



What HeLa Cells Are You Using?

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ABSTRACT

The HeLa cell line, named after the patient Henrietta Lacks, was one the first human cell lines to be used for tissue culture. In the decades since its origin, it has become a feature in labs across the world. Despite its longevity, repeated detection of most HeLa marker chromosomes have lead the scientific community to view HeLa as a stable cell line and its corresponding findings to be reproducible. However, to date no investigation has examined other meaningful aspects of HeLa's genomic variability, such as whether HeLa's modal chromosome number remains constant. Considering the importance of a cell line's karyotype with respect to reproducibility, I sought to examine the stability of HeLa's karyotype by examining HeLa's modal chromosome number as reported in the literature.

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BACKGROUND

Science has made great advances due to the ability to manipulate biological processes in a controlled manner. One of the most notable achievements was the establishment of cell lines. The most famous cell line was established by G.O. Gey at Johns Hopkins in 1951, after deriving the cells from the cervical cancer of Henrietta Lacks (HeLa) ([Gey and Coffman 1952](#), [Jones et al. 1971](#)). In the over half-century since, HeLa has made major contributions to science. Indeed a PubMed search for "HeLa" yields nearly 80,000 results.

Shortly after HeLa was established, scientists began attempting to make other types of cell lines, but had little means of properly identifying cell types. Early classification methods were primitive, with one assay screening for the production of glucose-6-phosphate dehydrogenase (G6PD), an enzyme thought to be found almost entirely in African Americans ([Gartler 1968](#)). Gartler *et al* observed G6PD in 20 human aneuploid cells (most of which he knew were collected from Caucasians) and lead him to discover a massive international cell contamination ([Gartler 1968](#)). The contaminant was HeLa, and the discovery unveiled a pandemic of HeLa contamination ([Culliton 1974](#)).

These hard lessons taught scientists the importance of accurately identifying cell lines and correctly attributing specific cellular properties to the appropriate corresponding cell line. Consequently, the HeLa contamination drove the development of better techniques for characterizing and differentiating between cells lines.

Early cytogenetic analysis of HeLa cells relied on Giemsa staining to produce distinct chromosome bands and examine HeLa's genomic landscape ([Chu and Giles 1958](#), [Nelson-Rees and Flandermeyer 1976](#), [Hsu and Moorhead 1956](#), [Seabright 1973](#)). This lead to the discovery of HeLa's numerous chromosome aberrations, and made identifying HeLa-specific marker chromosomes the highest priority ([Lavappa, Macy, and Shannon 1976](#), [Chen 2008](#)).

Today, most cytogenetic analysis of HeLa has been performed by FISH, and G-banding. ([Francke,](#)

Hammond, and Schneider 1973, Nelson-Rees et al. 1980, Kraemer et al. 1974, Heneen 1976, Stanbridge et al. 1981, Chen 2008). Along with G-banding, comparative genomic hybridization (CGH) also facilitates chromosome classification through hybridization to metaphase slides. The most comprehensive analysis of HeLa to date, occurred relatively recently following the advent of Spectral Karyotyping (SKY) technology.

HeLa cells possess a hypertriploid (3n+) karyotype and produce heterogeneous cell populations (Ghosh and Ghosh 1970, Leone, Hsu, and Pomerat 1955, Ghosh and Ghosh 1975). HeLa cells differ in both their total number of chromosomes and in the quantity of specific numerical chromosome groups (Hered 1960). When Chu and Giles *et al.* examined parental HeLa cell lines and a series of clones derived from the stock, they found wide variation in modal chromosome numbers (Chu and Giles 1958). Ghosh *et al.* discovered variation of stemline karyotype and rise of stable independent karyotype subpopulations from the "HeLa cell line (modal number 69)" (Ghosh and Ghosh 1975). Similarly, Macville *et al.* reported that 60% of the parental HeLa cells have a modal chromosome number of 78, and noted the emergence of a phenotypically distinct subpopulation of cells with their own, stable karyotype (N=73) (Macville et al. 1999, Tjio and Puck 1958).

Macville *et al.* undertook one the most extensive examinations of HeLa cell stability assessing the parental HeLa cell line's marker chromosomes and comparing their findings with several studies published a decade earlier (Macville et al. 1999). Macville *et al.* identified eight chromosome markers that had been previously published, in addition to identifying novel chromosome makers for HeLa (Macville et al. 1999). On the basis of this conserved marker chromosome expression, over a decade, Macville *et al.* determined the HeLa cell line to be stable (Macville et al. 1999). However, what Macville *et al.* and many other HeLa researchers failed to consider was the cell lines overall karyotype and the effects numerical and structure.

Macville *et al.* report a HeLa modal karyotype of 78 (range: 76-80) after performing SKY analysis on HeLa cells obtained at passage 90-102 from ATCC (Macville et al. 1999, ATCC). Interestingly, ATCC reports that the same HeLa cells have a different modal karyotype and a much broader karyotypic range (N=82;70-164) (ATCC). Not surprisingly, HeLa's modal karyotype varies widely between research publications (Table 1). One explanation is HeLa's inherent genomic instability. HeLa cells frequently experience abnormal mitoses with varying rates of chromosome missegregation (Chu and Giles 1958), ranging from 7.25%-10% (Shi and King 2005).

The gain or loss of even a single chromosome drastically changes a cells entire genomic landscape (Upender et al. 2004). Aneuploidy changes the expression of hundreds-to-thousands of genes, and directly alters the cell's phenotype (Pavelka et al. 2010, Ly et al. 2011, Upender et al. 2004, Gao et al. 2007, Gemoll et al. 2014). Indeed, each chromosome carries hundreds to thousands of genes, with capable of altering the expression of additional genes when they are over/underexpressed on other chromosomes (e.g. transcription factors), which in turn may affect the expression of other genes. Not surprisingly, under normal conditions aneuploidy is detrimental to cell survival because, as suggested by Amon *et al.*, "the severity of the phenotypes caused by aneuploidy correlates with the number of genes gained or lost" (Sheltzer and Amon 2011). Under abnormal/stressful conditions, aneuploidy, and consequentially the gene dosage imbalance, can improve cellular fitness and confer a selective advantage (Pavelka, Rancati, and Li 2010, Rancati et al. 2008, Duncan et al. 2012, Pavelka et al. 2010). Previous studies have shown genomic aberrations to HeLa's karyotype can directly influence its phenotype (Vogt 1959, Gille and Joenje 1989, Gey and Coffman 1952). Despite the importance of a cell's karyotype, the inconsistent reporting of HeLa's karyotype has largely been ignored (Chu and Giles 1958, Vogt 1959).

Aneuploidy is ubiquitous in cancer and a signature characteristic of the HeLa cell line (Nicholson and Cimini 2013, 2012, ATCC). Numerous studies report observing distinct HeLa subpopulations emerge from a parental stem-line HeLa population, possessing divergent but stable karyotypes (Stone and Kang 1964, Ghosh and Ghosh 1970, Dziekanowska and Szurman 1968, Spurna and Hill 1967). Others

have acknowledged HeLa's genomic instability, and some have even suggested that this may lead to more variable findings (Grenman, Shapira, and Carey 1988, Bonita, Eraydin, and Majumdar 1999, Putral et al. 2005, Koivusalo et al. 2005, Singer and Fishman 1974, Hsu 1961).

Accordingly, chromosome markers are reliable for cell line identification, but have been shown here to be inadequate markers of HeLa's genomic stability, and may in fact be confounding numerous studies results (Macville et al. 1999). If "HeLa" cells used in two labs both share the same "HeLa" marker chromosomes but differ in modal chromosome number, are the cells really the same or do the cells only share the same name? How does this difference in karyotype affect reproducibility? Interestingly, a similar controversy arose between different laboratories culturing the MCF-7 breast cancer cell line when they reported differences in protein expression and phenotype (Reddel et al. 1985, Graham et al. 1985, Graham et al. 1986, Osborne, Hobbs, and Trent 1987, Hand et al. 1983). Cytogenetic analysis between parental and independent derived subclones revealed extensive aneuploidy with the loss of marker chromosomes being rare but the formation of additional structural abnormalities occurring frequently (Whang-Peng et al. 1983) reflecting the cell line's inherent genomic instability and ongoing process of selection and adaptation. Accordingly, researchers conducted cytogenetic analysis of MCF-7 cells cultured in different laboratories and found several conserved chromosome translocations but also significant numbers of unique alterations characterizing each variant (Bahia et al. 2002, Osborne, Hobbs, and Trent 1987).

Studies attempting to definitively characterize HeLa's genomic constitution and assess the cell lines stability concluded the cell line to be stable following the detection of in part or whole of 18/20 HeLa marker chromosomes (Macville et al. 1999, Landry et al. 2013, Chen 2008). These studies emphasized the identification and similarities in the few marker chromosomes, rather than taking into account the differences chromosome-specific copy number and structural aberrations that directly impact the karyotype, and thus phenotype, as a whole.

In conclusion, the HeLa cell karyotype varies dramatically between laboratories. Consequently, since karyotypic changes even for one specific chromosome, either in structural composition or copy number alteration, directly effects the genomic landscape the karyotypic composition is critical to determining cellular phenotype. The conservation for certain specific marker chromosomes observed between laboratories confirms the identity and origin of the cell line in question, however falls short of supporting their reproducibility utility. Thus, in cancer research where the stakes are high and the need for novel, reproducible discovery is great I wonder if the HeLa cell line is still an appropriate model for research, other than to understand karyotypic changes or the dynamics of genomic instability.

Table 1 Karyotypic Variability Within HeLa Cell Lines Between Labs

HeLa Cell Line	Modal Chr. Number	Reference	REFERENCES
HeLa	82; 70-164	(ATCC)	Ash, J.F., R.M. Fineman, T. Kalka, M. Morgan, and B. Wire. 1984. "Amplification of sodium-and potassium-activated adenosinetriphosphatase in HeLa cells by ouabain step selection." <i>The Journal of cell biology</i> no. 99 (3):971-983. doi: 10.1083/jcb.99.3.971
HeLa	78; 76-80	(Macville et al. 1999)	ATCC. HeLa (ATCC™ CRMCL2 [®]) Product Sheet. In <i>Catalogue of Strains-II</i> , edited by American Type Culture Collection: J. E. Shannon and M. L. Macy~Eds.
HeLa	60; 57-63	(Francke, Hammond, and Schneider 1973)	
HeLa	65; 62-67	(Ash et al. 1984)	
HeLa	74; 69-77	(Mincheva, Gissmann, and Zur Hausen 1987)	
HeLa	84; 58-179	(Lavappa, Macy, and Shannon 1976)	
HeLa	80; 79-81	(Bottomley, Trainer, and Griffin 1969)	
HeLa	51	(Hughes 1965)	Bahia, H, JNE Ashman, L Cawkwell,

HeLa	60	(Obara et al. 1974)	M Lind, JRT Monson, PJ Drew, and J Greenman. 2002. "Karyotypic variation between independently cultured strains of the cell line MCF-7 identified by multicolour fluorescence in situ hybridization." <i>International journal of oncology</i> no. 20 (3):489-494.
HeLa	67	(Duesberg et al. 2011)	
HeLa	69	(Ghosh and Ghosh 1975)	
HeLa	71	(Czaker 1973)	
HeLa	67	(Popescu and DiPaolo 1989)	
HeLa	77	(Heneen 1976)	Bonita, D.M., N.B. Eraydin, and S.K. Majumdar. 1999. "Response of non-breast cancer cells to tamoxifen in the presence and absence of β -estradiol." <i>The Nucleus</i> . (42):49-55.
HeLa	69	(Singer and Fishman 1974)	
HeLa	57; 54-59	(Harris et al. 1965)	
HeLa	69; 67-70	(Cireli, Frimmel, and Schwarzacher 1966)	Bottomley, RH, AL Trainer, and MJ Griffin. 1969. "Enzymatic and chromosomal characterization of HeLa variants." <i>The Journal of cell biology</i> no. 41 (3):806-815.
HeLa	61; 59-62	(Cireli, Frimmel, and Schwarzacher 1966)	
HeLa	69; 66-71	(Spurna and Hill 1967)	
HeLa	70; 68-72	(Cerny, Korych, and Soukup 1964)	Cerny, M.B., B. Korych, and F. Soukup. 1964. "Verification of species characteristics of some cell lines in Czechoslovakia." <i>Journal Hygiene Epidemiology Microbial Immunology</i> no. 8:353-363.
HeLa Kyoto	65; 62-68	(Landry et al. 2013)	
HeLa <i>St1</i>	77	(Vogt 1959)	
HeLa <i>F870</i>		(Vogt 1959)	
HeLa D98/AH- 2	62; 58-65	(Stanbridge et al. 1981)	Chen, T.R. 2008. "Re-evaluation of HeLa, HeLa S3, and HEP-2 karyotypes." <i>Cytogenet Genome Res</i> no. 48 (1):19-24. doi: 10.1159/000132579.
HeLa- S3	68; 51-74	(Lavappa, Macy, and Shannon 1976)	
HeLa- S3	68	(Gille and Joenje 1989)	Chu, E.H., and N.G. Giles. 1958. "Comparative chromosomal studies on mammalian cells in culture. I. The HeLa strain and its mutant clonal derivatives." <i>J Natl Cancer Inst</i> no. 20 (2):383-401. doi: 07.551.11.4002.
HeLa- 20	112	(Gille and Joenje 1989)	
HeLa- 80	84	(Gille and Joenje 1989)	Cireli, E., J. Frimmel, and H.G. Schwarzacher. 1966. "Cytogenetische Studien an HeLa-Zellen. I. Chromosomen, DNS-Gehalt und Struktur der Interphasenkerne." <i>Cells Tissues Organs</i> no. 65 (1-3):170-181. doi: 10.1159/000142871.
M- HeLa- 76	49	(Savelyeva and Mamaeva 1987)	
HeLa- 20	50; 49-50	(Mamaeva, Litvinchuk, and Pinaev 1983)	
HeLa Ep. 1	72; (68-76)	(Norryd 1959)	Culliton, B.J. 1974. "HeLa Cells: Contaminating Cultures around the World." <i>Science</i> no. 184 (4141):1058-1059. doi: 10.1126/science.184.4141.1058.
HeLa	75; (73-76)	(Heneen 1976)	

HeLa 63 (Heneen 1976)
D98/AG

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