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Connecting the dots: Overlaps between autism and cancer suggest possible common mechanisms regarding signaling pathways related to metabolic alterations

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ABSTRACT

Common features between autism spectrum disorders (ASDs) and cancer have been discerned using methodologies from a number of disciplines, including genetics, bioinformatics and epidemiological studies. To understand such apparent overlaps between these two conditions and the mechanisms that may underlie these linkages, it is important to look at their multi-level systems context. Here we discuss ASDs and cancer linkages across levels ranging from genes to pathways and systems, as well as from the vantage points of mechanism and of clinical and epidemiological studies. Review of existing findings yielded evidence that ASDs and cancer overlap extensively in signal transduction pathways that are involved in metabolic processes. We hypothesize that further studies focusing on illuminating the relationships between ASDs and cancer, specifically with regard to signaling pathways that regulate metabolic activities, could help shed new insight on these conditions and develop treatment strategies that, by targeting underlying mechanisms, may be more efficient and effective for both conditions.

Introduction

ASDs are a highly variable spectrum of conditions emerging in early development, associated with many genes, various medical comorbidities, and levels of intelligence ranging from profoundly impaired to highly gifted. Historically they were defined behaviorally [1], and this remains the case today, given that no one genetic or physiological feature has yet been found consistently across all individuals who meet behavioral criteria for this spectrum disorder. In 2014, the Centers for Disease Control and Prevention (CDC) estimated that 1 in 68 children had ASDs as of 2010 [2]; this was a 30% increase over the figure announced in 2012. Given that these spectrum conditions clearly have major and apparently growing human, social, and economic impacts, a clearer understanding of their pathogenesis and mechanisms could have great public health significance.

The heterogeneity in ASDs is present between individuals across multiple levels, including nuances of behavioral manifestations as well as genetic, brain, physiological and medical features—and yet everyone with this diagnosis meets the same defining behavioral criteria, which include social impairments, communication difficulties, and restricted, repetitive, and stereotyped patterns of behavior. Cancers also involve great heterogeneity – not only are there many kinds of cancer, but within cancer types there is also heterogeneity. Tumor heterogeneity has been observed in many cancers including of breast, prostate, colon, brain, bladder and blood. Different tumor cells can show distinct morphological and phenotypic profiles, involving characteristic features at the levels of cellular morphology, gene expression, metabolic profiles, motility, proliferation, and metastatic potential.

A growing number of published studies from various disciplines and perspectives have identified ways that ASDs are also related to other conditions with very different phenotypes, such as other neurological diseases, cancer, metabolic conditions, and heart diseases [3–6]. While this additional dimension may add further complexity to our attempts to understand ASDs, on the other hand looking at ASDs in a framework that also includes other diseases and conditions may allow us to discern patterns and features that might not be so easily perceived by looking at ASDs – or for that matter at any of the other apparently related conditions – alone.

Recently researchers have looked for overlapping genes and pathways between ASDs and cancers, and studies to date have con-

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sistently observed them [7,8]. But it is not yet clear what common mechanism(s) between these two conditions and amongst the overlapping genes and pathways might exist. Here we discuss the possible relationships between ASDs and cancers, and propose a hypothesis of how they may overlap and what may contribute to their common features.

Genetic studies: ASDs and cancer share risk genes

The identification of autism risk genes that were also related to cancer was the first indication of an autism-cancer link. This evidence emerged from examining findings from studies of copy number variants and epigenetic modifiers, and data from genome-wide sequencing of individuals with ASDs. A recent study, which assessed characteristics of ASD risk genes based on protein functions, found that 43 specific genes associated with autism susceptibility also have associations with cancer [9]. These genes are involved in varieties of biological activities in relation to "chromatin remodeling and genome maintenance, transcription factors, and signal transduction pathways leading to nuclear changes" [9], which are known to be associated with tumorigenesis.

As of December 2016, the SFARI (Simons Foundation Autism Research Initiative) Gene-Human Gene Module recorded 859 human genes implicated as relevant to ASDs (https://gene.sfari.org/autdb/HG_Home.do). The Cancer Gene Census, in its release v80 (February 13th, 2017) of a list of all cancer census genes from COSMIC (the Catalogue Of Somatic Mutations In Cancer) recorded 616 genes for which mutations have been causally implicated in cancer (https://cancer.sanger.ac.uk/census). We compared the list of the SFARI genes to the list from the Cancer Gene Census, and found these two gene lists shared 77 genes in common (Table S1). These overlapping genes include both oncogenes such as *AR, BRAF, GNAS*, and *HRAS*, and tumor suppressor genes such as *APC, BRCA2, NF1*, and *TSC1*. It is notable that ASD associated genes include both oncogenes and tumor suppressor genes (TSG). Table S1 lists the ASD and cancer overlapping genes, their molecular function, as well as their roles in ASDs and cancer, in reference to SFARI and Cancer Gene Census. Oncogenes are genes that have the potential to cause cancer; while tumor suppressor genes, also called antioncogenes, are genes that could protect cells from becoming tumor cells. In tumor cells, oncogenes are often overexpressed or mutated, while tumor suppressor genes may not work properly. While these genes may play non-cancer-related roles with regard to how they contribute to the features of Autism Spectrum Disorder, it is possible that they may also affect the risk in these individuals of developing cancer.

Epidemiological and clinical studies: unclear if ASD diagnosis confers altered cancer risk

Although one might infer that if people with ASDs have genes in common with cancer, they may also have increased risk of developing cancer, whether the rates of cancer in ASDs are actually increased is rather unclear. A study conducted in 2010 reviewed 702 ASD cases and did not find correlations between ASD diagnosis and incidence of childhood cancer [10]. Later in the same year, an epidemiological study investigated the relationship between incidence of autism and rates of cancers based on state-wide prevalence of these two conditions, and found correlations between autism and *in situ* breast cancer. A database analysis published in 2015 that used data from the Taiwan National Health Insurance database compared the number of cancers in years 1997–2011 in patients with autism with a standardized incidence ratio (the expected number). The authors investigated over 8000 cases and found 20 cases with cancer, which "was significantly higher than a total number of expected cancers with a standardized incidence ratio (SIR) estimate of 1.94 (95% CI 1.18–2.99)"[11]. However, a recent study using data from the University of Iowa Hospitals and Clinics' electronic medical record reported that patients with ASDs had lower cancer rates [12]. More recently, another study using registry data from the Department of Health of Western Australia found that mothers of children with autism but without intellectual disability had an increased risk of cancer [13].

Thus, the evidence to date is inconsistent regarding whether people classified as having ASDs have different rates of cancers than the general population. It is possible that although ASDs have many genes in common, it is far from the case that all of these genes are carried in common across people with a ASD diagnosis; thus, as a group, people carrying this diagnosis may have neither higher nor lower cancer rates. This may be due to the opposing impacts of the involvement of both oncogenes and tumor suppress genes. It is also possible that subsets not yet identified within ASDs may have greater autism risk. For example, the above-cited study identifying greater risk of cancer in a subset of mothers of children with autism [13] suggests the value of designing studies to assess the risk of cancer outcomes in children of such mothers.

Cancer genes also play roles in neural development

It is not novel to find that genes and pathways that are implicated in neurological diseases have also been associated with cancer [14]. Conversely, cancer genes have also been identified as playing roles in neural development. For example, *BRCA1* (Breast cancer susceptibility gene 1), which is a breast and ovarian cancer tumor suppressor, has been found to be involved in brain development [15]. Chromatin regulators such as *EZH2* and *CHD8* have been found to play essential roles throughout neural development [16]. It would be of great interest to seek to identify common features in the contributions of these genes to neural development on the one hand and cancer on the other.

Both ASD and cancers involve altered cellular or system development. We examined the 77 ASD and cancer shared genes from Table S1 and found that they indeed were enriched for "Cell Development" under the category Biological Process (BP) of Gene Ontology (GO). To do this, we investigated the 77 genes in Molecular Signatures Database, MSigDB [17] v6.0 (http://www.broadinstitute.org/gsea/msigdb/index.jsp). Gene symbol was used as gene identifier to import the genes. We applied the "Compute Overlaps" tool from MSigDB website, under "Investigate gene sets" category, which uses the hypergeometric distribution to examine how the ASD and cancer common genes may overlap with GO-BP gene set. The result shown that the common genes were enriched for GO_CELL_DEVELOPMENT (p-value 2.27 e^{-23}, Table S2). These initial findings suggest that further investigations of the common features between ASDs and cancers regarding developmental processes might well be fruitful.

One implication of the fact that a remarkable number of ASD-associated genes are also associated with cancer, as well as the fact that cancer associated genes also function in neural development, is that the functions associated with these genes might be associated with processes whose disturbance can increase vulnerability to either cancer, ASDs or both, depending on circumstances. Such overlap might be due to pleiotropy, i.e. genes playing multiple roles and participating in diverse systems. It is possible that abnormalities or defects in the function of these gene in different systems—either during different developmental periods, or in the setting of differences in other pertinent genes—may potentially lead to different trajectories, culminating in some cases in neurological conditions and in other cases in cancer. There is also the possibility that identifying mechanisms operating in genes that