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Authors

Earnshaw, WC
Allshire, RC
Black, BE
et al.

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Esperanto for histones: CENP-A, not CenH3, is the centromeric histone H3 variant

W. C. Earnshaw · R. C. Allshire · B. E. Black · K. Bloom · B. R. Brinkley · W. Brown · I. M. Cheeseman · K. H. A. Choo · G. P. Copenhaver · J. G. DeLuca · A. Desai · S. Diekmann · S. Erhardt · M. Fitzgerald-Hayes · D. Foltz · T. Fukagawa · R. Gassmann · D. W. Gerlich · D. M. Glover · G. J. Gorbsky · S. C. Harrison · P. Heun · T. Hirota · L. E. T. Jansen · G. Karpen · G. J. P. L. Kops · M. A. Lampson · S. M. Lens · A. Losada · K. Luger · H. Maiato · P. S. Maddox · R. L. Margolis · H. Masumoto · A. D. McAinsh · B. G. Mellone · P. Meraldi · A. Musacchio · K. Oegema · R. J. O'Neill · E. D. Salmon · K. C. Scott · A. F. Straight · P. T. Stukenberg · B. A. Sullivan · K. F. Sullivan · C. E. Sunkel · J. R. Swedlow · C. E. Walczak · P. E. Warburton · S. Westermann · H. F. Willard · L. Wordeman · M. Yanagida · T. J. Yen · K. Yoda · D. W. Cleveland

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Abstract The first centromeric protein identified in any species was CENP-A, a divergent member of the histone H3 family that was recognised by autoantibodies from patients with scleroderma-spectrum disease. It has recently been suggested to rename this protein CenH3. Here, we argue that the original name should be maintained both because it is the basis of a long established nomenclature for centromere proteins and because it avoids confusion due to the presence of canonical histone H3 at centromeres.

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W. C. Earnshaw (✉) · R. C. Allshire
Wellcome Trust Centre for Cell Biology,
University of Edinburgh, Mayfield Road,
Edinburgh EH9 3JR Scotland, UK
e-mail: bill.earnshaw@ed.ac.uk

B. E. Black
Department of Biochemistry and Biophysics,
Perelman School of Medicine, University of Pennsylvania,
Philadelphia, PA 19104-6059, USA

K. Bloom · E. D. Salmon
Department of Biology, University of North Carolina at
Chapel Hill, Chapel Hill, NC 27599-3280, USA

B. R. Brinkley
Department of Molecular and Cellular Biology,
Baylor College of Medicine, Houston, TX 77030, USA

W. Brown
School of Biology, Medical School Queen's Medical
Centre, University of Nottingham,
Nottingham NG7 2UH, UK

I. M. Cheeseman
Whitehead Institute and Department of Biology, MIT,
Nine Cambridge Center, Cambridge, MA 02142, USA

K. H. A. Choo
Chromosome Research, Murdoch Childrens Research
Institute, Department of Paediatrics, Royal Children's
Hospital, Parkville, Victoria, Australia

G. P. Copenhaver
Department of Biology and the Carolina Center for Genome
Sciences, University of North Carolina at Chapel Hill,
Chapel Hill, North Carolina 27599-3280, USA

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Abbreviation
CENP-A Centromere protein A

Since the time of Linnaeus, scientific nomenclature has been based on precedent. Over the past several centuries, the tried and proven path to naming a species (or more recently, a protein) is first to *discover* one and then name it. In recent years, the rush of scientific progress, with multiple groups often simultaneously discovering and naming the same protein at the same time, has stressed the naming convention, and occasionally, groups of scientists have stepped in to rationalise the nomenclature.

In 2012, an article entitled 'A unified phylogeny-based nomenclature for histone variants' appeared in

J. G. DeLuca · K. Luger
Department of Biochemistry and Molecular Biology, Colorado State University, Fort Collins, CO 80523, USA

A. Desai · K. Oegema · D. W. Cleveland (✉)
Ludwig Institute for Cancer Research, University of California at San Diego, La Jolla, CA, USA
e-mail: dcleveland@ucsd.edu

S. Diekmann
Molecular Biology, FLI, Beutenbergstr. 11, 07745 Jena, Germany

S. Erhardt
ZMBH, DKFZ-ZMBH Alliance, University of Heidelberg, INF 282, 69120 Heidelberg, Germany

M. Fitzgerald-Hayes
Department of Biochemistry and Molecular Biology, University of Massachusetts, Amherst, MA 01003, USA

D. Foltz
Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, VA 22908, USA

T. Fukagawa
Department of Molecular Genetics, National Institute of Genetics, Mishima, Shizuoka 411-8540, Japan

R. Gassmann · H. Maiato
IBMC—Instituto de Biologia Molecular e Celular, Universidade do Porto, Porto, Portugal

D. W. Gerlich
Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA), Dr. Bohr Gasse 3, 1030 Vienna, Austria

D. M. Glover
Department of Genetics, University of Cambridge, Downing Street, Cambridge CB2 3EH, UK

G. J. Gorbsky
Cell Cycle and Cancer Biology, Oklahoma Medical Research Foundation, 825 NE 13th St, MS 48, Oklahoma City, OK 73104, USA

S. C. Harrison
Jack and Eileen Connors Structural Biology Laboratory, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School and Howard Hughes Medical Institute, Boston, MA, USA

P. Heun
Max Planck Institute of Immunobiology and Epigenetics, Stübeweg 51, 79108 Freiburg, Germany

T. Hirota
Cancer Institute of the Japanese Foundation for Cancer Research (JFCR), Ariake 3-8-31, Koto-ku 135-8550 Tokyo, Japan

L. E. T. Jansen
Instituto Gulbenkian de Ciência, 2780-156 Oeiras, Portugal

G. Karpen
Lawrence Berkeley National Lab, Life Sciences Division and UC Berkeley, Department of Molecular and Cell Biology, One Cyclotron Road, MS977, Berkeley, CA 94720, USA

G. J. P. L. Kops
Departments of Medical Oncology and Cancer Genomics Netherlands, University Medical Center Utrecht, 3584 CG Utrecht, The Netherlands

M. A. Lampson
Department of Biology, University of Pennsylvania, Philadelphia, PA, USA

S. M. Lens
Department of Medical Oncology, University Medical Center Utrecht, 3584 CG Utrecht, The Netherlands

A. Losada
Chromosome Dynamics Group, Molecular Oncology Programme, Spanish National Cancer Research Centre (CNIO), Melchor Fernández Almagro 3, 28029 Madrid, Spain

the journal *Epigenetics and Chromatin* (Talbert et al. 2012). This article had a lengthy list of distinguished authors from the chromatin/epigenetics community and represents an effort to unify the histone nomenclature. This proposed simplification of naming histone variants follows on the heels of a number of previous distinguished efforts, including the rationalisation of the caspase nomenclature in 1996 (Alnemri et al. 1996), and a proposed standard nomenclature for the kinesin proteins (Lawrence et al. 2004). The caspase proposal was universally adopted almost immediately, as the ten different caspases were known by a host of confusing names at that time. The kinesin article also has been widely influential.

While the proposal to unify the histone nomenclature may have much to recommend it, with respect to the specialized histone H3 variant found at all active centromeres from budding yeast to human, we suggest, for the reasons detailed below, that the scientific community should maintain the original nomenclature

P. S. Maddox
Institute for Research in Immunology and Cancer (IRIC), Department of Pathology and Cell Biology, Université de Montréal, P.O. Box 6128, Station Centre-Ville, Montréal, QC H3C 3J7, Canada

R. L. Margolis
Tumor Development Program, Sanford-Burnham Medical Research Institute, 10901 North Torrey Pines Road, La Jolla, CA 92037, USA

H. Masumoto
Department of Human Genome Research, Kazusa DNA Research Institute, 2-6-7 Kazusa-Kamatari, Kisarazu, Chiba 292-0818, Japan

A. D. McAinsh
Centre for Mechanochemical Cell Biology, Division of Biomedical Cell Biology, Warwick Medical School, University of Warwick, Coventry, UK

B. G. Mellone · R. J. O'Neill
Department of Molecular and Cell Biology, University of Connecticut, Storrs, CT 06269, USA

P. Meraldi
Physiology and Metabolism Department, Medical Faculty, University of Geneva, Geneva, Switzerland

A. Musacchio
Department of Mechanistic Cell Biology, Max Planck Institute of Molecular Physiology, Otto-Hahn-Straße 11, 44227 Dortmund, Germany

K. C. Scott · B. A. Sullivan
Institute for Genome Sciences and Policy, Department of Molecular Genetics and Microbiology, Duke University, 101 Science Drive, Durham, NC 27708, USA

A. F. Straight
Department of Biochemistry, Stanford University, Stanford, CA, USA

P. T. Stukenberg
Department of Biochemistry and Molecular Genetics, University of Virginia School of Medicine, Charlottesville, VA 22908, USA

K. F. Sullivan
Centre for Chromosome Biology, School of Natural Sciences, National University of Ireland, Galway, Galway, Ireland

C. E. Sunkel
IBMC—Instituto de Biologia Molecular e Celular and ICBAS—Instituto de Ciencias Biomédica Abel Salazar, Universidade do Porto, Porto, Portugal

J. R. Swedlow
Centre for Gene Regulation and Expression, College of Life Sciences, University of Dundee, Dundee DD1 5EH, UK

C. E. Walczak
Medical Sciences Program, Indiana University, 915 East 3rd St., Bloomington, IN 47405, USA

P. E. Warburton
Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

S. Westermann
Research Institute of Molecular Pathology (IMP), Dr. Bohr Gasse 7, 1030 Vienna, Austria

H. F. Willard
Institute for Genome Sciences and Policy, Duke University, 101 Science Drive, Durham, NC 27708, USA

L. Wordeman
Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle, WA 98195, USA

M. Yanagida
G0 Cell Unit, Okinawa Institute of Science and Technology Graduate University, Tancha 1919-1, Onnason 904-0495 Okinawa, Japan

T. J. Yen
Fox Chase Cancer Center, Philadelphia, PA 19111, USA

K. Yoda
Bioscience and Biotechnology Center, Nagoya University, Nagoya, Aichi, Japan

(CENP-A) that was established for the centromeric histone H3 variant and avoid the usage of the misleading name (CenH3) proposed by Talbert et al. (2012).

The first known centromeric protein was discovered in human cells and named CENP-A in 1985 (Earnshaw and Rothfield 1985). CENP-A was shown to be a histone in 1991 by the late Doug Palmer, working with Bob Margolis (Palmer et al. 1991). This conclusion was subsequently confirmed when the protein was cloned by Kevin Sullivan and colleagues (Sullivan et al. 1994). CENP-A has been widely referred to by this name over the subsequent 28 years, and the CENP nomenclature has now been extended as far as CENP-X for well-studied proteins.

It has now been suggested (Talbert et al. 2012) that the name CENP-A should be superseded by CenH3 so as to simplify multiple names now in use in multiple species for the histone H3 variant found only at active centromeres. The budding yeast homolog of CENP-A, CSE4, was described in 1995 (Stoler et al. 1995), as the product of the *Cse4* gene, which was discovered in a screen for mutations that affected chromosome segregation. A later addition was the *Drosophila* homologue, discovered in 2000 by homology with CENP-A and then named Cid (Henikoff et al. 2000). It is an important distinction to *Drosophila* geneticists that Cid was not named because of a pre-existing named mutation (in which case this name would have been retained by tradition). To the contrary, Cid was identified on the basis of sequence similarity and was known from the outset to be the *Drosophila* variant of CENP-A.

The name proposed in Talbert et al., CenH3, adds an unnecessary layer of confusion that is scientifically misleading: its use implies that this protein is *the* centromeric histone H3. This is simply not correct. A range of studies has revealed that regional centromeres contain not only CENP-A, but also lots of canonical histone H3. This canonical centromeric histone H3 is not just a 'stuffer' or contaminant of centromere chromatin. Studies ranging from biochemical fractionation (Ando et al. 2002; Foltz et al. 2006; Hori et al. 2008) to high-resolution light microscopy (Blower et al. 2002; Sullivan and Karpen 2004; Ribeiro et al. 2010) reveal that centromeric canonical H3 nucleosomes are interspersed with CENP-A nucleosomes and that specific components (e.g. CENP-C and the histone fold-containing CENP-T/W complex-Nishino et al. 2012) that make meaningful contacts with centromeric H3-containing chromatin are important for kinetochore assembly and function (Ohzeki et al. 2012). In fact, the interspersed H3 chromatin may represent a distinct chromosome domain, as it is post-translationally modified in a pattern that is distinct from both canonical heterochromatin and euchromatin (Sullivan and Karpen 2004). Recognising this, the term 'CenH3' would more appropriately refer to centromere-associated canonical histone H3 than it does to the centromere-specific CENP-A. Correspondingly, it is inappropriate as a name for the histone H3 variant that is found exclusively at centromeres.

While we appreciate the overall efforts to unify the nomenclature of histones from a phylogenetic perspective, our view is that the proposal by the many chromatin-oriented authors of the *Epigenetics and Chromatin* article (Talbert et al. 2012) to rename CENP-A as CenH3 does not take into account the extensive preceding literature on centromeres or kinetochores, or the scientific confusion raised by such a change. It is notable that while the signatories to this Commentary have been primary contributors to the centromere literature and all of us have published (some extensively) on CENP-A, none of us was consulted concerning the *Epigenetics and Chromatin* nomenclature proposal. As systems and other forms of integrative biology become increasingly prevalent and communities that do not normally interact are brought into contact (and potential conflict), other nomenclature issues such as this will arise when the same protein means different things to diverse groups of scientists. Thus, the importance of cross-communication between communities and respect for precedence in naming (in this case, the precedence of the well-established CENP nomenclature) may actually increase over the next few years.

Bearing in mind the confusion that will inevitably arise over whether the term CenH3 refers to canonical histone H3 interspersed with CENP-A at centromeres or to the CENP-A itself, we recommend that the proposed name CenH3 be abandoned and that this important marker for centromeric chromatin should be referred to by the name originally given to it in 1985—CENP-A.

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References

Alnemri ES, Livingston DJ, Nicholson DW, Salvesen G, Thornberry NA, Wong WW, Yuan J (1996) ICE/CED3 protease nomenclature. Cell 87:171

Ando S, Yang H, Nozaki N, Okazaki T, Yoda K (2002) CENP-A, -B, and -C chromatin complex that contains the I-type alpha-satellite array constitutes the prekinetochore in HeLa cells. Mol Cell Biol 22:2229–2241

Blower MD, Sullivan BA, Karpen GH (2002) Conserved organization of centromeric chromatin in flies and humans. Dev Cell 2:319–330

Earnshaw WC, Rothfield N (1985) Identification of a family of human centromere proteins using autoimmune sera from patients with scleroderma. Chromosoma (Berlin) 91:313–321

Foltz DR, Jansen LE, Black BE, Bailey AO, Yates JR, Cleveland DW (2006) The human CENP-A centromeric nucleosome-associated complex. Nat Cell Biol 8:458–469

Henikoff S, Ahmad K, Platero JS, van Steensel B (2000) Heterochromatic deposition of centromeric histone H3-like proteins. Proc Natl Acad Sci USA 97:716–721

Hori T, Amano M, Suzuki A, Backer CB, Welburn JP, Dong Y, McEwen BF, Shang WH, Suzuki E, Okawa K, Cheeseman IM, Fukagawa T (2008) CCAN makes multiple contacts with centromeric DNA to provide distinct pathways to the outer kinetochore. Cell 135:1039–1052

Lawrence CJ, Dawe RK, Christie KR, Cleveland DW, Dawson SC, Endow SA, Goldstein LS, Goodson HV, Hirokawa N, Howard J, Malmberg RL, McIntosh JR, Miki H, Mitchison TJ, Okada Y, Reddy AS, Saxton WM, Schliwa M, Scholey JM, Vale RD, Walczak CE, Wordeman L (2004) A standardized kinesin nomenclature. J Cell Biol 167:19–22

Nishino T, Takeuchi K, Gascoigne KE, Suzuki A, Hori T, Oyama T, Morikawa K, Cheeseman IM, Fukagawa T (2012) CENP-T-W-S-X forms a unique centromeric chromatin structure with a histone-like fold. Cell 148:487–501

Ohzeki J, Bergmann JH, Kouprina N, Noskov VN, Nakano M, Kimura H, Earnshaw WC, Larionov V, Masumoto H (2012) Breaking the HAC Barrier: histone H3K9 acetyl/methyl balance regulates CENP-A assembly. EMBO J 31:2391–2402

Palmer DK, O'Day K, le Trong H, Charbonneau H, Margolis RL (1991) Purification of the centromeric protein CENP-A and demonstration that it is a centromere specific histone. Proc Natl Acad Sci USA 88:3734–3738

Ribeiro SA, Vagnarelli P, Dong Y, Hori T, McEwen BF, Fukagawa T, Flors C, Earnshaw WC (2010) A super-resolution map of the vertebrate kinetochore. Proc Natl Acad Sci USA 107:10484–10489

Stoler S, Keith KC, Curnick KE, Fitzgerald-Hayes M (1995) A mutation in CSE4, an essential gene encoding a novel chromatin-associated protein in yeast, causes chromosome nondisjunction and cell cycle arrest at mitosis. Genes Dev 9:573–586

Sullivan BA, Karpen GH (2004) Centromeric chromatin exhibits a histone modification pattern that is distinct from both euchromatin and heterochromatin. Nat Struct Mol Biol 11:1076–1083

Sullivan KF, Hechenberger M, Masri K (1994) Human CENP-A contains a histone H3 related histone fold domain that is required for targeting to the centromere. J Cell Biol 127:581–592

Talbert PB, Ahmad K, Almouzni G, Ausio J, Berger F, Bhalla PL, Bonner WM, Cande WZ, Chadwick BP, Chan SW, Cross GA, Cui L, Dimitrov SI, Doenecke D, Eirin-Lopez JM, Gorovsky MA, Hake SB, Hamkalo BA, Holec S, Jacobsen SE, Kamieniarz K, Khochbin S, Ladurner AG, Landsman D, Latham JA, Loppin B, Malik HS, Marzluff WF, Pehrson JR, Postberg J, Schneider R, Singh MB, Smith MM, Thompson E, Torres-Padilla ME, Tremethick DJ, Turner BM, Waterborg JH, Wollmann H, Yelagandula R, Zhu B, Henikoff S (2012) A unified phylogeny-based nomenclature for histone variants. Epigenetics Chromatin 5:7