martins, & Wood, 2010].

Conclusions

Diverse, convergent lines of evidence suggest pleiotropic effects of autism-associated genes on risk of cancer. The primary implications of this finding are threefold. First, the search for the underlying genetic, epigenetic, and developmental bases of autism may be guided by overlap of genes underlying autism and genes that affect cancer risk, via effects on sex steroid-hormone metabolism, genomic-imprinting, and regulation of growth signaling pathways such as PI3K-Akt-mTOR. Second, the discovery of pharmacological therapies to help alleviate autism [Silva & Ehninger, 2009] can be guided, in part, by perspectives for the treatment of cancer that focus on the same growth-signaling pathways [e.g., Ciuffreda et al., 2010; Ghayad & Cohen, 2010]. Third, epidemiological studies are needed to robustly evaluate the hypothesis that risks of cancer, or specific cancers, are altered in individuals with autism and their relatives.

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