RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Weaver Syndrome and *EZH2* Mutations: Clarifying the Clinical Phenotype

Katrina Tatton-Brown,[1]* Anne Murray,[1] Sandra Hanks,[1] Jenny Douglas,[1] Ruth Armstrong,[2] Siddharth Banka,[3] Lynne M. Bird,[4] Carol L. Clericuzio,[5] Valerie Cormier-Daire,[6] Tom Cushing,[5] Frances Flinter,[7] Marie-Line Jacquemont,[8] Shelagh Joss,[9] Esther Kinning,[9] Sally Ann Lynch,[10] Alex Magee,[11] Vivienne McConnell,[11] Ana Medeira,[12] Keiichi Ozono,[13] Michael Patton,[14] Julia Rankin,[15] Debbie Shears,[16] Marleen Simon,[17] Miranda Splitt,[18] Volker Strenger,[19] Kyra Stuurman,[20] Clare Taylor,[21] Hannah Titheradge,[22] Lionel Van Maldergem,[23] I. Karen Temple,[24] Trevor Cole,[22] Sheila Seal,[1] Childhood Overgrowth Consortium, and Nazneen Rahman[1]

[1]Division of Genetics & Epidemiology, Institute of Cancer Research, Sutton, UK

[2]Department of Medical Genetics, Addenbrooke's Hospital, Cambridge, UK

[3]Centre for Genetic Medicine, Institute of Human Development, University of Manchester, Manchester, UK

[4]University of California, San Diego, and Rady Children's Hospital, San Diego, California

[5]Pediatric Genetics, University of New Mexico, Albuquerque, New Mexico

[6]Department of Medical Genetics, Hopital Necker Enfants Malades, Paris, France

[7]Clinical Genetics, Guy's and St Thomas' Foundation Trust, London, UK

[8]Unité de Génétique Médicale, CHU La Réunion, Réunion, France

[9]Clinical Genetics, West of Scotland Genetics Service, Glasgow, UK

[10]National Centre for Medical Genetics, Dublin, The Republic of, Ireland

[11]Northern Ireland Regional Genetics Service, Belfast City Hospital, Belfast, Northern Ireland, UK

[12]Servico de Genetica, Hospital S Maria, Lisbon, Portugal

[13]Department of Developmental Medicine (Pediatrics), Osaka University Graduate School of Medicine, Osaka, Japan

[14]Medical Genetics, St George's University of London, London, UK

[15]Peninsula Clinical Genetics Service, Royal Devon and Exeter Foundation NHS Trust, Exeter, UK

[16]Department of Clinical Genetics, Churchill Hospital, Oxford, UK

[17]Department of Clinical Genetics, Erasmus Medical Centre, Rotterdam, The Netherlands

[18]Institute of Human Genetics, International Centre for Life, Newcastle upon Tyne, UK

[19]Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

[20]Department of Clinical Genetics, VU University Medical Centre, Amsterdam, The Netherlands

[21]Institute of Medical Genetics, University Hospital of Wales, Cardiff, UK

[22]West Midlands Regional Genetics Service, Birmingham Women's Hospital, Birmingham, UK

[23]Centre de Génétique Humaine, Université de Franche-Comté, Besançon, France

[24]Human Genetics and Genomic Medicine, Faculty of Medicine, University of Southampton, Southampton, UK

Manuscript Received: 26 April 2013; Manuscript Accepted: 8 August 2013

Weaver syndrome, first described in 1974, is characterized by tall stature, a typical facial appearance, and variable intellectual disability. In 2011, mutations in the histone methyltransferase, *EZH2*, were shown to cause Weaver syndrome. To date, we have identified 48 individuals with *EZH2* mutations. The mutations were primarily missense mutations occurring throughout the gene, with some clustering in the SET domain (12/48).

*Correspondence to:
Dr. Kate Tatton-Brown, Division of Genetics & Epidemiology, Institute of Cancer Research, Sutton, UK.
E-mail: kate.tatton-brown@icr.ac.uk
Article first published online in Wiley Online Library (wileyonlinelibrary.com): 8 November 2013
DOI 10.1002/ajmg.a.36229

Truncating mutations were uncommon (4/48) and only identified in the final exon, after the SET domain. Through analyses of clinical data and facial photographs of *EZH2* mutation-positive individuals, we have shown that the facial features can be subtle and the clinical diagnosis of Weaver syndrome is thus challenging, especially in older individuals. However, tall stature is very common, reported in >90% of affected individuals. Intellectual disability is also common, present in ~80%, but is highly variable and frequently mild. Additional clinical features which may help in stratifying individuals to *EZH2* mutation testing include camptodactyly, soft, doughy skin, umbilical hernia, and a low, hoarse cry. Considerable phenotypic overlap between Sotos and Weaver syndromes is also evident. The identification of an *EZH2* mutation can therefore provide an objective means of confirming a subtle presentation of Weaver syndrome and/or distinguishing Weaver and Sotos syndromes. As mutation testing becomes increasingly accessible and larger numbers of *EZH2* mutation-positive individuals are identified, knowledge of the clinical spectrum and prognostic implications of *EZH2* mutations should improve.

Key words: *EZH2*; Weaver syndrome; histone methyl transferases

How to Cite this Article:
Tatton-Brown K, Murray A, Hanks S, Douglas J, Armstrong R, Banka S, Bird LM, Clericuzio CL, Cormier-Daire V, Cushing T, Flinter F, Jacquemont M-L, Joss S, Kinning E, Lynch SA, Magee A, McConnell V, Medeira A, Ozono K, Patton M, Rankin J, Shears D, Simon M, Splitt M, Strenger V, Stuurman K, Taylor C, Titheradge H, Van Maldergem L, Temple IK, Cole T, Seal S, Childhood Overgrowth Consortium, Rahman N. 2013. Weaver syndrome and *EZH2* mutations: Clarifying the clinical phenotype.

Am J Med Genet Part A 161A:2972–2980.

INTRODUCTION

Weaver et al. [1974] described two boys with accelerated osseous maturation, unusual facies, and camptodactyly and proposed that this constellation of phenotypic features constituted a novel clinical entity. Subsequent to this initial description over 50 individuals with similar and additional clinical features were reported and the condition became eponymously known as Weaver syndrome (OMIM 277590) [Majewski et al., 1981; Meinecke et al., 1983; Roussounis and Crawford, 1983; Tsukahara et al., 1984; Farrell and Hughes, 1985; Ardinger et al., 1986; Thompson et al., 1987; Greenberg et al., 1989; Kondo et al., 1990, 1991; Muhonen and Menezes, 1990; Ramos-Arroyo et al., 1991; Cole et al., 1992; Dumic et al., 1993; Scarano et al., 1996; Fryer et al., 1997; Proud et al., 1998; Derry et al., 1999; Freeman et al., 1999; Sarigul et al., 1999; Kelly et al., 2000; Ozkan and Bereket, 2000; Huffman et al., 2001; Crawford and Rohan, 2005; Coulter et al., 2008; Iatrou et al., 2008; Bansal and Bansal, 2009; Basel-Vanagaite, 2010; Mikalef et al., 2010]. However, because of the subtlety of the Weaver syndrome phenotype and the overlap with other overgrowth syndromes, particularly Sotos syndrome, the clinical diagnosis can be challenging, even for the experienced dysmorphologist. Thus the robustness of the many reported Weaver syndrome clinical associations is unclear.

In 2011, we and another independent group reported that constitutional *EZH2* mutations cause Weaver syndrome [Gibson et al., 2011; Tatton-Brown et al., 2011]. *EZH2* (Enhancer of Zeste homolog 2) is located at 7q36.1 and encodes a histone methyltransferase involved in chromatin modeling and transcriptional repression. In combination with EED (Embryonic Ectoderm Development protein, mouse, homolog of) and SUZ12 (Suppressor of Zeste 12, drosophila, homolog of), it forms the polycomb repressive complex 2 (PCR2) which catalyzes the methylation of lysine residue 27 of histone 3 (H3K27) resulting in chromatin compaction and repression of transcription [Cao et al., 2002]. *EZH2* activity is inhibited by AKT (v-akt murine thymoma viral oncogene homolog 1), a key component of the PI3K/mTOR growth regulatory pathway, through the phosphorylation of serine 21, which blocks binding of *EZH2* to histone 3 [Cha et al., 2005].

Somatic activating and inactivating mono- and biallelic *EZH2* mutations have been identified in multiple hematological malignancies [Chase and Cross, 2011]. A recurrent monoallelic activating Tyr646 mutation has been identified in lymphomas, particularly diffuse large cell B-cell type and follicular lymphomas [Morin et al., 2010; Sneeringer et al., 2010]. In contrast, inactivating mono- and biallelic missense and truncating mutations, throughout *EZH2*, are associated with poor prognosis myelodysplastic and myeloproliferative neoplasms [Ernst et al., 2010].

In our initial 2011 paper on *EZH2* and Weaver syndrome we described 19 individuals with *EZH2* mutations [Tatton-Brown et al., 2011]. Subsequent to this study we have extended our molecular and clinical analyses to identify, in total, 48 individuals with *EZH2* mutations from 39 unrelated families. Using data from these cases, we have defined the *EZH2* mutational spectrum and provide the first detailed evaluation of the clinical features associated with *EZH2*-related Weaver syndrome.

PATIENTS AND METHODS

Case Series

The research was approved by the London Multicentre Research Ethics Committee and consent was obtained from participating individuals and/or their parents. Individuals recruited to the Childhood Overgrowth Genetics (COG) study with variable overgrowth phenotypes were screened for mutations in *EZH2*. Forty-eight individuals, 20 males and 28 females, with *EZH2* mutations (termed *EZH2* mutation-positive individuals) were identified. The patients had been recruited from Clinical Genetics centers worldwide and included 25 from the UK; 10 from the USA; 3 from France; 2 from the Netherlands; 2 from Portugal; 2 from the Reunion Islands, and 1 from each of Austria, Belgium, the Republic of Ireland, and Japan. Clinical information, in the form of a standardized overgrowth questionnaire (routinely sent to recruiting physicians) and an *EZH2*-specific supplementary questionnaire, was requested for all *EZH2* mutation-positive individuals (see Fig. S1). Photographs were additionally received for 43 of the *EZH2* mutation-positive individuals. These were shown to a panel of five experienced dysmorphologists who assigned them to one of three phenotypic categories: (1) "typical Weaver syndrome," (2) "possible Weaver syndrome," or (3) "not Weaver syndrome." If a patient was assigned to the latter category and an alternative diagnosis such as Sotos syndrome was suspected, this was noted. Where possible, a majority score was used. However, if the results from the five panelists were divergent, an average (median) score was calculated and used. The patient's age when the photograph was taken was recorded as <1, 1–5, 5–10, or >10 years.

Molecular Studies

Four individuals (cases 19, 34, 40, and 46, Table SI) were identified to have *EZH2* mutations through exome sequencing as previously described [Snape et al., 2011; Tatton-Brown et al., 2011]. We subsequently performed Sanger sequencing of the full coding sequence and intron–exon boundaries of *EZH2* in 431 additional individuals from the COG study. We analyzed parental samples for the specific *EZH2* mutation identified in the proband, if samples were available.

Statistical Analyses

Independence of effects of phenotype group and age range was analyzed using a 4×3 contingency table, examining for deviation from the expected distribution (under the null hypothesis of independence of effects) using Pearson's chi-squared test (6df).

RESULTS

EZH2 Mutational Spectrum

We identified 48 *EZH2* mutations including 44 missense and 4 truncating variants (Fig. 1a). Variants were considered to be pathogenic if they were de novo, familial, and clearly segregating with the overgrowth phenotype or identical to a variant that had been classified as pathogenic in another individual. Thirty-eight variants fulfilled these criteria (Table SI). DNA was not available from both parents of two individuals with truncating variants; two individuals in whom the same amino acid residue, Arg684 and Glu148, had been substituted by a different amino acid as a de novo event in at least one other individual; one individual with an in-frame duplication and four individuals with missense variants. An additional patient had inherited a His618Tyr missense mutation from his father who did not have a clear overgrowth phenotype (Table SI). However, none of these variants were identified in over 2,000 in-house exomes from controls or breast cancer patients nor in over 6,000 exomes in the Exome variant server (http://evs.gs.washington.edu/EVS/) and all the missense variants affected highly conserved residues (Fig. 1b). Therefore, although we cannot be unequivocally certain of pathogenicity because the penetrance/expressivity of the mutations can be variable/mild, we considered it likely that these variants were causative of the overgrowth phenotype.

The 44 missense mutations were distributed throughout the gene with some clustering in the highly conserved SET domain (12/44, Fig. 1a). Two SET domain mutations, Arg684Cys and Ser652Cys, were seen recurrently: the Arg684Cys mutation in five unrelated individuals and the Ser652Cys mutation in two unrelated individuals. Only four truncating mutations were identified, all in the post-SET terminal exon, exon 20.

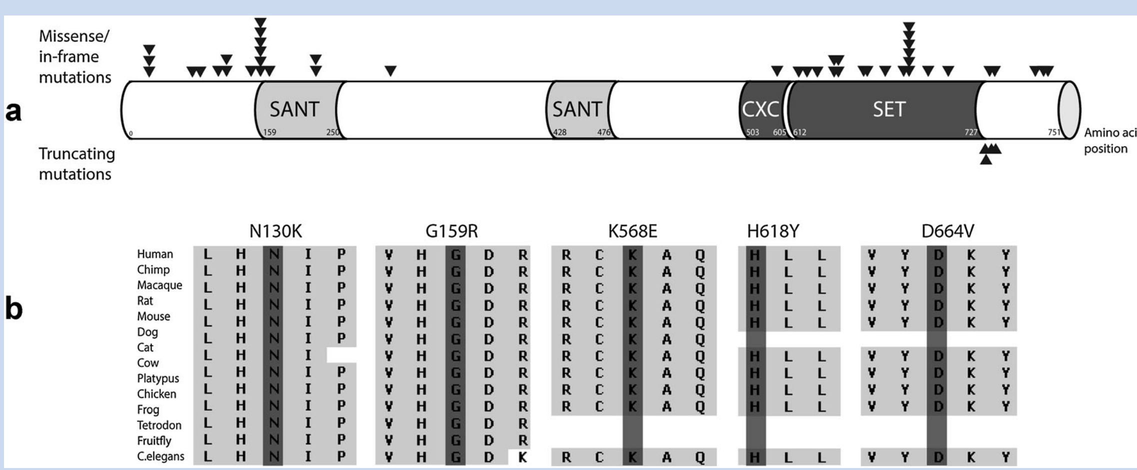

FIG. 1. (a) Distribution of *EZH2* missense and truncating mutations and (b) conservation of mutated residues in five cases with missense mutations (four where DNA from both parents was not available and one where the mutation was inherited from an unaffected father).

Clinical Features Associated With *EZH2* Mutations

The typical Weaver syndrome facial gestalt can be subtle and challenging to recognize. Among the 43 *EZH2* mutation-positive individuals in whom facial photographs were assessed and categorized, 20 were assigned to group 1 (classic Weaver syndrome), 11 to group 2 (possible Weaver syndrome) and 12 to group 3 (not typical for Weaver syndrome). In group 1, 10 individuals were at least 1 year and one individual was >10 years (with five and four individuals 1–5 years and 5–10 years, respectively). In group 2, one individual was <1 year, four were 1–5 years, two were 5–10 years, and four were >10 years and in group 3 there were no individuals who were <1 year, three were 1–5 years, one was 5–10 years, and eight were >10 years (Fig. 2). This distribution of ages and phenotypic group represented a significant excess of younger cases in group 1 and older cases in group 3 ($\chi^2 = 19.6$, $P = 0.003$ [6df]).

Facial features that characterized the 31 *EZH2* mutation-positive individuals considered to have classic and possible Weaver syndrome included ocular hypertelorism, almond shaped palpebral fissures, a broad forehead, and a pointed, "stuck-on" chin with horizontal skin crease and, in early childhood, large, fleshy ears, and retrognathia (Fig. 3). However, while those individuals with classic Weaver syndrome generally had all the listed features, individuals with possible Weaver syndrome had some but not all. Among the third "not Weaver syndrome" category, five individuals were thought to have Sotos syndrome and four were not considered to be dysmorphic. Additional, alternative, diagnoses proposed for category 3 patients included Kabuki syndrome and Peho syndrome, each suggested by one panelist for one affected individual.

The EZH2-related growth profile. Information regarding birth weight was available for 39 babies: 22 females and 17 males. Only 38% (15/39, including 11 females and four males) *EZH2* mutation-positive babies had a birth weight greater than two standard deviations above the mean (+2 SDs) with a median birth weight of +1.3 SDs and a range of −1.6 to +4.6 SDs. Birth length is likely to be a better correlate of an *EZH2* mutation with *EZH2* mutation-positive babies frequently described as long and skinny. Unfortunately, however, length is not always measured at birth and, even when it is, parental recall is not as accurate as for weight. However, of the 18 babies with *EZH2* mutations and a birth length recorded, 12 had a length greater than 2 SD above the mean with an overall range of −0.5 to +4.9 SDs (Table SI).

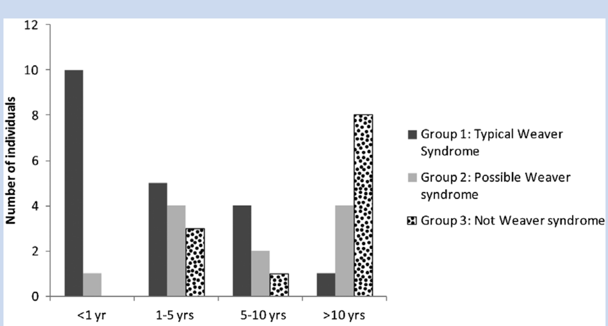

FIG. 2. Distribution of age and (facial) phenotypic groups.

Information regarding subsequent growth (height and head circumference) was available for 45 *EZH2* mutation-positive individuals of whom nine were adults (>18 years) and 36 were children (with ages between 0.4 and 16.6 years and a median age of 3.5 years). Thirty-five of the children and six of the adults [in total 41/45 (91%)] had a height at least 2 SD above the mean and in 14 children and 2 adults the height was at least +4 SDs (Fig. 4a, and Table SI). Included amongst the four individuals whose height was less than +2 SDs, were three adults who were reported to be tall as young children: case 4 was overgrown until she developed a severe scoliosis at the age of 18 months for which she subsequently required spinal surgery as a teenager; the height of case 42 was 5.7 SDs above the mean until the age of 3 after which growth velocity decelerated for no apparent reason and case 3 was reported to be tall as a child but information from childhood was unfortunately not available. In contrast to height, head circumference measurements in 40 *EZH2* mutation-positive children and adults ranged from −0.9 to +5.5 SDs with a median value of +1.8 SDs (Fig. 4b, and Table SI).

Most EZH2 mutation-positive individuals have a mild intellectual disability. Amongst the 45 *EZH2* mutation-positive individuals where information on intellect was provided, the majority had an intellectual disability (37/45, 82%) but this was most frequently mild (21/37, 57%). Twelve individuals had a moderate intellectual disability and only two had a severe disability. In addition, two individuals were said to have an intellectual disability but the degree of impairment was not provided. Eight individuals were reported to have normal intelligence, two individuals were considered too young to be able to assess the degree of intellectual impairment and no information was available for one individual.

Additional EZH2-associated clinical features. Poor coordination, often manifesting as clumsiness, was reported in 80% (28/35) of *EZH2* mutation-positive individuals. Hypotonia and hypertonia were reported in 44% (18/41) and 28% (11/39) of *EZH2* mutation-positive individuals, respectively, with a mixed picture of central hypotonia and peripheral hypertonia reported in three affected individuals. Additional clinical issues frequently reported included soft, doughy skin (49%, 17/35); camptodactyly sometimes in combination with additional joint contractures (45%, 17/38); hoarse, low-pitched cry (37%, 10/27), and umbilical hernia (43%, 17/40, Table SI). It is noteworthy that 8 of the 17 individuals with umbilical hernia required surgical repair. Although not specifically solicited on either the general or *EZH2*-specific questionnaire, flexion of the proximal and hyperextension of the distal interphalangeal joints (analogous to a mild boutonniere deformity) was identified through clinical examination of five affected adults. This deformity was not associated with any detriment to function but may be a useful diagnostic clue in older *EZH2* mutation-positive individuals.

Tumors occur, but not at high frequency, in EZH2 mutation-positive individuals. Tumors were reported in only two *EZH2* mutation-positive individuals: case 45 with a Glu745Lys missense mutation and a lymphoma diagnosed at the age of 13 years and case 31 with an Ala682Thr mutation, who developed acute lymphoblastic leukemia and neuroblastoma both at 13 months (Table SI). Despite the association between somatic inactivating mutations

FIG. 3. Facial appearance of *EZH2* mutation-positive individuals at (a) less than 1 year of age; (b) ages 1–5 years; (c) 5–10 years of age; (d) teenage/adults.

and chronic hematological malignancies, none of the latter were reported amongst the 48 *EZH2* mutation-positive individuals.

Imaging investigations in EZH2 mutation-positive Weaver syndrome. Osseous maturation was only assessed in 25 *EZH2* mutation-positive individuals but was advanced in all. Of interest, a discrepancy between the carpal and phalangeal bone maturation, with greater maturation reported for the carpal bones, was recorded for three affected individuals. However, this may be an underestimate of the number of *EZH2* mutation-positive individuals with a carpal/phalangeal bone age discrepancy as details additional to bone and chronological age were not requested on the clinical questionnaires.

Nine *EZH2* mutation-positive individuals, in whom brain imaging had been undertaken, had abnormal studies including four with isolated ventriculomegaly; one individual with ventriculomegaly and periventricular leukomalacia and four individuals each with either periventricular leukomalacia; pachygyria, and polymicrogyria; a small infracted area in the cerebellum or a persistent cavum septum pellucidum (Table SI).

Other clinical features. Other clinical features reported in more than one but less than 10 *EZH2* mutation-positive individual are shown in Table I. Until greater numbers of *EZH2* mutation-positive individuals are ascertained, it is not clear which of these features are true *EZH2* associations and which are coincidental, particularly for features that are common in the general population.

DISCUSSION

Through the identification of 48 *EZH2* mutation-positive individuals we have demonstrated that missense mutations are the primary

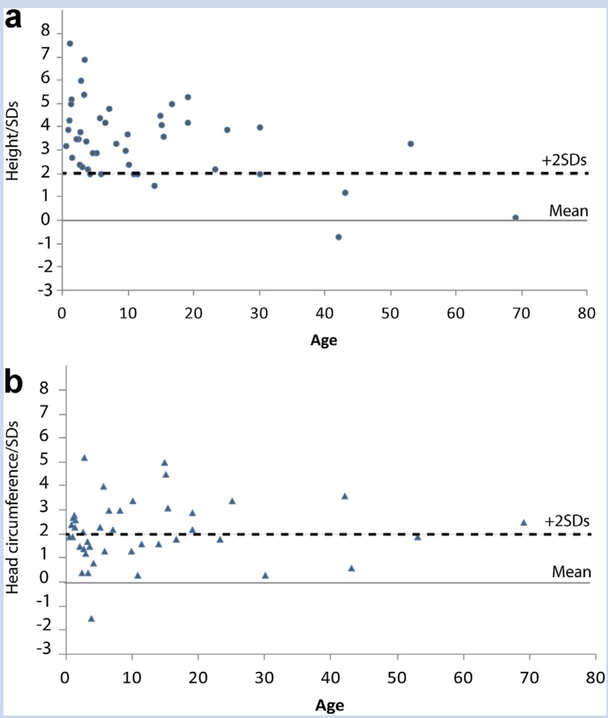

FIG. 4. Distribution of (a) height and (b) head circumference in *EZH2* mutation-positive individuals at varying ages.

TABLE I. Clinical Features Described in At Least Two But Less Than 10 *EZH2* Mutation-Positive Individuals

Skeletal abnormalities	
Clinodactyly	9
Scoliosis	6
Talipes equinovarus	5
Pectus excavatum/carinatum	4
Behavioral issues	
Temper tantrums	3
Attention deficit	2
Genito-urinary abnormalities	
Hydrocele	2
Congenital cardiac abnormalities	
VSD	2
Ophthalmological abnormalities	
Hypermetropia	3
Strabismus	2
Cutaneous	
Hemangioma	4
Café au lait macule	2
Hearing loss	2
Cleft palate	2
Tumors[a]	2

VSD, ventricular septal defect.
[a]Two *EZH2* mutation-positive individuals but with three tumors: neuroblastoma, ALL, and lymphoma.

EZH2 mutational mechanism in Weaver syndrome, present in over 90% of *EZH2 mutation-positive* individuals. To date, only four truncating mutations have been identified, all within the terminal exon, and therefore likely escape nonsense mediated RNA decay and result in a truncated protein that retains the SET domain. The predominance of missense mutations and the terminal location of the truncating mutations suggest that simple *EZH2* haploinsufficiency is unlikely to be the cause of Weaver syndrome. This is corroborated by phenotypic data published for five cases with deletions encompassing *EZH2* where tall stature or overgrowth is not reported although the authors have recently been informed of one case with tall stature and a 1.2 Mb deletion encompassing *EZH2* (http://decipher.sanger.ac.uk/). Functional studies to investigate the mechanism of pathogenesis would be of interest, particularly as the *EZH2* mutational spectrum in Weaver syndrome differs from the somatic mutational profile in hematological malignancies.

The clinical features associated with *EZH2* mutations are variable and rather non-specific, and clinical diagnosis is therefore challenging. Less than half (47%) of the *EZH2* mutation-positive individuals were considered to have the classic Weaver syndrome facial gestalt. However, it is noteworthy that the distribution of ages in the group 1 compared with group 3 are very different with over-representation of individuals <1 year of age in group 1 and individuals >10 years of age in group 3. This age distribution suggests that the facial phenotype is more easily recognized in younger childhood, that there is greater familiarity with the Weaver syndrome facial gestalt in this age range, or both. The data also suggest that review of photographs at younger ages may be helpful if a diagnosis of Weaver syndrome is being considered in older children or adults. The presence of additional features may also be helpful. Tall stature, with a height at least 2 SDs above the mean, is the most consistent *EZH2*-related clinical feature, present in ~90% of affected individuals. Intellectual disability is also common, present in ~80%, but can be very mild. Unfortunately both features are non-specific and generally common, which limits their utility as discriminating clinical features of Weaver syndrome.

More specific, but less frequent *EZH2*-related associations of Weaver syndrome, identified in 30–50% of affected individuals, include camptodactyly, hoarse, low cry, and soft, doughy skin. Many of these features are present in the neonatal period/early childhood and later resolve; they may be missed if a detailed neonatal/early childhood history is unavailable.

Five of the 48 individuals in our study were considered to have the facial features of Sotos syndrome, exemplifying the considerable clinical overlap between these two overgrowth conditions (Table II). The facial features associated with *NSD1* mutations are more distinctive than those of *EZH2*, and increased head circumference is more characteristic of *NSD1* mutations than *EZH2* mutations. However, robust clinical differentiation between these two conditions is not possible and thus *NSD1* mutation analysis should also be considered if *EZH2* testing is negative, and vice versa. Multi-gene testing, for example by next-generation sequencing targeted gene or exome assays, will be the optimal analysis allowing both genes to be analyzed.

The identification of constitutional *EZH2* mutations as a cause of Weaver syndrome has provided an objective means of

TABLE II. Molecular and Phenotypic Similarities and Differences Between *NSD1*-Positive Sotos Syndrome and *EZH2*-Positive Weaver Syndrome

Overgrowth syndrome	Causative gene	Growth profile in mutation-positive individuals[a]		Intellectual disability		Facial appearance	Associated clinical features
Weaver syndrome	*EZH2*	↑[b]Ht and OFC	40%	None	20%	Frontal bossing, round face, hypertelorism. Large, fleshy ears, retrognathia and "stuck-on chin" in early childhood	Camptodactyly
		↑Ht	50%	Mild	50%		Hoarse cry
		↑OFC	5%	Moderate	25%		Umbilical hernia
		Not overgrown	5%	Severe	5%		Soft, doughy skin
Sotos syndrome[c]	*NSD1*	↑Ht and OFC	50%	None	5%	Frontal bossing, dolicocephalic, down slanting palpebral fissures and malar flushing in childhood	Congenital heart anomalies
		↑Ht	20%	Mild	30%		Scoliosis
		↑OFC	20%	Moderate	45–50%		Renal abnormalities
		Not overgrown	10%	Severe	20%		Seizures

[a]The numbers are represented as approximate percentages of affected individuals.
[b]Data from Tatton-Brown et al 2005b.
[c]The arrow represents an increase of at least +2 standard deviations.
Abbreviations, Ht, height; OFC, occipito-frontal circumference; SD, standard deviations.

diagnosing a frequently subtle condition, but there is still much to learn. The molecular mechanism by which *EZH2* mutations result in Weaver syndrome is unknown and the relationship between the clinical manifestations of germline and somatic *EZH2* mutations is intriguing. For example, three missense mutations Gly159Arg, Arg684Cys, and Tyr733*, have been reported somatically in myeloid malignancies and were identified constitutionally in eight unrelated individuals in the current series. None of these individuals has developed a malignancy although, in contrast to our series with constitutional mutations comprised predominantly of affected children, the majority of individuals with myeloid malignancies are typically >60 years. There are currently very little data about the phenotype of individuals with Weaver syndrome in late adulthood, but the available evidence suggests they may be at increased risk of hematological malignancies. Long-term follow-up studies should be able to address this in due course but until these data are available we would recommend clinical vigilance and investigation of any potential tumor related symptoms rather than a specific surveillance program. It would also be of interest to investigate if any of the individuals with hematological malignancies in whom somatic *EZH2* mutations have been identified, in fact have constitutional mutations and undiagnosed Weaver syndrome. Given the mild and subtle phenotype of Weaver syndrome, this is plausible and readily evaluated through analyses of buccal DNA.

Although the current study has allowed characterization of the *EZH2*-mutation phenotype and is, to our knowledge, the world's largest cohort, it is a small series. With genetic analysis becoming ever more accessible, the number of individuals identified with an *EZH2* mutation is likely to increase rapidly. This will facilitate understanding of the phenotype at all ages, genotype–phenotype associations and more accurate prognostic information. In turn, this will allow optimal management for individuals with Weaver syndrome.

WEB RESOURCES

The URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), www.ncbi.nlm.nih.gov/omim

Exome variant server, http://evs.gs.washington.edu/EVS/

DECIPHER, http://decipher.sanger.ac.uk/

UniProt website, www.uniprot.org

ACKNOWLEDGMENTS

We are grateful to all the families with childhood overgrowth conditions who participated in this research and to the many clinicians who recruited them into the study. We would particularly like to thank the five dysmorphologist who undertook the facial phenotyping (F. Elmslie, S. Mansour, M, McEntagart, A. Saggar, and T. Homfray) and the clinicians who form the Childhood Overgrowth Consortium:

M-C. Addor, M. Akgul, D. Amor, K. Anderson, R. Anderson, S. Andries, H. Archer, R. Armstrong, P. Ashton-Prolla, M. Bahceci, D. Baralle, A. Barnicoat, M. Barrow, G. Baujat, G. Baynam, P. Beales, K. Becker, E. Beckh-Arnold, A. Ben-Yehuda, J. Berg, B. Bernhard, S. Bhal, M. Bhat, J. Birch, L. Bird, M. Bitner, E. Blair, J. Bliek, M. Blyth, A. Bottani, L. Bradley, A. Brady, F. Breatnach, L. Brueton, B. Buehler, A. Burke, J. Burn, J. Campbell, N. Canham, B. Castle, K. Chandler, R. Chandrasena, E. Chang, C. Chu, C. Christenden, D. Cilliers, A. Clarke, J. Clayton-Smith, C. Clericuzio, V. Clowes, T. Cole, A. Colley, A. Collins, F. Connell, J. Cook, H. I. Cordeiro, Cox, E. Crocker, Y. Crow, V. Culic, T. Cushing, T. Dabir, A. Dalton, S. Danda, R. Davidson, S. Davies, R. Day, M. De Roy, V. de Soberanis, D. Dearnaley, N. Dennis, C. Deshpande, B. Desouza, L. Devlin, A-M. Differ, R. Dinwiddie, A. Dixit, A. Dobbie, J. Dominguez, A. Donaldson, D. Donnai, M. Doz, J. Dupont, D. Eastwood, M. Edwards, I. Ellis, F. Elmslie, R. Evans, F. Faravelli, H. Firth, R.

Fisher, T. Fiskerstrand, D. Fitzpatrick, A. Flanagan, F. Flinter, P. Foley, N. Foulds, W. Foulkes, J. Franklin, A. Fryer, A. Gallagher, S. Garcia, C. Gardiner, M. Gardner, C. Garrett, B. Gener, M. Gerrard, R. Gibbons, Y. Gillerot, H. Goel, D. Goudie, K. Gowrishankar, C. Graham, A. Green, N. Gregersen, J. Hale, J. Harper, R. Harrison, H. Hughes, A. Henderson, P. Henman, R. Hennekam, E. Hobson, M. Holder, S. Holder, T. Homfray, D. Horovitz, Z. Huma, J. Hurst, W-L. Hwu, A. Irvine, M. Irving, L. Izatt, M-L. Jacquemont, S. Jagadeesh, L. Jenkins, C. Jessen, D. Johnson, E. Jones, L. Jones, D. Josifova, S. Joss, Dr. Kanabar, P. Kannu, K. Keppler-Noreuil, B. Kerr, H. Kingston, J. Kingston, U. Kini, E. Kinning, A. Krause, A. Kumar, D. Kumar, K. Lachlan, W. Lam, P. Lapunzina, M. Lees, N. Leonard, I. Lewis, J. Liebelt, A. Livesey, C. Longman, T. Lopponen, Dr Lozano, A. Lucassen, P. Lunt, S.A. Lynch, S. Lyonnet, J. MacDonnell, A. Magee, E. Maher, S. Maitz, A. Male, S. Mansour, V. McConnell, T. McDevitt, M. McEntagart, G. McGillivray, R. McGowan, S. McKee, C. McKeown, C. Meany, A. Medeira, S. Mehta, V. Meiner, K. Metcalfe, K. Milstein, S. Mohammed, G. Monaghan, T. Montgomery, A. Morgan, B. Morland, P. Morrison, J. Morton, R. Mudgal, A. Munaza, V. Murday, S. Nampoothiri, K. Nathanson, K. Neas, A. Nemeth, G. Neri, R. Newbury-Ecob, C. Ockeloen, C. Oley, C. Owen, K. Ozono, C. Panarello, S-M. Park, M. Parker, C. Patel, M. Patton, S. Payne, D. Pilz, M. Pinkney, B. Plecko, M. Pocha, C. Pottinger, K. Prescott, S. Price, K. Pritchard-Jones, A. Proctor, O. Quarrell, W. Raith, J. Rankin, L. Raymond, G. Rea, W. Reardon, E. Reid, H. Rees, O. Rittinger, M. Robards, A. Roposch, E. Rosser, A. Rothschild, D. Rourke, D. Ruddy, A. Saggar, N. Saleh, V. Saletti, J. Sampson, R. Sandford, H. Santos, A. Sarkar, R. Scott, I. Scurr, A. Selicorni, R. Semple, S. Sharif, A. Shaw, C. Shaw-Smith, D. Shears, J. Shelagh, M. Simon, G. Smith, S. Smithson, M. Splitt, M. Stevens, A. Stewart, F. Stewart, H. Stewart, K. Stopps, K. Stuurman, M. Suri, A. Swain, E. Sweeney, G. Tanateles, A. Taylor, C. Taylor, M. Teixeira, K. Temple, E. Thomas, E. Thompson, F. Thonney, M. Tischowitz, J. Tolmie, S. Tomkins, S. Turkmen, A. Turner, P. Turnpenny, M. Van-Haelst, L. Van Maldergem, P. Vasudevan, C. Verellen, I.C. Verma, J. Vigneron, E. Wakeling, L. Wainwright, L. Walker, P. Wheeler, K. White, D. Williams, L. Wilson, R. Winter, G. Woods, M. Wright, N. Yachelevich, A. Yeung, A. Zankl

REFERENCES

Ardinger HH, Hanson JW, Harrod MJ, Cohen MM Jr, Tibbles JA, Welch JP, Young-Wee T, Sommer A, Goldberg R, Shprintzen RJ. et al. 1986. Further delineation of Weaver syndrome. J Pediatr 108: 228–235.

Bansal N, Bansal A. 2009. Weaver syndrome: A report of a rare genetic syndrome. Indian J Hum Genet 15:36–37.

Basel-Vanagaite L. 2010. Acute lymphoblastic leukemia in Weaver syndrome. Am J Med Genet Part A 152A:383–386.

Cao R, Wang L, Wang H, Xia L, Erdjument-Bromage H, Tempst P, Jones RS, Zhang Y. 2002. Role of histone H3 lysine 27 methylation in Polycomb-group silencing. Science 298:1039–1043.

Cha TL, Zhou BP, Xia W, Wu Y, Yang CC, Chen CT, Ping B, Otte AP, Hung MC. 2005. Akt-mediated phosphorylation of EZH2 suppresses methylation of lysine 27 in histone H3. Science 310:306–310.

Chase A, Cross NC. 2011. Aberrations of EZH2 in cancer. Clin Cancer Res 17:2613–2618.

Cole TR, Dennis NR, Hughes HE. 1992. Weaver syndrome. J Med Genet 29:332–337.

Coulter D, Powell CM, Gold S. 2008. Weaver syndrome and neuroblastoma. J Pediatr Hematol Oncol 30:758–760.

Crawford MW, Rohan D. 2005. The upper airway in Weaver syndrome. Paediatr Anaesth 15:893–896.

Derry C, Temple IK, Venkat-Raman K. 1999. A probable case of familial Weaver syndrome associated with neoplasia. J Med Genet 36:725–728.

Dumic M, Vukovic J, Cvitkovic M, Medica I. 1993. Twins and their mildly affected mother with Weaver syndrome. Clin Genet 44:338–340.

Ernst T, Chase AJ, Score J, Hidalgo-Curtis CE, Bryant C, Jones AV, Waghorn K, Zoi K, Ross FM, Reiter A, Hochhaus A, Drexler HG, Duncombe A, Cervantes F, Oscier D, Boultwood J, Grand FH, Cross NC. 2010. Inactivating mutations of the histone methyltransferase gene EZH2 in myeloid disorders. Nat Genet 42:722–726.

Farrell SA, Hughes HE. 1985. Weaver syndrome with pes cavus. Am J Med Genet 21:737–739.

Freeman BM, Hoon AH Jr, Breiter SN, Hamosh A. 1999. Pachygyria in Weaver syndrome. Am J Med Genet 86:395–397.

Fryer A, Smith C, Rosenbloom L, Cole T. 1997. Autosomal dominant inheritance of Weaver syndrome. J Med Genet 34:418–419.

Gibson WT, Hood RL, Zhan SH, Bulman DE, Fejes AP, Moore R, Mungall AJ, Eydoux P, Babul-Hirji R, An J, Marra MA, Chitayat D, Boycott KM, Weaver DD, Jones SJ. 2011. Mutations in EZH2 cause Weaver syndrome. Am J Hum Genet 90:110–118.

Greenberg F, Wasiewski W, McCabe ER. 1989. Weaver syndrome: The changing phenotype in an adult. Am J Med Genet 33:127–129.

Huffman C, McCandless D, Jasty R, Matloub J, Robinson HB, Weaver DD, Cohen MM Jr. 2001. Weaver syndrome with neuroblastoma and cardiovascular anomalies. Am J Med Genet 99:252–255.

Iatrou IA, Schoinohoriti OK, Tzerbos F, Pasparakis D. 2008. Treatment of macroglossia in a child with Weaver syndrome. Int J Oral Maxillofac Surg 37:961–965.

Kelly TE, Alford BA, Abel M. 2000. Cervical spine anomalies and tumors in Weaver syndrome. Am J Med Genet 95:492–495.

Kondo I, Mori Y, Kuwajima K. 1990. A Japanese male infant with the Weaver syndrome. Jinrui Idengaku Zasshi 35:257–262.

Kondo I, Mori Y, Kuwajima K. 1991. Weaver syndrome in two Japanese children. Am J Med Genet 41:221–224.

Majewski F, Ranke M, Kemperdick H, Schmidt E. 1981. The Weaver syndrome: A rare type of primordial overgrowth. Eur J Pediatr 137:277–282.

Meinecke P, Schaefer E, Engelbrecht R. 1983. The Weaver syndrome in a girl. Eur J Pediatr 141:58–59.

Mikalef P, Beslikas T, Gigis I, Bisbinas I, Papageorgiou T, Christoforides I. 2010. Weaver syndrome associated with bilateral congenital hip and unilateral subtalar dislocation. Hippokratia 14:212–214.

Morin RD, Johnson NA, Severson TM, Mungall AJ, An J, Goya R, Paul JE, Boyle M, Woolcock BW, Kuchenbauer F, Yap D, Humphries RK, Griffith OL, Shah S, Zhu H, Kimbara M, Shashkin P, Charlot JF, Tcherpakov M, Corbett R, Tam A, Varhol R, Smailus D, Moksa M, Zhao Y, Delaney A, Qian H, Birol I, Schein J, Moore R, Holt R, Horsman DE, Connors JM, Jones S, Aparicio S, Hirst M, Gascoyne RD, Marra MA. 2010. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. Nat Genet 42:181–185.

Muhonen MG, Menezes AH. 1990. Weaver syndrome and instability of the upper cervical spine. J Pediatr 116:596–599.

Ozkan B, Bereket A. 2000. Excessive growth in a girl with Weaver syndrome. J Pediatr Endocrinol Metab 13:1147–1153.

Proud VK, Braddock SR, Cook L, Weaver DD. 1998. Weaver syndrome: autosomal dominant inheritance of the disorder. Am J Med Genet 79:305–310.

Ramos-Arroyo MA, Weaver DD, Banks ER. 1991. Weaver syndrome: A case without early overgrowth and review of the literature. Pediatrics 88:1106–1111.

Roussounis SH, Crawford MJ. 1983. Siblings with Weaver syndrome. J Pediatr 102:595–597.

Sarigul A, Yilmaz M, Ates S, Yurdakul Y. 1999. A case with Weaver syndrome operated for congenital cardiac defect. Pediatr Cardiol 20:375–376.

Scarano G, Della Monica M, Lonardo F, Neri G. 1996. Novel findings in a patient with Weaver or a Weaver-like syndrome. Am J Med Genet 63:378–381.

Snape K, Hanks S, Ruark E, Barros-Nunez P, Elliott A, Murray A, Lane AH, Shannon N, Callier P, Chitayat D, Clayton-Smith J, Fitzpatrick DR, Gisselsson D, Jacquemont S, Asakura-Hay K, Micale MA, Tolmie J, Turnpenny PD, Wright M, Douglas J, Rahman N. 2011. Mutations in CEP57 cause mosaic variegated aneuploidy syndrome. Nat Genet 43:527–529.

Sneeringer CJ, Scott MP, Kuntz KW, Knutson SK, Pollock RM, Richon VM, Copeland RA. 2010. Coordinated activities of wild-type plus mutant EZH2 drive tumor-associated hypertrimethylation of lysine 27 on histone H3 (H3K27) in human B-cell lymphomas. Proc Natl Acad Sci USA 107:20980–20985.

Tatton-Brown K, Douglas J, Coleman K, Baujat G, Cole TR, Das S, Horn D, Hughes HE, Temple IK, Faravelli F, Waggoner D, Turkmen S, Cormier-Daire V, Irrthum A, Rahman N. 2005. Genotype-phenotype associations in Sotos syndrome: An analysis of 266 individuals with NSD1 aberrations. Am J Hum Genet 77:193–204.

Tatton-Brown K, Hanks S, Ruark E, Zachariou A, Duarte Sdel V, Ramsay E, Snape K, Murray A, Perdeaux ER, Seal S, Loveday C, Banka S, Clericuzio C, Flinter F, Magee A, McConnell V, Patton M, Raith W, Rankin J, Splitt M, Strenger V, Taylor C, Wheeler P, Temple KI, Cole T, Douglas J, Rahman N. 2011. Germline mutations in the oncogene EZH2 cause Weaver syndrome and increased human height. Oncotarget 2:1127–1133.

Thompson EM, Hill S, Leonard JV, Pembrey ME. 1987. A girl with the Weaver syndrome. J Med Genet 24:232–234.

Tsukahara M, Tanaka S, Kajii T. 1984. A Weaver-like syndrome in a Japanese boy. Clin Genet 25:73–78.

Weaver DD, Graham CB, Thomas IT, Smith DW. 1974. A new overgrowth syndrome with accelerated skeletal maturation, unusual facies, and camptodactyly. J Pediatr 84:547–552.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher’s web-site.