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Epigenetic Causes of Overgrowth Syndromes

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Abstract

Human overgrowth disorders are characterized by excessive prenatal and/or postnatal growth of various tissues. These disorders often present with tall stature, macrocephaly, and/or abdominal organomegaly and are sometimes associated with additional phenotypic abnormalities such as intellectual disability and increased cancer risk. As the genetic etiology of these disorders have been elucidated, a surprising pattern has emerged. Multiple monogenic overgrowth syndromes result from variants in epigenetic regulators: variants in histone methyltransferases *NSD1* and *EZH2* cause Sotos syndrome and Weaver syndrome, respectively, variants in DNA methyltransferase *DNMT3A* cause Tatton-Brown-Rahman syndrome, and variants in chromatin remodeler *CHD8* cause an autism spectrum disorder with overgrowth. In addition, very recently, a variant in histone reader protein *SPIN4* was identified in a new X-linked overgrowth disorder. In this review, we discuss the genetics of these overgrowth disorders and explore possible common underlying mechanisms by which epigenetic pathways regulate human body size.

Keywords: tall stature, epigenetic modifications, histone, methylation, WNT signaling

Regulation of organismal body size remains a fundamental mystery in modern biology and medicine (1). One powerful genome-wide approach is to look for common variants in the form of single nucleotide polymorphisms that are associated with human stature in the general popula-

tion. Indeed, the most recent iteration of such efforts yielded thousands of genomic loci that are significantly associated with variation in human height (2). However, in many of these loci, there are multiple single nucleotide polymorphisms in nearby genes that are in linkage disequilibrium with the causative variant, which makes it difficult to identify which gene in a particular locus actually modulates height. Additionally, the sheer number of significant loci, each with a small effect size, could present a challenge to harness meaningful biological insight from such studies. An alternative approach to understanding regulation of body growth and body size is by studying monogenic childhood growth disorders. When a variant has a large effect on childhood growth, the affected child may present to the health care provider as short stature or tall stature. Indeed, there are hundreds of monogenic conditions that can present with short stature (3). However, not every gene in which variants cause short stature is categorically growth regulating, because variants can have detrimental effects on normal physiological processes, such as DNA repair, which then secondarily and nonspecifically limit childhood growth. In contrast to short stature, tall stature or overgrowth conditions are relatively uncommon, and one could argue that these conditions offer a unique opportunity to gain insights into how the trajectory or limit on body size and body growth could be reset or extended.

Human overgrowth disorders constitute a group of clinical conditions in which there is excessive prenatal and/or postnatal growth of some tissues. Overgrowth can either be generalized or segmental. Segmental overgrowth shows a localized or patchy distribution, often due to somatic variants. Generalized overgrowth may affect only specific tissues but shows a widespread distribution, usually manifesting as tall stature, macrocephaly, and/or abdominal organomegaly and is often due to germline variants. Overgrowth disorders are sometimes associated with additional phenotypic abnormalities, such as developmental delay, intellectual disability, and increased cancer risk. In some cases, a hormonal cause can be identified, such as pituitary gigantism (4), where the presence of an adenoma in the anterior pituitary results in excessive growth hormone production driving growth of the long bones, causing tall stature, and of other tissues. However, many cases of overgrowth appear not to be hormonally mediated, and further genetic analysis is needed to identify the underlying cause.

In the past decade, technological advances in high-throughput sequencing have accelerated the genetic diagnosis of generalized overgrowth syndromes, and it has become increasingly apparent that many of these monogenic conditions involve variants affecting the epigenetic landscape across the genome, such as variants in epigenetic regulators like DNA and histone methyltransferases (5). In this review, we discuss the genetics of these overgrowth disorders and explore possible common underlying mechanisms to gain insights into the regulation of body size. What will not be covered in this review includes segmental overgrowth disorders such as PIK3CA-related overgrowth spectrum and overgrowth caused by localized (rather than genome-wide) epigenetic abnormalities, such as the imprinting defects in Beckwith-Wiedemann syndrome.

Sotos and Sotos-like Syndrome

Sotos syndrome (OMIM 117550), originally referred to as cerebral gigantism (6), is an overgrowth syndrome with prenatal onset, such that the birth length and head circumference are often above the normal range (7, 8). Growth is rapid in the first years of life with bone age advanced, but final

adult height may or may not be above normal. Patients with Sotos syndrome typically have macrocephaly with dysmorphic facial features, such as prominent forehead and elongated occipital-frontal axis. Learning disability and intellectual disability are also common. A modest increase in cancer risk (about 3% prevalence) has been report for neuroblastoma and teratoma in patients with Sotos syndrome (9).

Genetic analysis identified autosomal dominant loss-of-function variants in the *NSD1* gene or deletion in the 5q35 region that includes the *NSD1* gene (10). *NSD1* encodes a transcriptional coregulator protein that contains the SET domain, which is commonly found in histone methyltransferases (11). NSD1 has been shown to methylate histone H3 at lysine residue 36 (H3K36) and H4 at lysine residue K20 (H4K20) (11). Interestingly, NSD1 also has other notable protein domains including 2 PWWP domains that bind demethylated histone H3K36 (12) and multiple PHD domains that bind methylated histone H3K4 and H3K9 (13), suggesting that NSD1 is a bifunctional protein that could serve both as a histone writer and reader. Missense variants in patients with Sotos syndrome have been found in the SET, PWWP, and PHD domains of *NSD1* (14), suggesting all 3 functional domains are important for the regulation of body growth (Fig. 1). Curiously, *NSD1* belongs to a family of genes with 2 other members, *NSD2* and *NSD3*, all of which share strong sequence similarities. Both NSD2 and NSD3 proteins also contain SET, PWWP, and PHD domains present in NSD1, and yet genetic analysis of patients in non-NSD1 overgrowth cases have not identified causative variants in *NSD2* or *NSD3*, suggesting that, despite the strong sequence similarities, other NSD genes do not substantially contribute to human overgrowth (15).

Efforts have been made to identify genetic variants in patients who were diagnosed with Sotos or Sotos-like syndrome based on clinical evaluation but were negative on genetic testing for *NSD1*. For example, in 2 unrelated individuals with a Sotos-like syndrome, Luscan et al identified heterozygous nonsense variants in *SETD2,* which, like *NSD1*, has a SET domain and functions as a histone methyltransferase for H3K36. The condition has since been renamed as Luscan-Lumish syndrome (OMIM 616831). Similarly, in three unrelated individuals, 1 of which was previously diagnosed with Sotos-like syndrome (now renamed as Malan syndrome, OMIM 614753), Malan et al identified heterozygous missense variants or deletion of the gene *NFIX* (16). *NFIX* is 1 of the 4 genes (the other 3 being *NFIA, NFIB,* and *NFIC*) that encodes a nuclear factor one (NFI) transcription factor that binds to the DNA dyad-symmetric consensus sequence TTGGC(N5)GCCAA (17). The epigenetic role of *NFIX* is unclear, but it has been shown that NFI can bind to histone H1 (18) and H3 (19). In addition, NFI has been shown to functionally interact with BRG1 (20), a member of the SWI/SNF family of ATP-dependent chromatin remodeler that regulates movement and restructuring of DNA wrapped around histone proteins, allowing for changes in gene expression and DNA accessibility (21).

Weaver and Weaver-like Syndrome

Weaver syndrome (OMIM 277590), first reported in 1974 (22), shows substantial phenotypic overlap with Sotos syndrome, characterized by pre- and post-natal overgrowth, advanced bone age, and variable intellectual disability. Individuals with Weaver syndrome have characteristic facies that are distinct from those Sotos syndrome and that include a broad forehead, almond-

shaped palpebral fissures, and ocular hypertelorism (23). Other typical clinical features include umbilical hernia; hoarse, low-pitched cry; deep-set nails; prominent fingertip pads; soft, doughy skin; and camptodactyly of the fingers and/or toes (24, 25).

In 2012, genetic analysis identified heterozygous de novo variants in the *EZH2* gene (26, 27). The EZH2 protein forms the core component of the polycomb repressive complex 2 (PRC2) with 3 other proteins, EED, SUZ12, and RbAp46/48 (28). This complex catalyzes the trimethylation of histone H3 at lysine residue 27 (H3K27), which is a chromatin mark commonly associated with gene repression, with EZH2 itself being the catalytic subunit for this reaction. Structurally, EZH2 contains 2 SANT domains for histone and chromatin binding, a SET domain responsible for its histone methyltransferase activity, and several other domains for interactions with PRC2 core components. Interestingly, the vast majority of *EZH2* variants found to date in Weaver syndrome are either missense variants or truncating variants in the last exon (Fig. 1). The lack of early truncating variants suggests that Weaver syndrome is not caused by simple haploinsufficiency of *EZH2*. Consistent with this concept, we and others showed that Weaver syndrome is caused by a partial loss of histone methyltransferase activity (29, 30).

The fact that Weaver syndrome is caused by decreased PRC2 enzymatic activity suggests that variants in other PRC2 members might also cause Weaver or Weaver-like overgrowth syndrome. Missense variants in *EED* (31) and *SUZ12* (32) have since been identified in cohorts of patients with Weaver-like overgrowth syndrome (which are now referred to as Cohen-Gibson syndrome, OMIM 617561, and Imagawa-Matsumoto syndrome, OMIM 606245). To date, no causative variant has yet been identified in Weaver or Weaver-like overgrowth for the fourth component of the PRC2 core complex, RbAp46/48 (encoded by *RBBP7*), or *EZH1*, which is a homolog of *EZH2* that could also participate in PRC2 complex activity in place of *EZH2*.

Similar to Sotos syndrome, Weaver syndrome is also associated with an increase in cancer risk for Hodgkin disease, acute lymphoid leukemia, and neuroblastoma (33). The mechanistic connection between overgrowth syndrome and cancer risk is unclear, but it suggests that normal organismal growth and abnormal malignant growth might utilize similar regulatory mechanisms (34).

Tatton-Brown Rahman Syndrome

Tatton-Brown-Rahman syndrome (TBRS), initially known as DNMT3A overgrowth syndrome, is characterized by increased height and/or head circumference, obesity, variable intellectual disability, and seizures. Subtle dysmorphic features are present such as round face with coarse features and thick, horizontal, low-set eyebrows (35). In 2014, genetic analysis in a cohort of 152 individuals with overgrowth in whom variants in *NSD1* and *EZH2* had been excluded identified 13 de novo variants in *DNMT3A*, which encodes 1 of the 3 DNA methyltransferases *(DNMT1*, *DNMT3A*, and *DNMT3B*) in humans. Both *DNMT3A* and *DNMT3B* are responsible for de novo DNA methylation, in which methyl groups are added to CpG dinucleotides at previously unmethylated DNA sequences for establishment of new epigenetic patterns, as opposed to DNA methylation by *DNMT1,* which is responsible for maintenance of DNA methylation during cell division. A follow-up study that included 55 additional patients confirmed the initial study with additional de novo *DNMT3A* variants identified (36). The vast majority of these variants were located within one of the three

known functional domains: the PWWP domains that binds methylated H3K36 (37), the ADD domain that binds unmethylated H3K4 (38), and the MTase domain responsible for DNA methylation activity (35) (Fig. 1). Although missense mutation is the most common causal variant identified, frameshift and stop-gain variants are also present throughout the coding region, suggesting that loss of function, including haploinsufficiency, of *DNMT3A* are responsible for the disorder. Subsequent whole genome bisulfite sequencing of peripheral blood cells in TBRS patients demonstrated focal, canonical hypomethylation of genomic DNA, supporting the hypothesis that these variants are indeed loss-of-function (39). Interestingly, somatic Arg882 mutations in DNMT3A are causally associated with acute myeloid leukemia, (40) but that exact missense mutation is rarely found in TBRS. To date, an increased risk of acute myeloid leukemia, or malignancies in general, has not been demonstrated (41). Variants in *DNMT3B*, which also function as a de novo DNA methyltransferase like *DNMT3A*, causes facioscapulohumeral dystrophy (OMIM 619478) (42) and immunodeficiency-centromeric instability-facial anomalies syndrome (OMIM 242860) (43), neither of which is characterized by overgrowth.

Epigenetic abnormalities in DNA methylation that affect growth can occur in other clinically important settings. For example, recent evidence suggests that newborns conceived through assisted reproductive technology show widespread differences in DNA methylation with less overall methylation across the genome (44). This observation may explain why some imprinting defects may occur at a higher rate in children conceived using assisted reproductive technology. These abnormalities include both Silver-Russell syndrome (45), which leads to fetal growth retardation, and Beckwith Wiedemann syndrome (46), which leads to fetal overgrowth.

Chromodomain Helicase DNA-binding Protein 8-related Overgrowth

Chromodomain helicase DNA-binding protein 8 (CHD8), similar to BRG1 mentioned earlier, is an ATP-dependent chromatin remodeling complex that regulates chromatin dynamics, causing changes in DNA accessibility and gene expression (21). Variants in CHD8 were initially identified in patients with autism spectrum disorder (ASD) (47). Subsequently, resequencing of the CHD8 gene in 3730 children with developmental delay or ASD revealed that CHD8 variants defined a subtype of ASD characterized by macrocephaly, early and rapid postnatal growth, facial dysmorphism, gastrointestinal problems, and sleep disorders. Of the 15 patients with CHD8 variant, 12 had macrocephaly and 13 had tall stature (48). Another detailed evaluation of 27 unrelated patients with pathologic CHD8 variants similarly found that 85% of patients had tall stature or increased head circumference (49). In a separate study of patients with overgrowth and intellectual disability, 12 individuals were identified with *CHD8* variants (5). The vast majority of these variants are truncating or stop-gain, presumably loss-of-function variants in *CHD8* (Fig. 1). Like all other members of the CHD family (CHD1-9), CHD8 protein contains a tandem chromo domain near the N-terminus, followed by an ATP-dependent helicase domain, and 2 BRK domains near the C-terminus. One of the main functions of CHD chromatin remodeler is to facilitate nucleosome assembly (50), that is, to guide the formation of histone-DNA complexes after DNA replication, although it may also participate in regulation of gene expression alongside SWI/SNF chromatin remodelers like BRG1. The functional difference between individual CHD family proteins could depend on specific protein-protein interactions. For example, CHD8, has been shown to bind beta-catenin (51), a mediator of canonical WNT signaling pathway; WDR5 (51), a member of the MLL complex that is a H3K4 his-

tone methyltransferase (52); and BRPF1 (53), an epigenetic reader for acetylated histone (54). Interestingly, variants in other members of the CHD chromatin remodeler are associated with several different neurodevelopmental disorders, but only *CHD8* is known to cause human overgrowth.

SPIN4 Causes an X-linked Overgrowth Disorder

Recently, we studied an adolescent male with overgrowth of prenatal onset (+4.8 SD for length at birth) who presented with extreme tall stature, advanced bone age, enlarged liver and spleen, and macrocephaly. However, unlike in most other overgrowth syndromes, psychomotor and intellectual development appeared to be normal. The patient's mother and maternal grandmother were mildly tall for their family background, suggesting an X-linked condition with a more severe phenotype in males. Exome sequencing identified a hemizygous frameshift variant in *SPIN4* on the X-chromosome of the patient, which was also present in the maternal grandmother and mother but not in other family members (55). SPIN4 belongs to a family of Spindlin proteins that also includes SPIN1, SPIN2A, and SPIN2B. Previous studies have identified all Spindlin proteins to contain 3 Tudor-like domains (56), which are known to recognize and bind methylated lysine and arginine residues of histones and other proteins (57), therefore suggesting that Spindlin proteins could function as histone readers (58). Indeed, we showed that the human SPIN4 protein normally recognizes a broad range of modified histones, while the frameshift variant has vastly diminished histone binding. Two lines of mice carrying truncating *Spin4* variants were generated, and in both lines the hemizygous male knockout and heterozygous female developed overgrowth, recapitulating the growth phenotype in the family. We further demonstrated that, similar to SPIN1 (59), SPIN4 promotes canonical WNT signaling and that loss of SPIN4 may contribute to a WNT-inhibitory environment in favor of maintaining stem cells in the growth plate, thus increasing bone growth. Our findings added another likely epigenetic modulator to the growing list of genes implicated in human overgrowth (Table 1). Interestingly, *SPIN4* is the first of such gene that recognizes modified histones but does not possess enzymatic activity or, at least until now, have not been identified as part of any enzymatic protein complex, like *SUZ12* in PRC2. Future genetic analysis of tall-stature patients will help clarify the genotypic and phenotypic spectrum of the disease.

A Roadmap Toward a Unifying Model of Epigenetic-related Overgrowth Disorders

Based on the abovementioned overgrowth conditions, an unexpected concept has emerged—that human overgrowth can be caused multiple highly diverse epigenetic abnormalities involving epigenetic writers and readers and DNA methylation; histone methylation at H3K36, H4K20, and H3K27; and chromatin remodeling (Fig. 2 and Table 1). These findings pose an intriguing mystery: why do such disparate epigenetic abnormalities produce such similar phenotypic overgrowth effects? This mystery can be divided into a two-part question: (1) Is there crosstalk among epigenetic modifications implicated in different overgrowth syndromes causing convergence to a common epigenetic landscape? (2) If such an overgrowth epigenetic landscape does exist, how does it drive cellular or physiological changes that could result in human overgrowth?

Crosstalk Between H3K36, H3K27 and DNA Methylation

Epigenomic studies in recent years have provided interesting insights into the first question. In 2019, a sensing pocket in EZH2 was identified as detecting H3K36 methylation (63). Unmodified H3K36 appears to activate PRC2 activity while methylated H3K36 appears to suppress its activity, suggesting that H3K36 methylation by NSD1/SETD2 may create a less permissive epigenetic landscape for H3K27 trimethylation by PRC2. Interestingly, this effect appears to be reciprocal, such that dimethylation of either H3K36 or H3K27 dramatically reduces the rate of trimethylation of the other residue (64). At first sight these findings might seem paradoxical because NSD1 and EZH2 appear to have opposing actions and yet both cause overgrowth.

However, careful examination of the epigenetic crosstalk may provide a possible solution. Indeed, the methylation status at H3K36 and H3K27 are inversely correlated across the genome, such that H3K27me1 colocalizes with H3K36me3 along the bodies of actively transcribed genes (65). However, another end result of this reciprocal relationship is that H3K27me2 colocalizes with H3K36me2 across the genome, many of which are in the intergenic regions (66). Based on these observations, Deevy and Bracken proposed a hypothesis where H3K36me2 and H3K27me2 across a broad region of the genome may function as the "default" chromatin state to limit aberrant deposition of activating H3K36me3 or repressive H3K27me3 marks (67). As mentioned earlier, DNMT3A has a PWWP domains that recognizes both H3K36me2 and H3K36me3, with preferential binding to H3K36me2. Consequently, DNMT3A colocalizes with H3K36me2 in the intergenic region across the genome (68). In *Nsd1*-ablated mouse ES cells, decreased H3K36me2 in the intergenic regions led to a decreased DNMT3A localization and redistribution toward the H3K36me3-enriched gene body regions (69).

Therefore, the current body of work suggest a model where intergenic regions of the genome are enriched with histone mark H3K36me2, H3K27me2, and DNMT3A binding, and, consequently, variants in any 1 of *NSD1/SETD2*, PRC2 (*EZH2, EED, SUZ12*) or *DNMT3A* could disrupt this "default" chromatin state, albeit in different directions (67). Importantly, even if we do not fully understand the mechanisms by which the default chromatin state modulates growth, it might still provide a useful diagnostic tool if the "overgrowth" chromatin state can be defined and measured in patients' cells.

How About NFIX, CHD8, and SPIN4?

A very recent study showed evidence that the antagonism of *NSD1* on PRC2 is dependent on *SMARCB1* (70), which is the core subunit of the SWI/SNF chromatin remodeler. Considering that Malan syndrome (a Sotos-like syndrome) is caused by variants in *NFIX* that functionally interact with the same SWI/SNF chromatin remodeler (20), this latest discovery may provide important insight into the mechanistic connection between Malan syndrome and Sotos syndrome.

The main function of the CHD family of chromatin remodeling complexes is to facilitate histone-DNA interaction and organize nucleosome spacing during DNA replication. Another function of these chromatin remodelers is to regulate chromatin accessibility during transcription, although it is unclear if that process involves a change in histone modification. Interestingly, a recent study

showed that CHD8 suppression led to significant reduction of H3K36me3 along the actively transcribed gene bodies (71). This study therefore demonstrated that decreased CHD8 activity could affect chromatin state.

A Working Hypothesis that Involves WNT Signaling

As discussed previously, there is some evidence that a shared "overgrowth epigenomic landscape" may explain the shared phenotype of the various human overgrowth disorders. However, the molecular connection of such a landscape with accelerated cellular and organismal growth remains elusive. We propose that one (of the many) plausible pathways could involve canonical WNT/beta-catenin signaling. WNT signaling plays a crucial role in regulating stem cell behavior both during embryonic development (72) and in adult tissues (73). Specifically, WNT signaling appears to play a dual role in controlling both stem cells self-renewal and differentiation in a dose-dependent manner, with low levels of WNT signaling favoring renewal and high levels favoring differentiation (74, 75).

Recent evidence suggests that WNT signaling is regulated by some of the same epigenetic mechanisms that have been implicated in overgrowth disorders. For example, genome-wide studies showed that EZH2 colocalizes with and regulates beta-catenin targeted genes across the genome (76, 77). Similarly, CHD8 was found to regulate WNT/beta-catenin signaling (51) via its ability to interact with histones (78). In the growth plate, WNT signaling is necessary for normal chondrocyte proliferation and differentiation (79), but the resting zone, in which the skeletal stem cells reside (80), is maintained in a WNT-inhibitory environment (81). Our recent study of an X-linked overgrowth disorder involving *SPIN4* showed evidence that *SPIN4* promotes canonical WNT/beta-catenin signaling (55). We also showed evidence that loss of *Spin4* in mice results in a WNT-inhibitory environment in the resting zone of the growth plate, which might promote stem cell maintenance and thus enhance longitudinal bone growth.

Taken together, these findings suggest the following working hypothesis to explain the common overgrowth phenotype resulting from variants in disparate epigenetic regulators. Epigenetic writers, such as *NSD1, EZH2, DNMT3A*, and chromatin remodelers like *CHD8* may result in a similar overgrowth epigenomic landscape that could, for example, involve disrupted H3K36me2, H3K27me2, and DNA methylation in the intergenic regions. We propose that the altered epigenomic landscape may affect the genomic recruitment of transcription factors important for WNT/beta-catenin signaling, which is normally mediated by histone readers like *SPIN4*. The end result is altered WNT/beta-catenin signaling in stem cells that results in overgrowth of the skeleton, visceral organs, and/or brain.

Conclusions

Overgrowth syndromes can be caused by variants in multiple genes that participate in a wide variety of epigenetic pathways, including DNA methylation, various types of histone methylation, and chromatin remodeling. The reason that such disparate epigenetic abnormalities produce such a similar overgrowth phenotype remains unclear. However, recent evidence suggests this shared phenotype may be related to crosstalk among these disparate epigenetic mechanisms, leading to a

shared overgrowth epigenomic landscape, which in turn may modulate final common growth-regulating pathways, such as WNT/beta-catenin signaling. A better understanding of the molecular mechanisms by which epigenetic perturbations cause human overgrowth may provide important insights into development of epigenetic therapies, such as epidurgs (82) and epigenetic editing (83), for the care and management of overgrowth syndromes.

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Disclosures

No conflict of interest declared.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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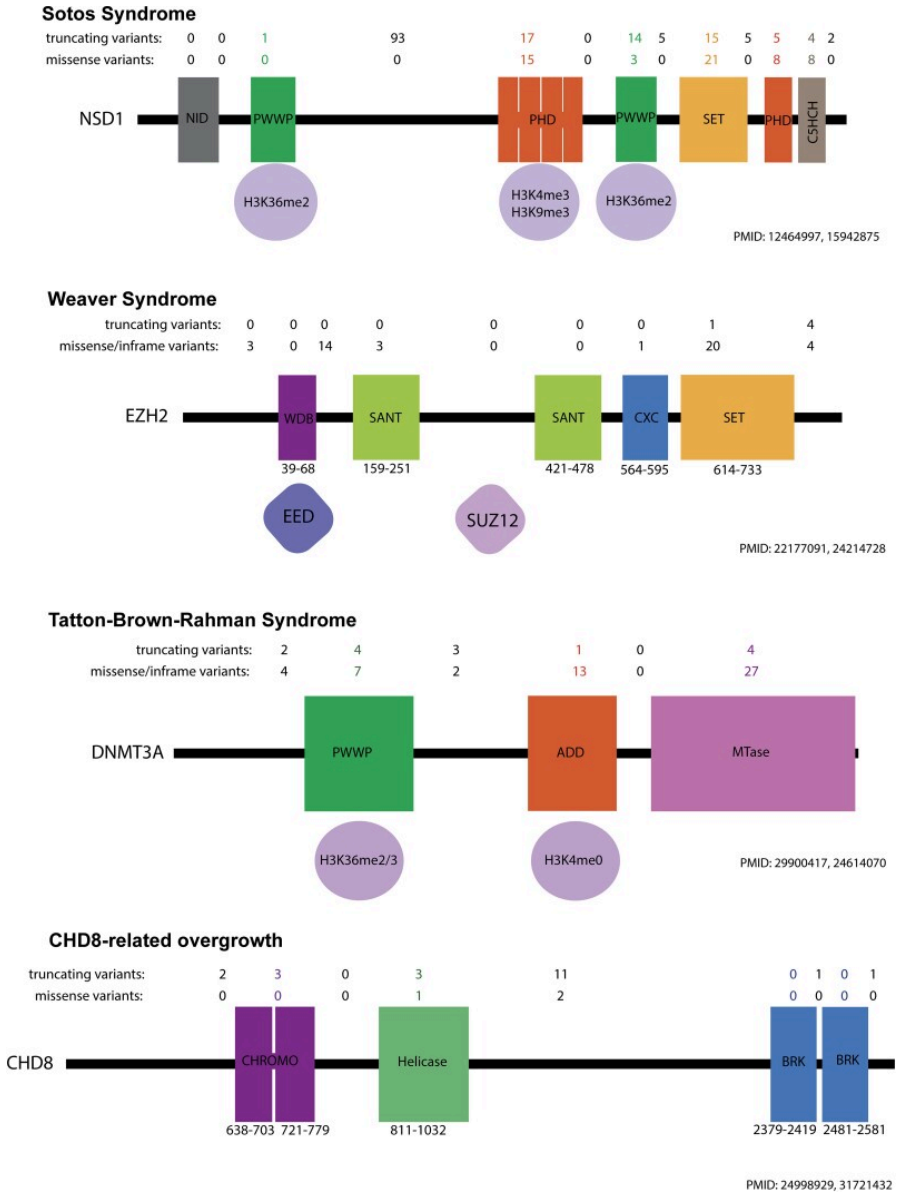
Figures and Tables

Figure 1.



Schematic diagrams of NSD1, EZH2, DNMT3A, and CHD8 proteins. Rectangles indicate functional domains; circles, ovals and diamonds indicate other proteins that interact with these domains. The numbers above each diagram indicate the number of reported variants within or between functional domains. Citations are shown as PubMed ID numbers.

Table 1.

Monogenic overgrowth syndromes caused by variants in epigenetic regulators

Gene	Epigenetic function	Overgrowth syndrome	Reference
NSD1	Histone methylation (H3K36, H4K20) Histone reader (H3K4me, H3K9me)	Sotos syndrome (OMIM 117550)	(10)
SETD2	Histone methylation (H3K36)	Luscan-Lumish syndrome (OMIM 616831)	(60, 61)
NFIX	Histone Binder (unmodified H1, H3)	Malan syndrome (OMIM 614753)	(16, 62)
EZH2	Core component of PRC2 complex for histone methylation (H3K27)	Weaver syndrome (OMIM 277590)	(26, 27)
EED	Core component of PRC2 complex for histone methylation (H3K27)	Cohen-Gibson syndrome (OMIM 617561)	(31)
SUZ12	Core component of PRC2 complex for histone methylation (H3K27)	Imagawa-Matsumoto syndrome (OMIM 606245)	(32)
DNMT3A	DNA methylation	Tatton-Brown Rahman syndrome (OMIM 615879)	(35)
CHD8	ATP-dependent chromatin remodeler	Intellectual developmental disorder with autism and macrocephaly (OMIM 615032)	(48, 49)
SPIN4	Histone reader (H3K4me, H4K20me)	X-linked overgrowth disorder	(55)

Figure 2.

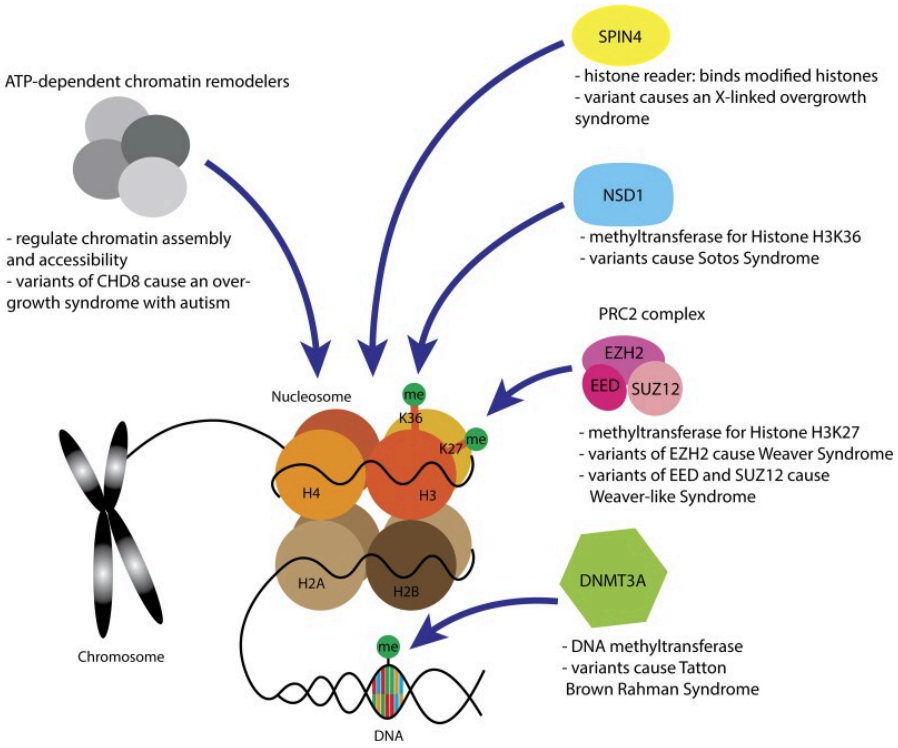


Diagram depicting epigenetic mechanisms involved in overgrowth syndromes. In the cell nucleus, the double helix DNA is packaged around histones forming nucleosomes, the repeating structural unit of chromatin and chromosome. Variants in genes that regulate DNA or histone modifications, which in turn affect gene expression, could result in a variety of over-growth syndromes.