Mutations in the DNA methyltransferase gene DNMT3A cause an overgrowth syndrome with intellectual disability

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Overgrowth disorders are a heterogeneous group of conditions characterized by increased growth parameters and other variable clinical features such as intellectual disability and facial dysmorphism\(^1\). To identify new causes of human overgrowth, we performed exome sequencing in ten proband-parent trios and detected two \textit{de novo} DNMT3A mutations. We identified 11 additional \textit{de novo} mutations by sequencing \textit{DNMT3A} in a further 142 individuals with overgrowth. The mutations alter residues in functional \textit{DNMT3A} domains, and protein modeling suggests that they interfere with domain-domain interactions and histone binding. Similar mutations were not present in 1,000 UK population controls (13/152 cases versus 0/1,000 controls; \(P < 0.0001\)). Mutation carriers had a distinctive facial appearance, intellectual disability and greater height. \textit{DNMT3A} encodes a DNA methyltransferase essential for establishing methylation during embryogenesis and is commonly somatically mutated in acute myeloid leukemia\(^3\)\(^-\)\(^4\). Thus, \textit{DNMT3A} joins an emerging group of epigenetic DNA- and histone-modifying genes associated with both developmental growth disorders and hematological malignancies\(^5\).

Control of human growth is highly complex and is influenced by common and rare genetic variation\(^6\). The study of human overgrowth syndromes, which are characterized by increased prenatal and postnatal growth relative to age-related peers, has provided important insights into fundamental biological processes involved in growth control\(^1\). As many growth disorders present as non-familial cases with a distinctive phenotype, we hypothesized that \textit{de novo} gene mutations might underlie some cases. To investigate this, we are conducting trio-based exome sequencing in individuals with overgrowth and their parents using the Illumina TruSeq exome enrichment array. Specifically, we perform sequencing with an Illumina HiSeq 2000, align the data with Stampy, perform variant calling with Platypus, perform variant annotation with SAVANT and identify potential \textit{de novo} variants using a custom R script.

Review of the first ten trios identified two with apparent \textit{de novo} mutations in \textit{DNMT3A} (encoding DNA (cytosine-5)-methyltransferase 3A), which were of immediate interest because of the functional relationship of \textit{DNMT3A} with \textit{EZH2}, a known overgrowth predisposition gene mutated in Weaver syndrome\(^7\)\(^,\)\(^8\). By Sanger sequencing, we confirmed that the \textit{DNMT3A} mutations, which resulted in an in-frame deletion (p.Trp297del) in COG0274 and a nonsynonymous substitution (p.Leu648Pro) in COG0553, were present in the probands but not in their parents (Table 1 and Supplementary Fig. 1).

To further evaluate the role of \textit{DNMT3A}, we sequenced the full coding sequence and intron-exon boundaries of the gene by Sanger sequencing in an additional 142 individuals with overgrowth in whom mutations in \textit{NSD1}, \textit{EZH2} and \textit{PTEN} and dysregulation of the 11p15 growth-regulatory region had been excluded and for whom parental DNA was also available (Supplementary Table 1). We identified an additional 11 \textit{de novo} \textit{DNMT3A} mutations. Thus, in total, we found 13 different \textit{de novo} \textit{DNMT3A} mutations in 152 individuals with overgrowth phenotypes: 10 nonsynonymous mutations, 2 small frameshifting insertions and 1 in-frame deletion (Fig. 1, Table 1 and Supplementary Fig. 1). These data establish \textit{DNMT3A} mutations

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Received 17 December 2013; accepted 12 February 2014; published online 9 March 2014; corrected after print 25 April 2014; doi:10.1038/ng.2917
as a cause of a new human disorder that we have termed 'DNMT3A overgrowth syndrome'.

A consistent phenotype, characterized by a distinctive facial appearance, tall stature and intellectual disability, was evident among the 13 individuals with de novo DNMT3A mutations (Fig. 2 and Table 1). Facial gestalt was characterized by a round face, heavy horizontal eyebrows and narrow palpebral fissures (Fig. 2). Height was greater in all individuals, ranging from 1.8 to 4.2 (mean of 3.0) s.d. above the mean with reference to UK 1990 growth data14. Head circumference was also greater, ranging from 1.2 to 5.1 (mean of 2.5) s.d. above the mean. Intellectual disability, which was described as moderate in 11 individuals and mild in the remaining 2, is also a key feature of the condition. Other less frequent clinical features were variably present (Table 1). More detailed phenotyping in larger series is required to evaluate whether these features are consistently associated with DNMT3A mutations and to better define the clinical spectrum of this new overgrowth syndrome.

In eukaryotic DNA, methylation preferentially occurs at cytosine bases, which are converted to 5-methylcytosine by four DNA methyltransferase enzymes—DNMT3A, DNMT3B, DNMT1 and DNMT3L2. DNMT3A and DNMT3B are essential for establishing new methylation marks after DNA replication and for establishing sex-dependent methylation marks for imprinted genes during gametogenesis3–5. The somatic mutational spectrum thus differs from the de novo mutations we identified in overgrowth cases: we did not detect any mutations affecting Arg882, and only 2 of the mutations we report (resulting in p.Arg749Cys and p.Pro904Leu substitutions) are present in the remaining 167 confirmed somatic DNMT3A mutations in hematological malignancies listed in the Catalogue of Somatic Mutations in Cancer (COSMIC) database (Supplementary Table 2). Protein structure modeling suggests that the somatic mutations altering Arg882 affect DNA binding, and functional analyses have demonstrated that alterations at this residue result in reduced methyltransferase activity, possibly through a dominant-negative mechanism6,16,19. To explore the potential impact of the DNMT3A

![Figure 1](https://example.com/figure1.png)

**Figure 1** DNMT3A structure and summary of variants. Schematic of the protein structure of DNMT3A with de novo variants identified in overgrowth cases indicated above the protein and nonsynonymous variants identified in controls indicated below the protein.

**Table 1** DNMT3A mutations and associated clinical features

| Case ID | Mutation | Protein alteration | Height (s.d.) | OFC (s.d.) | Age (years) | Intellectual disability | Other clinical features |
|---------|----------|-------------------|--------------|-----------|-------------|------------------------|------------------------|
| COG0274 | c.889G→T | p.Trp297del | 2.6          | 2.2       | 3.0         | Moderate              | Seizures              |
| COG1770 | c.929T>A  | p.Ile310Asn | 2.9          | 3.7       | 9.0         | Moderate              | Vertebral dysplasia    |
| COG1670 | c.934_937dupTCTT | p.Ser312fs | 3.2          | 2.8       | 20.5        | Moderate              | Atrial septal defect  |
| COG0141 | c.1594G>A | p.Gly532Ser | 2.3          | NA        | 5.9         | Moderate              | Atrial septal defect  |
| COG0422 | c.1643T>A | p.Met548Lys | 1.9          | 1.2       | 4.1         | Moderate              | Ventriculomegaly       |
| COG1288 | c.1645T>C | p.Cys549Arg | 1.8          | 3.8       | 11.3        | Moderate              | Umbilical hernia       |
| COG0593 | c.1943T>C | p.Leu648Pro | 3.4          | 5.1       | 19.0        | Moderate              | Scoliosis              |
| COG1688 | c.2099C>T | p.Pro700Leu | 2.8          | 2.1       | 13.0        | Mild                  | Scoliosis              |
| COG1695 | c.2245C>T | p.Arg749Cys | 4.0          | 3.8       | 12.0        | Moderate              | Ventriculomegaly       |
| COG1512 | c.2297dupA | p.Arg767fs | 3.8          | 1.6       | 8.2         | Moderate              | Ventriculomegaly       |
| COG1771 | c.2512A>G | p.Asn838Asp | 4.2          | 1.7       | 13.4        | Mild                  | Atrial septal defect  |
| COG0109 | c.2705T>C | p.Phe902Ser | 2.7          | 1.3       | 9.8         | Moderate              | Atrial septal defect  |
| COG1677 | c.2711C>T | p.Pro904Leu | 3.7          | 1.2       | 11.0        | Moderate              | Atrial septal defect  |

s.d. refers to the mean (UK 1990 growth data)14. NA, not available; OFC, occipito-frontal circumference.

*Age at which growth parameters were measured.

DNMT3A is one of the most frequently mutated genes in acute myeloid leukemia (AML)3,4,16. Somatic DNMT3A mutations are detected in approximately one-third of cytogenetically normal AML cases and have also been reported in other hematological neoplasms, such as myelodysplastic syndrome (MDS)17,18. Over half of the somatic DNMT3A mutations target a single residue, Arg882, with the remainder being nonsynonymous and truncating mutations scattered throughout the gene3,16. The somatic mutational spectrum thus differs from the de novo mutations we identified in overgrowth cases: we did not detect any mutations affecting Arg882, and only 2 of the mutations we report (resulting in p.Arg749Cys and p.Pro904Leu substitutions) were also present in the 167 confirmed somatic DNMT3A mutations in hematological malignancies listed in the Catalogue of Somatic Mutations in Cancer (COSMIC) database (Supplementary Table 2).
mutations identified in overgrowth cases, we undertook protein structure modeling, in which the residues altered by nonsynonymous mutations in the MTase domain appeared to be located at the interaction interface with the ADD domain, whereas those in the ADD domain were close to the histone H3-binding region (Fig. 3). The Arg767 residue in the MTase domain that was altered by a frameshifting insertion was situated at the interface between DNMT3A and DNMT3L. Thus, whereas none of the overgrowth-associated mutations appear likely to affect DNA binding, their positions and the role of the ADD domain in recognizing unmethylated lysine 4 of histone H3 suggest that they might interfere with domain-domain interactions and histone binding, thereby disrupting de novo methylation.

Taken together, these data are intriguing, as they show both clear differences and some overlap between the DNMT3A mutational spectra in malignancies and overgrowth. The mechanism of pathogenesis in the DNMT3A overgrowth syndrome is currently unclear, although a simple haploinsufficiency model appears unlikely given the small proportion of truncating mutations. Of note, mice heterozygous for a Dnmt3a null allele are grossly phenotypically normal, although it is unclear whether this is because loss of one copy of Dnmt3a is not associated with overgrowth or because the overgrowth phenotype is too subtle to detect in mice. Further functional and mutational analyses will be of interest to extend and illuminate these observations. Long-term follow-up of individuals with DNMT3A overgrowth syndrome, with a particular focus on cancer incidence, will also be of interest. Thus far, none of the probands have developed malignancies, although the oldest is only 29 years of age. Hematological malignancies with somatic DNMT3A mutations typically occur in middle-aged individuals, and it is thus possible that increased cancer risk only manifests at older ages.

DNMT3A joins an emerging family of genes with dual roles in the pathogenesis of syndromic overgrowth and myeloid neoplasms. Other similar genes include EZH2 and NSD1 (ref. 5). The overgrowth phenotypes associated with constitutional mutations in EZH2 and NSD1, which are called Weaver syndrome and Sotos syndrome, respectively, are similar to each other and to DNMT3A overgrowth syndrome. Somatic EZH2 mutations, both activating and inactivating, occur in AML and in myeloproliferative neoplasms and myelodysplastic syndromes with poor prognosis. Somatic NSD1 point mutations are rare, but the NUP90-NSD1 fusion protein, generated through a recurrent t(5;11)(q35.3;p15.5) translocation, is present in approximately 5% of childhood AML cases. Both EZH2 and NSD1 are histone methyltransferases that have key roles in regulating transcription through histone modification and chromatin modeling. EZH2 catalyzes the trimethylation of lysine residue 27 in histone H3 (H3K27me3) and is associated with transcriptional repression, whereas NSD1 preferentially catalyzes methylation of lysine residue 36 of histone H3 (H3K36me1), which is primarily associated with transcriptional activation. Of note, another gene involved in chromatin modification that is often mutated in AML and MDS, ASXL1, is also associated with a growth disorder. Constitutional de novo truncating mutations of ASXL1 cause Bohring-Opitz syndrome, a rare disorder characterized by severe undergrowth, severe intellectual disability, a characteristic facial appearance and flexion deformities. This suggests that other epigenetic regulatory genes that are somatically mutated in hematological malignancies, such as TET2, IDH1 and IDH2, would be worth evaluating in developmental growth disorders.

URLs. 1958 Birth Cohort Collection, http://www.cls.ioe.ac.uk/; Picard, http://picard.sourceforge.net/.

METHODS

Methods and any associated references are available in the online version of the paper.

Accession codes. DNMT3A mutation nomenclature corresponds to Ensembl transcript ENST00000264709.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

ACKNOWLEDGMENTS

We thank the families for their participation in our research and the physicians and nurses who recruited them. Samples were collected through the Childhood Overgrowth Collaboration; a full list of collaborators is presented in the Supplementary Note. We are grateful to M. Warren-Perry, D. Dudakia and J. Bull for assistance in recruitment and to E. Moran (New York University Hospital for Joint Diseases) and A. Murray (University Hospital of Wales) for their clinical input.
for COG1770 and COG0109, respectively. We thank A. Strydom for assistance in preparing the manuscript. We are grateful to G. Lunter and M. Munz (Wellcome Trust Centre for Human Genetics, Oxford University) for their contributions to the development of the custom annotation tool SAVANT. We acknowledge use of services provided by the Institute of Cancer Research Genetics Core Facility, which is managed by S.H. and N.R. We acknowledge National Health Service (NHS) funding to the Royal Marsden/Institute of Cancer Research National Institute for Health Research (NIHR) Biomedical Research Centre. We also thank Mariani Foundation Milan for supporting the clinical activity of Genetica Clinica Pediatrica, Fondazione MBMM, AO San Gerardo Monza. This research was supported by the Wellcome Trust (100210/Z/12/Z) and by the Institute of Cancer Research, London.

AUTHOR CONTRIBUTIONS
S.S., E. Ramsay, S.d.V.D., S.H. and E.O. undertook the molecular analyses. E. Ruark undertook the bioinformatics analyses. A.Z. coordinated recruitment. S.S., E. Ramsay, S.d.V.D., S.H. and E.O. undertook the molecular analyses.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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ONLINE METHODS

Case subjects. Individuals with overgrowth were recruited through the Childhood Overgrowth Study. The research was approved by the London Multicentre Ethics Committee (reference MREC/01/2/44), and informed consent was obtained from all participants and/or families. DNA was extracted from peripheral blood and was available from all probands and their parents. Detailed phenotypic information was also obtained through a standardized questionnaire and photographs. Specific consent to publish facial photographs was obtained. A full list of collaborators is given in the Supplementary Note.

Control samples. We used lymphocyte DNA from 1,000 population-based controls obtained from the 1958 Birth Cohort Collection, a continuing follow-up study of individuals born in the UK in 1 week in 1958. Biomedical assessment was undertaken during 2002–2004, at which point point blood samples and informed consent were obtained for the creation of a genetic resource.

Exome sequencing. We prepared DNA libraries from 1.5 µg of blood-derived genomic DNA using the Paired-End DNA Sample Preparation kit (Illumina). DNA was fragmented using Covaris technology, and libraries were prepared without size selection on a gel. We performed target enrichment using the TruSeq Exome Enrichment kit (Illumina) targeting 62 Mb of the human genome. Captured DNA libraries were PCR amplified using the supplied paired-end PCR primers. Sequencing was performed with an Illumina HiSeq 2000, generating 2 × 101-bp reads.

Exome variant calling and de novo mutation detection. We mapped sequencing reads to the human reference genome (hg19) using Stampy (version 1.0.14)\(^27\). Duplicate reads were flagged using Picard version 1.60. Median coverage of the target at 15× was 91% across the 1,030 individuals (1,000 controls and 30 individuals from the 10 overgrowth trios), with a median of 47,215,315 reads mapping to the target. We used Platypus version 0.1.5 to perform variant calling\(^28\) and SAVANT (a custom strand-aware variant annotation tool written in Python), which follows Human Genome Variation Society (HGVS) nomenclature and ensures consistent annotation of indels, shifting them to their most 3′ position in the transcript. The SAVANT script is available upon request. We used an R script to identify variants present in cases but not in either of their parents, and this script is available upon request.

DNMT3A mutation analysis. We performed Sanger sequencing of PCR products from genomic DNA to confirm the mutations identified by exome sequencing and to mutationally analyze the gene in the overgrowth series. We designed PCR primers to amplify the 22 coding exons and intron-exon boundaries of DNMT3A in 4 multiplex PCR reactions (Supplementary Table 1). PCR was carried out using a Qiagen Multiplex PCR kit according to the manufacturer’s instructions. Products were sequenced with the original PCR primers or with internal sequencing primers (exons 3, 6, 8, 10, 14 and 22) using the BigDye Terminator Cycle Sequencing kit and an ABI 3730 Genetic Analyzer (Applied Biosystems). Sequences were analyzed using Mutation Surveyor software v3.97 (SoftGenetics) and were verified by manual inspection. All mutations were confirmed by bidirectional sequencing of a second, independently amplified PCR product.

Statistical analysis. The frequencies of mutations in cases and controls were compared using a two-sided Fisher’s exact test.

Protein structural modeling. The model of the DNMT3A-DNMT3L complex was created using the crystal structures of the DNMT3A ADD domain (Protein Data Bank (PDB) 3A1B), the DNMT3A MTase domain (PDB 2QRY) and full-length DNMT3L (PDB 2PVC). Bound DNA was positioned by superposing the crystal structure of bacterial cytosine methyltransferase HhaI in complex with DNA (PDB 1MHT). First, the structure of partial DNMT3L in complex with DNMT3A was superposed on the structure of full-length DNMT3L to show the interactions of full-length DNMT3L with DNMT3A. Subsequently, the ADD domain of DNMT3A was positioned by superposing it onto the homologous region of the second molecule of full-length DNMT3L. Finally, DNA was positioned by superposing the crystal structure of bacterial cytosine methyltransferase HhaI in complex with DNA onto the MTase domain of DNMT3A, placing the DNA at the SAM/DNA-binding region. The image was generated using PyMOL visualization software (PyMOL Molecular Graphics System, version 1.6.0.0, Schrödinger).

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**Corrigendum: Mutations in the DNA methyltransferase gene **\textit{DNMT3A}** cause an overgrowth syndrome with intellectual disability**

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\textit{Nat. Genet.} 46, 385–388 (2014); published online 9 March 2014; corrected after print 25 April 2014

In the version of this article initially published, the protein alterations for three cases (COG1770, COG1670 and COG0141) were listed incorrectly in Table 1. The correct protein alterations for these three cases are p.Ile310Asn, p.Ser312fs and p.Gly532Ser, respectively. These errors have been corrected in the HTML and PDF versions of the article.