Causes & Prevalence

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Autism genes keep turning up chromatin

JM LaSalle*

Abstract

Introduction

Autism-spectrum disorders are complex genetic disorders collectively characterised by impaired social interactions and language as well as repetitive and restrictive behaviours. Of the hundreds of genes implicated in autism-spectrum disorders, those encoding proteins acting at neuronal synapses have been most characterised by candidate gene studies. However, recent unbiased genome-wide analyses have turned up a multitude of novel candidate genes encoding nuclear factors implicated in chromatin remodelling, histone demethylation, histone variants and the recognition of DNA methylation. Furthermore, the chromatin landscape of the human genome has been shown to influence the location of *de novo* mutations observed in autism-spectrum disorders as well as the landscape of DNA methylation underlying neurodevelopmental and synaptic processes. Understanding the interactions of nuclear chromatin proteins and DNA with signal transduction pathways and environmental influences in the developing brain will be critical to understanding the relevance of these autism-spectrum disorder candidate genes and continued uncovering of the 'roots' of autism aetiology. The aim of this review was to discuss the relevance of chromatin in autism-spectrum disorders.

Conclusion

Considering the many roles that chromatin plays at the interface of genetic and environmental factors in regulating gene expression and epigenetic states, it is perhaps not surprising that genomic approaches keep uncovering chromatin-encoding genes.

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Introduction

The functional and cognitive deficits of autism-spectrum disorders (ASDs) characterised by deficits in social interactions and communication, as well as repetitive interests and behaviours appear to be by nature disorders of the neuronal synapse[1]. So perhaps not surprising has been a prioritisation of genes for intense investigation in ASD research to include genes encoding neurotransmitters and their receptors, neuronal adhesion molecules, synaptic signal transduction pathways and neuronal growth factors. Yet, a number of rare Mendelian disorders, such as Rett syndrome, Cornelia de Lange syndrome and Coffin-Siris syndrome have pointed to the importance of chromatin remodelling factors and DNA methylation in human brain development. Thus, analysis of ASD by human genetics has led to the greater appreciation of 'epigenetics', a term used to describe the additional layers and players on top of DNA that confer long-lasting and reversible gene expression modifications without changing the underlying genetic sequence[2].

An excellent example of a recently uncovered connection between nuclear epigenetic and transcriptionally regulatory factors in ASD is a recent meta-analysis of four exome sequencing publications[3], together representing 965 ASD probands and 121 predicted disruptive mutations in protein-coding genes[4–7]. This study demonstrated a significant over-representation of genes with functions in chromatin regulation and early developmental expression with variants found in ASD probands but not unaffected siblings[3].

Here, I will attempt to demystify chromatin and to summarise the recent crop of chromatin genes implicated in ASD with the goal of future understanding of their functional relevance to the human chromatin landscape underlying synaptic function.

Discussion

Autism genes acting in nucleosome packaging

Chromatin can be defined simply and collectively as genomic DNA and associated proteins within the nucleus. Not so simple is the vast assortment of chromatin factors dedicated to the fine-tuning of DNA packaging and the enzymatic functions involved in changing chromatin states as cells undergo tissue and developmental differentiation. Nucleosomes are the primary unit of chromatin organisation that serve to keep DNA molecules condensed and regulated by only releasing genes into the open conformation when their accessibility is needed. Nucleosomes are made up of histone core protein subunits H2A/B, H3 and H4 that form the spool-like nucleosome and linker subunit H1 that connects the nucleosomes. The tightness of wrapping at specific genes or genomic locations within nucleosome arrays is influenced by a number of variables affecting histone protein subunits, namely variant histone proteins and post-translational modifications.

Post-translational modifications are covalent changes to specific amino acids in the core histone subunits that can be detected by specific antibodies and examined genome-wide. Certain histone modifications, such a histone H3K4 trimethylation (H3K4me3) and H3K27 or H3K9 acetylation mark active gene promoters, while marks such a H3K27 or H3K9 trimethylation (H3K27me3, H3K9me3) are associated with transcriptionally silent genes[2].

FOR CITATION PURPOSES: *LaSalle JM*. Autism genes keep turning up chromatin. OA Autism 2013 Jun 19;1(2):14.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
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Review

However, in pluripotent stem cells, a subgroup of developmental genes regulated by polycomb group complexes contain both active (H3K4me3) and repressive (H3K27me3) marks, but remain in an inactive but poised state, waiting for an external signal. The regulation of each histone modification requires specific enzymes that add or remove the methyl or acetyl group. Interestingly, several genes found mutated in ASD encode histone demethylases, such as *KDM5C*, a demethylase of histone H3K4 implicated in gene repression and *JMJD1C*, a demethylase for histone H3K9 implicated in hormone-dependent transcriptional activation (Table 1).

Table 1 Chromatin genes implicated in autism spectrum disorders

Gene name	Aliases	Human chromosome location	Human disease	Protein function	Interacting proteins	References
MECP2	Methyl CpG-binding protein 2, *ARBP*	Xq28	Rett syndrome, autism (rare mutation or aberrant methylation)	Binds mCpG, repression, chromatin dynamics	Sin3a, HDAC, ATRX, YB1, SMC1A	9, 42–46
ATRX	*RAD54, XH2*	Xq21.1	Thalassaemia, intellectual disabilities	SWI/SNF chromatin remodelling, ATPase/helicase domain	MeCP2, SMC1A	13,47
H2AFY	*MACROH2A1.1*	5q31.1	Autism (association)	Histone H2 variant, X chromosome inactivation	HDAC1, PARP1	8,48
SMC1A	Cohesin, *CDLS2*	Xp11.22	Cornelia de Lange syndrome	Chromosome cohesion	ATRX, SMC3, MeCP2, CTCF	13
MACROD2		20p12.1	Autism (association)	O-acetyl-ADP-ribose deacetylase, binds this metabolite from histone deacetylation		11
KDM5C	*JARID1C, SMCX*	Xp11.22	ASD, ID (rare mutations)	Histone demethylase of H3K4, gene repression	HDAC, REST	49–52
MBD1	*CXXC3*	18q21	Autism (rare mutations), also rare variants in related genes *MBD4, MBD5*	Binds mCpG, links mCpG to H3K9me3	SETDB1, AFT7IP	9,53,54
ARID1B	*BAF250B*	6p25.3	Coffin-Siris syndrome, mental retardation autosomal dominant type 12 (*MRD12*), autism (rare)	Component of SWI/SNF chromatin remodelling complex, AT-rich binding domain	SWI/SNF complex proteins in nBAF	14,15
SMARCC1	*BAF155*	3p31.21	Autism (rare mutation)	Component of SWI/SNF chromatin remodelling complex and neuronal BAF complex (nBAF)	ARID1A, ARID1B, SMARCC2	5
SMARCC2	*BAF170*	12q13.2	Autism (rare mutation)	Component of SWI/SNF chromatin remodelling complex and nBAF	ARID1A, SMARCC1, HDAC1/2	5
JMJD1C	*TRIP8*	10q21.3	Autism (rare mutation, translocation, abnormal methylation)	Histone demethylase for H3K9, hormone-dependent transcriptional activation	Thyroid hormone receptor, androgen receptor	5,25,55,56
CHD8	*AUTS18*	14q11.2	Autism (rare mutation), also rare autism variants in family members *CHD1*, *CHD3*, *CHD7*)	ATP-dependent chromatin helicase, negative regulator of Wnt signalling pathway by regulating beta-catenin (*CTNNB1*)	p53, histone H1, CTNNB1, CTCF, MLL complex proteins WDR5, RBBP5, CHD7 (mutated in CHARGE)	5,6,16

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Competing interests: none declared. Conflict of interests: none declared.
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Review

Histone variant proteins are generally encoded by separate genes and can substitute for the canonical histone subunit in specific situations. For instance, the histone H2A subunit has a variant encoded by the autosomal gene *H2AFY/MACROH2A1.1* that was identified as an autism candidate gene by a genome-wide association study[8]. *MACROH2A1.1* is generally associated with repressed chromatin, such as the inactive X chromosome[9]. But because it also contains binding sites for cellular metabolites through the macro domain, *MACROH2A1.1* may have a more dynamic role in modulation of gene expression in response to environmental signals[10]. A related family member encoding gene, *MACROD2* was also found on a separate chromosome in an ASD genome-wide association study[11]. The macro domain of *MACROD2* binds a cellular metabolite that emerges from histone deacetylation reactions[10], linking both histone variant and histone modification events.

Chromatin remodelling and the importance of energy

Changing chromatin states during neuronal lineage commitment is an active process requiring the appropriate external signals, as well as energy in the form of ATP. The engines that carry out the active process of changing chromatin are called 'chromatin remodelling complexes'. Each chromatin remodelling complex contains an ATPase with a variable group of associated protein factors. A neuron-specific protein ATPase subunit BAF53b defines a neuronal chromatin remodelling complex that is required for long-term memory and synaptic plasticity in mice[12].

In humans, mutations in chromatin remodelling complex factor subunit genes appear to be a recurrent theme in neurodevelopmental disorders and autism (Table 1). Several components of the SWI/SNF specific chromatin remodelling complexes, including SMARCC1, SMARCC2, ARID1A, ARID1B and ATRX are encoded by genes in which rare autism mutations have been observed[5,6,13–15]. In addition, several exome sequencing studies in autism have identified rare mutations in genes encoding the ATP-dependent chromatin helicases CHD8, with additional variants found in family members CHD1, CHD3 and CHD7[5,6,16]. CHD8 serves as an important regulator of beta-catenin and Wnt signalling pathways in neuronal development[17].

The dynamics of histone methylation and DNA methylation in development

Mammalian neurons require extensive methyl modifications throughout development and post-natal life for many molecules, particularly nucleotides and proteins. As mentioned above, several important post-translational modifications of histone core subunits within nucleosomes involve methylation, including the activating H3K4me3 and polycomb repressive H3K27me3 marks. Histone methylation is more stable than acetylation or phosphorylation, suggesting a long-lived component to these epigenetic marks[18]. The other major epigenetic layer of information is DNA methylation. In the mammalian genome, CpG sites are targets for methylation carried out by a family of DNA methyltransferases. Over evolutionary history, eukaryotic organisms have gradually acquired more DNA methylation, with humans having a nearly saturated genome of ~80% of possible CpG sites methylated in human embryonic stem cells[19].

Both histone and DNA methylation patterns are highly dynamic processes in early development that correlate with dynamic changes in cell lineage and differentiation events. Interestingly, mutations in autism have been found in several genes encoding proteins involved in demethylase reactions, which are the removal of methyl groups from histones or DNA (Table 1). For example, mutations in the X-linked gene *KDM5C* have been found in individuals with intellectual disability (ID) and ASD, and this gene encodes a histone demethylase enzyme that removes the active H3K4me3 mark, thus repressing gene expression. Genome-wide, prefrontal cortex neurons from human infants in their first year of life exhibit a large excess of H3K4me3 actively marked genes compared to later ages, suggesting that histone demethylation reactions are rampant in early post-natal life[20]. Interestingly, generalised disruption of the H3K4me3 landscape was observed in autism frontal cortex samples compared to controls, including several genes with known neurodevelopmental functions[21]. Together, these results suggest that histone demethylation reactions may be critical early life events that may become dysregulated in autism.

Chromatin influences on *de novo* mutations in autism

In addition to chromatin genes being mutated in autism, chromatin itself has been recently shown to influence the genomic locations of *de novo* mutations observed in monozygotic twins concordant for autism[22]. In this whole genome sequencing study, de novo variants were not randomly distributed throughout the genome, but instead clustered into 'hotspots' enriched for simple repeats and DNAse I hypersensitivity in embryonic stem cells, a mark of open active chromatin not bound by nucleosomes. DNA methylation also impacts mutation rates, as spontaneous deamination of methylated CpG sites is a frequent mutation type found in mammals and accounted for 15% of the de novo variants found in autism.

Chromatin influences on DNA methylation and synaptic genes

Chromatin can also influence DNA methylation levels in human tissues and cell lines. Genome-wide, ES cells

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Review

and mature human tissues have high saturation of CpG methylation, except at conserved clusters of CpGs called CpG islands that have been protected from DNA methylation and are found at many gene promoters. However, genome-wide DNA methylation detection has revealed the presence of methylome landscape features called 'partially methylated domains' (PMDs) which are genomic landscape features of the human methylome characterised by lower levels of methylation in the range of 40%–70% compared to the >70% methylation observed over the rest of the genome[19]. PMDs are also characterised by reduced gene expression compared to highly methylated domains and the more repressive histone marks such as H3K27me3 and H3K9me3. What is particularly interesting about PMDs is that they are both tissue-specific and developmentally regulated and they are highly enriched for tissue-specific and developmental genes, particularly those involved in neuronal development, immune responses and synaptic transmission[23,24]. While the presence of PMDs was previously thought to be limited to primary and tumour cell lines, we recently identified placenta as a normal human tissue that contains PMDs covering 37% of the genome[23].

Autism candidate genes with mutations found from genetic studies are highly enriched in PMDs compared to highly methylated parts of the genome[24]. Specifically, genes that are highly methylated in neuronal cells, but within PMDs in placenta or fibroblasts include many genes acting at the synapse and implicated in autism, including *CNTNAP2*, *CACANA1C*, *GABRB3*, *CHRNA7*, *SYNGAP1*, *NRXN1*, *SCNA1* and *SHANK3* (Figure 1)[23]. Furthermore, a recent study of monozygotic twins characterised for ASD-associated traits and DNA methylation differences identified several differentially methylated genes that also localise to PMDs (*NRXN1*, *GABRB3*, *SNRPN*, *SNURF*) or chromatin genes (*JMJD1C*, *MBD4*) already implicated in ASD[25]. While understanding the relationship between genomic methylation patterns and gene regulation is still in its infancy, the first glimpses of the DNA methylation and chromatin landscape is beginning to uncover a pathway of synaptic genes that may be coordinately epigenetically regulated and dysregulated by both genes and environmental factors.

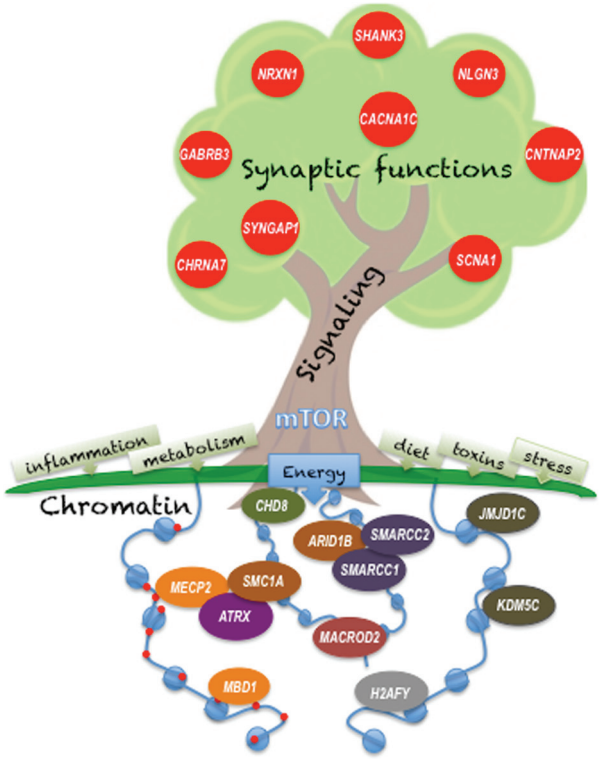

Figure 1: Chromatin factors at the roots of autism aetiology. An analogy of a tree with deep roots is used to illustrate several points about chromatin factors implicated in autism. Candidate gene approaches for ASD have justifiably prioritised the investigation of low hanging fruit (large red circles) for genes that encode proteins with known functions at neuronal synapses. But these synaptic proteins are connected to signal transduction pathways that make changes to gene expression patterns through chromatin dynamics within the neuronal nucleus. The mTOR pathway, which integrates metabolic and nutrient sensing signals into energy, is central to the signalling pathways and to supply energy for chromatin remodelling events. But just as the roots and trunk of a tree are bidirectional pathways for the tree, information within the nucleus stored in the form of chromatin provides information back to the synapse to regulate levels of synaptic proteins during synaptic pruning and scaling. Levels of DNA methylation (small red dots) and readers of DNA methylation (MECP2, MBD1, etc.) may act as chromatin sensors of many environmental factors including diet and chemical toxins during the maturation of synapses. Furthermore, chromatin factors such as MACROD2 and JMJD1C have metabolic sensing properties, so that factors such as stress and inflammation may alter chromatin dynamics of neurons with long lasting effects. Thus, in the future, it will be important to continue to dig beneath the surface to unearth the chromatin factors and epigenetic pathways in the aetiology of ASD in order to fully understand these complex genetic disorders.

FOR CITATION PURPOSES: *LaSalle JM*. Autism genes keep turning up chromatin. OA Autism 2013 Jun 19;1(2):14.

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Review

The multiple factors influencing chromatin and ASDs

Genetics

The examples in Table 1 are of rare mutations found in genes that encode proteins involved in chromatin regulation, but a larger genetic effect is likely to come from mutations and genetic variants that lie outside the protein coding exons but influence the binding and actions of chromatin factors and DNA methylation patterns. While it is tempting to think about epigenetic layers as completely independent of the DNA sequence, the genetic code ultimately determines the chromatin state that occurs during developmental programming. As an example, CpG islands are defined by CpG density at the sequence level and are protected from DNA methylation by a property called G–C skew, also at the sequence level[26]. But in Fragile X syndrome, an expanded CCG triplet repeat at the CpG island promoter of *FMR1* alters this protection, resulting in methylation and transcriptional repression[27]. But in addition to the obvious gene regulatory regions, repetitive regions of the genome classically considered to be 'off the map' for consideration as disease-causing mutation may also impact neighbouring chromatin and gene expression. As a clear example, facioscapulohumeral muscular dystrophy results from a loss of a critical number of repeats in a microsatellite repeat array on chromosome 4 that results in chromatin and gene expression changes to the *DUX4* retrogene[28]. As genome-wide sequencing technologies have now opened up the entire genome for examination, many more examples of genetic variation, particularly repeats causing methylation and chromatin changes relevant to phenotypes are expected.

Sex differences

Differences between males and females in phenotypes and disease susceptibilities is foremost a genetic difference, due to the chromosomal differences of XX versus XY. However, the differential developmental program enacted in males versus females results in large differences in sex hormones, which can also have effects on epigenetics as well as phenotype. Since autism has a strong male bias for susceptibility, it is important to consider both chromosomal and hormonal influences that may be influencing gene expression and phenotypes.

The epigenetic process of X chromosome inactivation that occurs in females largely serves as a mechanism of dosage compensation by inactivating one of the two X chromosomes in each cell. The inactive X chromosome creates a large heterochromatic domain within the nucleus, called the Barr body. Interestingly, simply having the Barr body present appears to create global sex differences in DNA methylation levels, as females have detectably lower global levels of DNA methylation, and increasing the number of X chromosomes further reduces the methylation on autosomes[29]. Furthermore, human brain transcriptome data analysed for sex differences revealed that male-biased transcripts were enriched for chromatin functions, as well as roles in extracellular matrix formation/glycoproteins, immune response and cell cytoskeleton[30].

In addition, not all genes on the inactive X chromosome are inactivated, and the genes that 'escape' X inactivation in females are revealing some interesting insights into sex differences in chromatin[31]. *KDM5C/JARID1C*, listed in Table 1 for its involvement in ASD and ID, is a gene that escapes X chromosome inactivation[32]. In addition, the gene encoding O-linked-*N*-acetylglucosamine (O-GlcNAc) transferase that regulates chromatin remodelling factors, is expressed lower in males than females and further reduced by prenatal stress[33]. These inherent epigenetic and brain transcriptional sex differences should be further examined in future studies of the female protective effect in autism.

Environmental toxins

Modern humans are surrounded by a stunning array of environmental toxins, primarily man-made chemicals that are in our air, water, food and furniture. While a single chemical compound is unlikely to arise a 'smoking gun' for autism risk, some exposures have been demonstrated to modestly increase risk for ASD[34]. In the nascent field of environmental epigenetics of relevance to ASDs, there appears to be two emerging themes from multiple studies. First, many different exposures individually appear to result in reduced global levels of DNA methylation[35]. Second, is that there are sex differences in susceptibility to environmental factors. In our recent mouse model of perinatal exposure to the common flame retardant polybrominated biphenyl ether in a genetically and epigenetically susceptible *Mecp2* mouse mutant, we observed deficits in sociability, early post-natal growth and brain DNA methylation levels only in females, and the interaction effects in spatial learning were only observed in females[36]. The males of this model were more genetically susceptible because *Mecp2* is X-linked, but this and other studies raise the question of whether females, which have a lower baseline level for DNA methylation saturation, may be more susceptible to the multiple chemical insults on the dynamic methylome described in the previous section.

Nutrition and metabolism

Fortunately, nutritional factors, particularly folate, B vitamins and choline, can help to counteract the assault by chemical pollutants on DNA methylation levels. A likely pathway of this action is the one carbon metabolism cycle, which supplies the methyl donors from the diet for methylation reactions mediated

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OA Autism
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Review

by SAM to both DNA and proteins. Multiple chemical exposures utilise the SAM inhibitor glutathione for detoxification and therefore prevent the high saturation of DNA methylation in brain[34,37].

There are several additional examples of cellular and organismal metabolic cycles serving to regulate gene expression through modifications to chromatin reviewed elsewhere[18]. Oxygen and glycolysis are required for the action of the JMJC histone demethylases (family includes *JMJD1C* from Table 1). Acetyl-CoA produced from the citrate cycle provides the donor for histone acetylation reactions and the sexually dimorphic regulator O-linked-*N*-acetylglucosamine transferase mentioned above uses a byproduct of the hexosamine biosynthetic pathway derived from glycolysis. The histone deacetylase SIRT1 is modulated by NADH and diurnal metabolic cycles. And as mentioned above, multiple chromatin proteins contain macro domains that translate metabolic changes into chromatin and gene expression changes[10].

A central signal transduction pathway regulating the nutrient sensing and metabolic changes to chromatin is mediated by the mammalian target of rapamycin (mTOR). mTOR mediates the signals from the PI3K/AKT signal transduction cascade, promoting protein synthesis and anabolism, and is also becoming a central pathway disrupted in several syndromic forms of ASD, including Fragile X syndrome and tuberous sclerosis[38].

Immune responses

There is accumulating evidence for immune dysregulation playing a role in the pathogenesis of ASD. For example, maternal fever or influenza infection during pregnancy increases ASD risk and several animal models that mimic an acute maternal immune response result in autistic-like features in the offspring. Mothers of children with ASD exhibit autoantibodies and altered cytokine profiles indicative of systemic immune activation[39].

While there is much to be still learned in this area, neuronal and immune dysfunction could be occurring in parallel during the pathogenesis of ASD through chromatin pathways. Both T and B cell lineages of adaptive immune responses undergo coordinated changes in DNA methylation and chromatin marks that could become dysregulated by a variety of genetic and environmental risk factors. For example, *FOXP3* is a marker of regulatory T cells, a subset of $CD4^+$ T cells primed in early life to recognise common environmental antigens and inhibit later inappropriate immune responses. Interestingly, regulatory T cell fate determination is an epigenetic event of *FOXP3* promoter demethylation induced by repeated Ca^{+2}-mediated signal transduction and prevented by the mTOR pathway[40,41].

Conclusion

Considering the many roles that chromatin plays at the interface of genetic and environmental factors in regulating gene expression and epigenetic states, it is perhaps not surprising that genomic approaches keep uncovering chromatin-encoding genes. An ongoing understanding of the complex dynamic changes that chromatin undergoes in the developing brain is likely to help to make sense of the regulatory pathways connecting the diversity of genes implicated in ASD. Furthermore, since chromatin events are integrated with environmental, nutrient and metabolic cellular sensors, they may help explain how these complex genetic disorders are further modified by environmental risk and protective factors.

Acknowledgements

I thank Dr. Dag Yasui for critical reading of the manuscript, members of the UC Davis MIND Institute, Children's Centre for Environmental Health, Genome Centre and Epigenome club for helpful discussions and insights, members of my laboratory for their hard work and dedication to autism research, and ongoing support of research programs from the National Institutes of Health (R01ES021707, R21ES021330, R01NS081913, R01NS076263), Department of Defence (AR110194) and the International Rett Syndrome Foundation.

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FOR CITATION PURPOSES: *LaSalle JM*. Autism genes keep turning up chromatin. OA Autism 2013 Jun 19;1(2):14.

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OA Autism
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Review

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FOR CITATION PURPOSES: *LaSalle JM*. Autism genes keep turning up chromatin. OA Autism 2013 Jun 19;1(2):14.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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FOR CITATION PURPOSES: *LaSalle JM*. Autism genes keep turning up chromatin. OA Autism 2013 Jun 19;1(2):14.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.