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Forum

Autism and Cancer Share Risk Genes, Pathways, and Drug Targets

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Autism is a neurodevelopmental disorder, diagnosed behaviorally by social and communication deficits, repetitive behaviors, and restricted interests. Recent genome-wide exome sequencing has revealed extensive overlap in risk genes for autism and for cancer. Understanding the genetic commonalities of autism(s) and cancer(s), with a focus on mechanistic pathways, could lead to repurposed therapeutics.

Autism is a neurodevelopmental disorder, diagnosed by behavioral symptoms including impaired social interactions and communication, repetitive behaviors, and restricted interests [1]. Extraordinarily high heritability for autism spectrum disorder (ASD) has been detected in twin studies, with a range of 50–90% concordance between monozygotic twins, compared with 0–30% between dizygotic twins and siblings, and approximately 1% prevalence in the general population, along with a high male:female ratio [2]. International consortia searching for the genetic causes of ASD quickly recognized that autism is not a monogenic disorder. Hundreds of *de novo* and familial risk genes, copy number variants, and epigenetic modifiers have been identified through linkage analysis, genome wide-association studies, and exon and whole-genome sequencing of individuals with ASD over the past 2 years [2–5].

Table 1 summarizes the characteristics of risk genes for ASD that are also risk genes for cancers, extending the original finding that the PI3K-Akt-mTOR signaling axis (involving PTEN, FMR1, NF1, TSC1, and TSC2) was associated with inherited risk for both cancer and ASD [6–9]. Recent genome-wide exome-sequencing studies of *de novo* variants in ASD and cancer have begun to uncover considerable additional overlap. What is surprising about the genes in Table 1 is not necessarily the number of risk genes found in both autism and cancer, but the shared functions of genes in chromatin remodeling and genome maintenance, transcription factors, and signal transduction pathways leading to nuclear changes [7,8]. Chromatin remodeling factors important in altering nucleosome accessibility for transcription and genome maintenance mechanisms include *CHD8*, *CHD7*, *CHD2*, *ARID1B*, and *ATRX*. *ATRX* may exert a more specific function in telomere maintenance, analogous to other Swi2/Snf2 family factors, such as *ERCC6, RAD54, HTLF, SHPRH*, or *RAD16*, which function in dedicated DNA repair pathways. Proteins involved in histone methyltransferase reactions important in setting the histone code include *ASHL1*, *EHMT1*, *EHMT2*, *KMT2C*, *KMT2D*, and *SUV420H1. PHF2, KDM5B*, and *KDM6B* are histone demethylases, and *MACROD2* encodes a nuclear factor regulated by a metabolite of histone deacetylation. Ubiquitin modifications to histones and other proteins are implicated by the risk genes *CUL3*, *HERC2*, *MIB1*, *TBL1XR1*, *TRIP12*, *UBE3A*, and *WAC*. Transcription factors genetically implicated in both autism and cancer include *ADNP*, *PAX5*, *FOXP1*, *TCF7L2*, and *TBLXR1*. Interestingly, these nuclear factors are downstream of several key signal transduction pathways also genetically implicated in ASD and cancer, including *PTEN* [7]. *PTEN* functions in the AKT signaling pathway, where its phosphatase activity is needed for AKT downregulation. Nuclear PTEN also regulates recombinational DNA repair, a key genome maintenance pathway (see below). It is unclear whether this is related to its signaling function or a consequence of a second independent *PTEN* activity, but this dual function may provide the rationale for the dominant role of PTEN in cancer and autism. Other genes encoding common tumor signaling pathways include *MET8*, *PTK7*, and *HRAS*, while p53, AKT, mTOR, WNT, NOTCH, and MAPK are components of signaling pathways regulating the nuclear factors described above.

Autism is comorbid with several monogenic neurodevelopmental disorders, including Fragile X (*FMR1*), Rett syndrome (*MECP2*), Phelan-McDermid (*SHANK3*), 15q duplication syndrome (*UBE3A*), neurofibromatosis (*NF1*), tuberous sclerosis (*TSC1* and *TSC2*), and Cornelia de Lange syndrome (*NIPBL* and *SMC1A*) (Table 1). Neurofibromatosis and tuberous sclerosis are directly associated with tumors, but such tumors are benign and rarely associated, if at all, with malignancies. However, mutations in *NF1*, *TSC1*, or *TSC2* enhance the risk for developing cancer [6]. Notably, *NF1, TSC1*, and *TSC2* function like *PTEN* in the AKT pathway of mTOR control. Mutations in transcriptional factor genes also mediate downstream signaling pathways that include key proteins implicated in cell proliferation or differentiation pathways implicated in cancer and autism, such as mTOR, RAS GTPases, MAP kinases, AKT, EIF4E, WNT, ERK, PI3K, and CHD8. A risk gene originally identified in individuals with cancer may present as a *de novo* mutation in a small number of individuals with ASD, or may be implicated in ASD through interactome analysis of interrelated genes and interacting proteins, such as within a signaling pathway (Table 1).

What does tumor cell proliferation have in common with brain development and neuronal synapse formation? Similar to cancers, 'autisms' are best conceptualized in the plural. ASD encompasses a broad range of putative causes, symptom presentations, and outcomes, including

Table 1. Characteristics of Risk Genes Implicated in Both Autism and Cancer[a]

Gene Symbol	Gene Name	Human Chromosome Location	Protein Function	Interacting Proteins	Autism-Related Neurodevelopmental Syndrome	Cancer Susceptibility or Pathway	Refs (PMID)
ADNP	Activity-dependent neuroprotector homeobox	20q13.13	Potential transcription factor. May mediate some neuroprotective peptide VIP-associated effects	SMARCA4, SMARCC2, ARID1A	Helsmoortel-Van der Aa syndrome	p53, WNT	25891009
ANK2	Ankyrin 2, Neuronal	4q25	Attaches integral membrane proteins to cytoskeletal elements and regulates cell motility, activation, proliferation, and contact	DMD, DCTN4, ACTF1	Long (Electrocardiographic) QT Syndrome 4	Proteoglycans	25863124
ARID1B	AT Rich Interacting Domain 1B (SWI1-like), BRG1-Binding protein	6q25.3	Subunit of SWI/SNF chromatin remodeling complex	ARID1A, SMARCA2, RELB, SMAD9, ASF1A	Coffin–Siris syndrome	ESR1, WNT; prostate cancer	25891009
ASH1L	Lysine N-Methyltransferase 2H	1q22	Histone methyltransferase specifically methylating Lys-36 of histone H3 (H3K36me)	SMAD7, HIST1H3A	Autism, susceptibility	Lysine degradation	26402605
ATRX	RAD54, Alpha Thalassemia/Mental Retardation Syndrome X-linked	Xq21.1	SWI/SNF ATP-dependent DNA motor protein that acts in heterochromatin and at telomeres	CBX5, DAXX, HDAC1, SMC1A, SMC3	Alpha-thalassemia/mental retardation syndrome	Breast cancer, telomeres	24779060
CHD2	Chromodomain Helicase DNA Binding Protein 2, ATP-dependent helicase	15q26.1	SWI/SNF ATP-dependent DNA motor protein that acts as a chromatin remodeling factor and transcriptional regulator, and also in DNA repair	SUMO1, PARK7	Epileptic encephalopathy, childhood-onset	Chromatin regulation	25891009
CHD7	Chromodomain Helicase DNA Binding Protein 7, ATP-dependent helicase	8q12.2	SWI/SNF ATP-dependent DNA motor protein that acts as a chromatin remodeling factor and transcriptional regulator	CHD8, PBRM1, SMARCC1, SMARCC2, SMARCE1	CHARGE syndrome	WNT signaling, chromatin regulation	24768552
CHD8	Chromodomain Helicase DNA Binding Protein 8, HELSNF1, AUTS18	14q11.2	SWI/SNF ATP-dependent DNA motor protein that acts as a chromatin remodeling factor and transcriptional regulator	RBBP5, WDR5, CTNNB1, USF1, CTCF	Autism, susceptibility	WNT signaling, chromatin regulation	25891009
CUL3	Cullin 3	2q36.2	Core component of multiple cullin-RING-based BCR (BTB-CUL3-RBX1) E3 ubiquitin–protein ligase complex	KLHL3, NEDD8, KEAP1, RBX1, CASP8	Autism, susceptibility	WNT signaling, chromatin regulation	25363768
DNMT3A	DNA (5-cytosine)-methyltransferase 3A	2p23.3	Required for genome-wide *de novo* methylation; essential for establishment of DNA methylation patterns during development	DNMT3L, DNMT3B, UHRF1	Autism, susceptibility	Chromatin regulation	26402605

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