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Autism and cancer share risk genes, pathways and drug targets

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Abstract

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.

Keywords

Autism; cancer; gene; signaling pathway; chromatin remodeling; DNA repair

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, as compared to 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, exon and whole genome sequencing of individuals with ASD over the last 2 years [2–5].

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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, 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 *MET* (mitogen inducible gene 8), *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*, *TSC2*) and Cornelia de Lange syndrome (*NIPBL*, *SMC1A*) (Table 1). Neurofibromatosis and tuberous sclerosis are directly associated with tumors, but such tumors are benign and rarely if at all associated with malignancies. However, mutations in *NF1*, *TSC1* or *TSC2* do 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 which 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, 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, *e.g.* within a signaling pathway (Table 1).

What does tumor cell proliferation have in common with brain development and neuronal synapse formation? Like cancers, “autisms” are best conceptualized in the plural. ASD encompasses a broad range of putative causes, symptom presentations, and outcomes, including both macrocephaly and microcephaly, suggesting deficits in the cellular commitment to proliferation versus differentiation, similar to cancer. This difference may be in the life stage of cellular proliferation. Errors associated with genome maintenance during fetal life may occur at critical time periods for proliferation of neuronal precursors that affect prenatal brain development, resulting in neurodevelopmental disorders, whereas errors more commonly occur during adult life in cell types susceptible to tumors. Biological mechanisms with potential commonalities between genes implicated in both cancers and autisms may be revealed from a closer investigation of the specific actions of genes and converging pathways identified in both [8]. For example, *UBE3A*, which is duplicated in ~1–2% of ASD, encodes the ubiquitin E3 ligase protein E6-AP, first named as an E6 interacting protein that degrades p53 in human cervical cancer [10].

The intersection between autism and cancer in genome maintenance pathways is novel and particularly compelling. A large cohort of autism and cancer genes affect genome maintenance including signaling molecules (*PTEN*), DNA repair factors (*ERCC6, SMARCA2*), structural chromosome components such as cohesins (*NIPBL*, *SMC1A*, *SMC2*), factors needed for Alternative Lengthening of Telomeres (*ATRX*), and post-translational modifiers (*TRIP12*, *UBE3A*, *HERC2*). The functional overlap goes beyond this common gene set, as genomes from individuals with ASD show mutational hotspots and a high incidence of copy number variations. These genetic events signal pathological outcomes of DNA replication stress. Many neuron-specific genes are rather large with primary transcripts in the Mbp range. Such genes are at particular risk for transcription-DNA replication conflicts that underpin a significant amount of genome instability [11]. While these genes are typically transcribed only in terminally differentiated cells, any miscoordination of transcriptional control, DNA replication, differentiation, and cell cycle phasing will greatly increase the risk of mutations targeted to these genes encoding critical brain functions. Transcription-coupled repair, the pathway defined by *ERCC6*, is of particular importance for terminally differentiated cells and long transcription units. Overall too little is known about DNA repair in terminally differentiated cells and more studies are needed to evaluate other pathways such as recombinational DNA repair in differentiated cells and somatic genomic instability in neurons. Thus, similar to cancer, the inherited risk for autism may be compounded by further somatic mutations associated with mutations in known risk genes that may be biased for genes with neuronal functions.

The functional overlap of genes and pathways between autism and cancer would suggest that individuals with autism may carry a higher cancer risk. While there is some epidemiological evidence of higher cancer risk in children, adolescents, and young adults with ASD [9, 12], the absolute number of cases is low and more studies need to be conducted, particularly in adults, as cancer incidence is significantly correlated with age.

Mouse models with mutations in many of these genes have been widely used in both cancer and autism research. Some of these mutant mouse models recapitulate behavioral and biological features of autism [13]. These model systems are proving useful in understanding

the consequences of specific mutations on overgrowth of brain regions, unusual patterns of white matter connectivity, aberrant numbers of synapses, and altered morphology of dendritic spines, in parallel to understanding cell proliferation, cell cycle, DNA repair, and epigenetic causes in malignancies.

Considerable translational value can be gained from a new focus to understand the genetic commonalities of autism(s) and cancer(s). Importantly, mechanistic similarities can be leveraged into therapeutic strategies. It may be possible to repurpose available cancer drugs with reasonable safety profiles as targeted treatments for ASD. For example, evaluation of a rapamycin analogue in tuberous sclerosis patients included outcome measures for ASD features, along with seizures, sleep disturbances and academic skills (NCT01289912, ClinicalTrials.gov). Stratifying individuals with ASD who harbor a risk gene for autism that is also a risk gene for cancer may enable therapeutic development of personalized medicines based on the specific causal mutation.

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Table 1

Characteristics of risk genes implicated in both autism and cancer

Gene name	aliases	Human chrom 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 of the 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 remodelimg 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 telomere	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, also 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 signalling, 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 signalling, 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 signalling, chromatin regulation	25363768
DNMT3A	DNA (5-cytosine)-methyltransferase 3A	2p23.3	Required for genome-wide de novo methylation and is essential for the establishment of DNA methylation patterns during development	DNMT3L, DNMT3B, UHRF1	Autism, susceptibility	Chromatin regulation	26402605

Gene name	aliases	Human chrom location	Protein function	Interacting proteins	Autism related neurodevelopmental syndrome	Cancer susceptibility or pathway	Refs (PMID)
DYRK1A	Dual-specificity tyrosine phosphorylation-regulated kinase 1A	21q22.13	serine/threonine kinase implicated in cell survival, proliferation and differentiation	HIPK2, SFN, YWHAB, YWHAE, DCAF	Down syndrome, mental retardation, autosomal dominant 7	NOTCH signalling, translation regulation	17583556
EHMT1	Euchromatic Histone-Lysine N-Methyltransferase, KMT1D, CLP	9q34.3	Histone methyltransferase of H3K9me and H3K9me2 in euchromatin	MDM2, p53, SUV39H1, HIST1H3A, CTBP1, SUV39H1	Kleefstra syndrome	cellular senescence, NOTCH, lysine degradation	24779060
ERBB2IP	ERBB2 Interacting protein	5q12.3	Acts as an adapter for the receptor ERBB2, inhibits NOD2-dependent NF-kappa-B signaling and proinflammatory cytokine secretion	ERBB2, SMAD2, SMAD3, NRG2, PKP4	Autism, susceptibility	TGFb signalling, cervical and colon cancer	26402605
ERCC6	Cockayne's Syndrome B	10q11.23	SWI/SNF ATP-dependent DNA motor protein that acts in transcription-coupled DNA repair	Cockayne's Syndrome-A/ERCC8 TFIIH, SMARCA5/SNF2H, BAZ1B/ WSTF, SF3B1, DEK, MYO1C, MYBBP1A, DDX21, KIAA1530/ UVSSA.	High confidence ASD candidate gene	transcription-coupled DNA repair	24768552
FOXP1	Forkhead box P1	3p13	Forkhead box transcription factor and putative tumor suppressor	CTBP1, FOXP2, FOXP4, MYC, NCOR2	Autism, susceptibility	WNT, Notch signaling	25363768
HERC2	HECT And RLD Domain Containing E3 Ubiquitin Protein Ligase 2	15q13	E3 ubiquitin-protein ligase that regulates repair proteins on damaged chromosomes, regulates replication fork progression	UBE3A, SUMO1, RNF8, BRCA1	Mental retardation, autosomal recessive 38 (MRT38)	Class I MHC Ag presentation and processing	24779060
HRAS	Harvey Rat Sarcoma Viral Oncogene Homolog, p21RAS	11p15.5	RAS oncogene family members that bind GTP and GDP, with intrinsic GTPase activity	RAF1, SOS1, RIN1, ABL2, CAV1	Costello syndrome	oncogene, MAPK pathway	24768552
INTS6	Integrator complex subunit 6, DICE1	13q14.3	Component of the Integrator complex, involved in the small nuclear RNAs transcription and processing, tumor supressor	UPF1, UPF2, INTS1, INTS3, INTS8	Autism, susceptibility	lung cancer	26402605
KDM5B	Lysine (K)-Specific Demethylase 5B, JARID1B	1q32.1	Histone demethylase that demethylates K4 of histone H3	ARID1B, RB1, HDAC1, PAX9	Autism, susceptibility	Retinoblastoma, chromatin regulation	25363768
KDM6B	Lysine (K)-Specific Demethylase 6B, JMJD3	17p13.1	Histone demethylase that specifically demethylates K27 of histone H3	ESR1, CSNK2B, HIST1H3D	Autism, susceptibility	Chromatin regulation	25363768
KMT2C	Lysine (K)-Specific Methyltransferase 2C, MLL3		Histone methyltransferase that methylates K4 of histone H3	NCOA6, ASCL2, ASH2L, AK1, TSC22D1	Autism, susceptibility	Lysine degradation	26402605
KMT2D	MLL2	12q13.12	Histone methylatransferase of K4me	ESR1, PAXIPI, RBBP5, SMAD1, SMAD9	Kabuki syndrome	Lysine degradation	25891009
MECP2	Methyl CpG binding protein 2, AUTSX3	Xq28	chromosomal protein and transcriptional regulator that binds to methylated DNA	SIN3A, SMARCA2, ATRX	Rett syndrome	Chromatin regulation	24779060

Gene name	aliases	Human chrom location	Protein function	Interacting proteins	Autism related neurodevelopmental syndrome	Cancer susceptibility or pathway	Refs (PMID)
MET	AUTS9, HGFR, c-Met	7q31	Receptor tyrosine kinase that transduces signals from ECM by binding HGF, activates RAS-ERK, AKT, or PLC pathways	HGF, CBL, GRB2, UBC, PTPN1	Autism, association	Hereditary papillary renal carcinoma (RCCP), glioma,	19548256
MIB1	Mindbomb E3 Ubiquitin Protein Ligase 1	18q11.2	E3 ubiquitin-protein ligase that mediates ubiquitination of Delta receptors, which act as ligands of Notch proteins	NOTCH1, UBC, UBE2N, DAPK1	Autism, susceptibility	Notch signaling	26402605
NF1	Neurofibromin 1, NFNS	17q11.2	Negative regulator of RAS signal pathway	GADD45A, SMARCC1, SMARCD1, GTF2A1	Neurofibromatosis, type 1	Leukemia, juvenile myelomonocytic (JMML), Ras, MAPK pathways	24768552
NIPBL	Nipped-B Homolog (Drosophila), CDLS1	5p13.2	cohesion protein that facilitates enhancer-promoter interactions in *Drosophila*	SMC3, HDAC1, HDAC2, ATAD5	Cornelia de Lange syndrome 1	colorectal and gastric cancer	24768552
PAX5	Paired Box 5, ALL3, BSAP	9p13.2	Paired box transcription factor involved in B cell development, neural development, spermatogenesis; recurrent translocations in lymphoma	EP300, CEBBP, ETS1, TBP, EBF1	Autism, susceptibility	Leukemia, acute lymphoblastic, susceptibility (ALL3), WNT pathway	25418537
PHF2	PHD Finger Protein 2	9q22.31	Lysine histone demethylase that is recruited to trimethylated Lys-4 of histone H3 (H3K4me3) at rDNA promoters and promotes expression of rDNA	TP53, RBBP7, SUZ12, EZH2	Autism, susceptibility	Chromatin regulation	26402605
PTEN	MMAC1	10q23.3	tumor suppressor, dual-specificity protein phosphatase	NEDD4, AKT1, PTK2, UBC, SLC9A3R1	Macrocephaly/autism syndrome	Cowden syndrome, glioblastoma, mTOR pathway, recombinational DNA repair	24768552
PTK7	Protein Tyrosine Kinase 7 (Inactive)		Inactive tyrosine kinase involved incononical and non-cononical Wnt signaling pathways, function in cell adhesion, cell migration, cell polarity, proliferation, actin cytoskeleton reorganization and apoptosis	DVL1, DVL2, DVL3, CTNNB1, WNT9B	Autism, susceptibility	WNT and AKT signaling	26402605
SMC1A	Structural Maintenance Of Chromosomes 1A	Xp11.22	chromosome cohesion during cell cycle and DNA repair	SMC3, RAD21, STAG2, SMC2, SSU72	Cornelia de Lange syndrome 2	genome maintenance, colorectal cancer	24768552
SMC2	Structural Maintenance Of Chromosomes 2	9q31.1	critical for mitotic chromosome condensation and for DNA repair	SMC1A, SMC4, NCAPH, NCAPH2, NCAPD2	High confidence ASD candidate gene	Genome maintenance	24768552
SUV420H1	Lysine N-Methyltransferase 5B, KMT5B	11q13.2	Histone methyltransferase that specifically trimethylates K20 of histone H4	TP53BP1, NCOA2, YWHAQ	Autism, susceptibility	Lysine degradation	26402605
TBL1XR1	Transducin (Beta)-Like 1 X-linked Receptor 1, TBLR1, IRA1	3q26.32	F-box-like protein recruits ubiquitin/19S proteosome complex to nuclear hormone	TBL1X, HDAC3, NCOR1, THRB, CACNA1C, CACNA1E	Autism, susceptibility	NOTCH1, PPARalpha metabolism	26069883

Gene name	aliases	Human chrom location	Protein function	Interacting proteins	Autism related neurodevelopmental syndrome	Cancer susceptibility or pathway	Refs (PMID)
			receptors, degradation of N-Cor for transcriptional activation				
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TCF7L2	T-Cell-Specific Transcription Factor 4	10q25.2	High mobility group (HMG) box-containing transcription factor that plays a key role in the Wnt signaling pathway	TCF7, CTNNB1, RUVBL2	Autism, susceptibility	WNT signalling	25363768
TNRC6B	Trinucleotide Repeat Containing 6B	22q13.1	Plays a role in RNA-mediated gene silencing by both micro-RNAs (miRNAs) and short interfering RNAs (siRNAs)	TP53, AGO1, CDK4, EIF2C1	Autism, susceptibility	PI-3K	25363768
TRIO	Trio Rho Guanine Nucleotide Exchange Factor	5p15.2	Promotes the exchange of GDP by GTP, coordinates cell-matrix and cytoskeletal rearrangements necessary for cell migration and cell growth	RAC1, RAC3, HCRTR2, DISC1, CDC5L	Autism, susceptibility	NOTCH, Rho GTPase	26402605
TRIP12	Thyroid hormone receptor interating protein, E3 Ubiquitin-Protein Ligase For Arf	2q36.3	E3 ubiquitin-protein ligase involved in ubiquitin fusion degradation pathway, suppresses spreading of Ub-chromatin at damaged chromosomes	MYC, TRADD, SMARCC1, CDKN2A, SMARCE1, THRB, PSMC5, TMEFF2	Autism, susceptibility	Class I MHC Ag presentation and processing	25418537
TSC1	Tuberous Sclerosis 1, LAM	9q34.13	Negative regulation of mTORC1 signalling	TSC2, MAPK1, RHEB, AKT1, IKBKB	Tuberous sclerosis	MTOR, AKT pathway	24768552
TSC2	Tuberous Sclerosis 2, TSC4, LAM	16p13.3	Negative regulation of mTORC1 signalling	TSC1, RHEB, YWHAZ, YWAB	Tuberous sclerosis	MTOR, AKT pathway	24768552
UBE3A	E6AP Ubiquitin-Protein Ligase, ANCR	15q11.2	E3 ubiquitin-protein ligase, cofactor for nuclear hormone receptors, maternal mutations cause Angelman syndrome, imprinted in brain, in cervical cancer degrades p53 in presence of E6	RAD23A, HERC2, RING1B, ESR1, RARA	Angelman syndrome (del), Dup15q syndrome (dup)	Class I MHC Ag presentation and processing, PEDF, estrogen	24779060
WAC	WW Domain Containing Adaptor With Coiled-Coil	10p12.1	Acts as a linker between gene transcription and histone H2B monoubiquitination at K120	UBC, UBQLN4, POL2R2A	Autism, susceptibility	chromatin regulation	26402605

*Genes summarized in Table 1 were identified as autism risk genes from publications in the cited references identified by PIMD numbers in the far right column. Information describing each gene was assembled from sources compiled within GeneCards and OMIM databases.