Aldred Scott Warthin's Family 'G': The American Plot Against Cancer and Heredity (1895–1940)

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Abstract According to many, the genetic technology used in cancer is a promising test case of twenty-first century 'genomic medicine'. However, it is important to realize that accounting for the genetic or hereditary factors in cancer medicine is not new. Since at least the eighteenth century, medical doctors and patients have tried to establish links between heredity and cancer. Following the excitement over the rediscovery of Gregor Mendel's theory of hereditary transmission (1900), there was renewed interest in the question of a linkage between heredity and cancer. Researchers began to pay attention to the statistical use of family studies as a means to calculate Mendelian ratios of disease inheritance. In 1913, the Michigan University pathologist Aldred Scott Warthin (1866–1931) published his first study of a pedigree with a so-called inherited susceptibility for cancer. Family G's susceptibility was associated with the risk of creating an 'inferior stock'. Given the number of studies on heredity and disease and the vogue for eugenics at the beginning of the twentieth century, one would have expected strong support for Warthin's study. Family G (one of the longest systematically studied cancer genealogies in the world and currently associated with Lynch syndrome) might have been accepted (if not for purely scientific reasons) as part of the eugenics gospel as an exemplary case of a degenerative stock. After all, Warthin was a rising star within the American medical establishment and had become part of John Kellogg's eugenic priesthood in Michigan. Ultimately, none of these likely

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scenarios materialized. I will show in this chapter how the cancer idiom of heredity that was associated with shame, fatalism and stigmatization came to be regarded as counterproductive in the fight against cancer and was suppressed at the time by the powerful American Society for the Control of Cancer.

Keywords Lynch syndrome • Family G • Eugenics • Colorectal cancer • Genetic condition • Family history

1 Introduction

Many consider cancer genetics to be the most promising test case of genomic medicine of the twenty-first century. Cancer, which is now accepted as a family of genetic traits and diseases, is inextricably bound to the discovery in the 1990s of specific genes collectively known as 'mismatch repair genes'. Although this understanding of cancer was innovative in terms of the science and technology involved in cancer medicine, it is important to realize that accounting for genetic and hereditary factors is nothing new in and of itself. It has long been known that cancer in the human species may run in families. Since at least the eighteenth century, medical doctors and patients have tried to establish links between heredity and cancer. As for other medical conditions, heredity's visibility, meaning and legitimacy have fluctuated over time. The same holds true for the role of a family's history in medical research and medical practice.

Collecting and understanding family histories has been part of medicine since the early nineteenth century. However, it was not until the 1850s that medical researchers developed an interest in family trees as a means to study and visualize the influence of heredity on cancer. The use of genealogical methods by medical researchers interested in the hereditary transmission of cancer is best exemplified by Paul Broca's (1824–1880) much-cited history of the so-called 'cancer family' of Madame Z[1]. After publication of Broca's pioneering study, international discussion about medical family studies and cancer continued as part of an ongoing debate on the question: 'Is cancer a hereditary disease?' At that time, there was no consensus concerning the nature and the magnitude of the hereditary factor in cancer. The American pathologist Aldred Scott Warthin (1866–1931) and his pedigree of Family 'G' were very much part of this debate from the days of Weismannism (1890s) to the age of brave new biology (1930s).

In her book *Moments of Truth in Genetic Medicine*, Lindee has provided an intriguing window on the amount of labour involved in the construction and maintenance of scientifically legitimate human pedigrees.[2] Pedigrees as a token of family identity blend folk, emotional, social and technical knowledge. From the nineteenth century to the present time, pedigrees as an integral part of medical family research have had multiple roles in framing illness, disease and social

[1]Lynch 1985, 12–13; Carlson 2001, 147.

[2]Lindee 2005.

abilities. The father of eugenics Francis Galton's (1822–1911) early use of pedigrees was exemplary in his study of the inheritance of genius and artistic ability.[3] To further our understanding of how the use of pedigrees as a tool in medical research has changed over time and within specific contexts, studies are needed that focus on the multidimensional historical trajectories of family studies. Thus, in this chapter on the genesis of a specific American cancer pedigree, I focus on Family G. This family was one of the longest systematically studied cancer genealogies in the world and is currently associated with the occurrence of hereditary non-polyposis colorectal cancer or Lynch syndrome. I will show how science, medicine and the public sphere have shaped and reshaped the identities of Family G and their pedigree as an object and tool of medical research from the 1890s to the 1930s in the American context.

2 The Birth of a Medical Pedigree: Family G

From 1893 to 1900, the young American pathologist Aldred Scott Warthin spent his time in pathology laboratories in Vienna, Austria, and Dresden and Freiburg, Germany. Warthin, who had a strong interest in the biological sciences, must have taken notice of the various scientific and popular discussions about the hereditary transmission of diseases or mental qualities during his study trips. It is likely that Warthin also took the opportunity in Austria and Germany to study the expanding literature on the biological and medical aspects of family research. If so, he must have noticed that the results from medical family research were as diverse as the methods of compilation since they were based on family histories, hospital records and replies to enquiries.[4] Most doctors at the time treated hereditary aspects as part of a nosographical description, whatever their views on the magnitude of the hereditary factor and the mechanism of transition. They usually spoke in terms of a potentiality and disposition to disease as part of a constitutional diathesis. In general, the term 'heredity' stood for a tendency for certain maladies to develop within a family.[5] Only the predisposition to develop the disease was inherited, not the disease characteristics. Expression depended on circumstances, for example, shock, misery or strain. The perspective of plasticity of expression was compatible with existing medical traditions and biological theories. Furthermore, the more often the disease characteristics occurred in pedigrees, the greater the chance that they would return in later generations.[6]

In 1895, upon his return to the University of Michigan, Warthin was appointed a demonstrator in pathology. Barely a year later, he assumed charge of the pathology

[3] Kevles 1985; Paul 1998.

[4] Gausemeier 2005.

[5] Snow 1893, 15; Butlin 1887; Butlin 1895; Jacobsen 1946, 13–17; Krush 1977.

[6] Snelders et al. 2007, 226.

laboratory where he worked at the university hospital in Ann Arbor.[7] Warthin loved to take a roundabout route home from work through Ann Arbor's German quarters. The familiar laborious German atmosphere and the chance of practising the German language made him feel comfortable. During one of these rounds, he ran into his family's young seamstress Pauline G, who looked unusually depressed. He questioned Pauline about her grief and learned that cancer was rampant in her family. Quite a number of her relatives seemed to have cancer, have died of cancer or were about to die of cancer. Pauline felt vulnerable and was afraid that she too would get cancer. Unfortunately, history would prove her fears to be correct. Like her mother, Pauline fell victim to a rapidly developing cancer of the uterus.

Although Pauline had initially only provided meagre details about her family history, her narrative corroborated Warthin's ideas about a family susceptibility or hereditary disposition to disease. Warthin thought that his own family was a cancer resistant and Pauline's was cancer susceptible. He had always been surprised about the nature of family histories and the so-called cancer statistics that were used in discussions about familial cancers. Rarely were clinical examinations supported by microscopic examinations, and only occasionally was an entire family history obtained extending over several generations. Moreover, most statistics provided little information beyond the fact of the multiple occurrence of cancer in certain family groups or generations.

Since Warthin was in charge of the pathological laboratory of a state hospital, this meant that he controlled a 'heavy traffic' of dead bodies from the general Michigan population. Warthin was aware of the fact that in terms of statistics, he was lucky. He had access to a significantly more representative collection of family histories and anatomic specimens than could be found in the more highly reputed charity hospitals of larger cities. Starting from the seamstress' story, Warthin and his co-workers painstakingly documented stacks of coded pedigree charts year in and year out, thus showing both the genealogy and pathology of countless relatives of cancer-susceptible families.

The point of departure of what is now known as 'Warthin's Family G' was the seamstress's German grandfather and grandmother. In the 1830s, the couple had crossed the Atlantic and settled in what was known as 'wild Washtenaw County' in what is now the Freedom Township near Ann Arbor. Like many others, Pioneer G and his wife purchased a land grant from the US government following the Indian Removal Act. They cleared woodlands, built a small log farmhouse, cultivated crops and bred children. In 1856, at the age of 60, Pioneer G died of what is believed to be cancer. He left his wife, who had no history of cancer, and ten children. If his granddaughter Pauline had not passed the information of a presumed familial cancer burden to Warthin, it is doubtful that Pioneer G and his offspring would

[7]This impressionistic account of Warthin's early research work on medical hereditarianism is based on

Warthin 1914; Stone 1927; Simpson 1931; Lynch 1985; Bentley historical library, University of Michigan; Aldred Scott Warthin papers, 1893–1931; Box 1: 'Dear friend' letters from Vienna (1893/1894); and Sir William Osler correspondence (1899–1919).

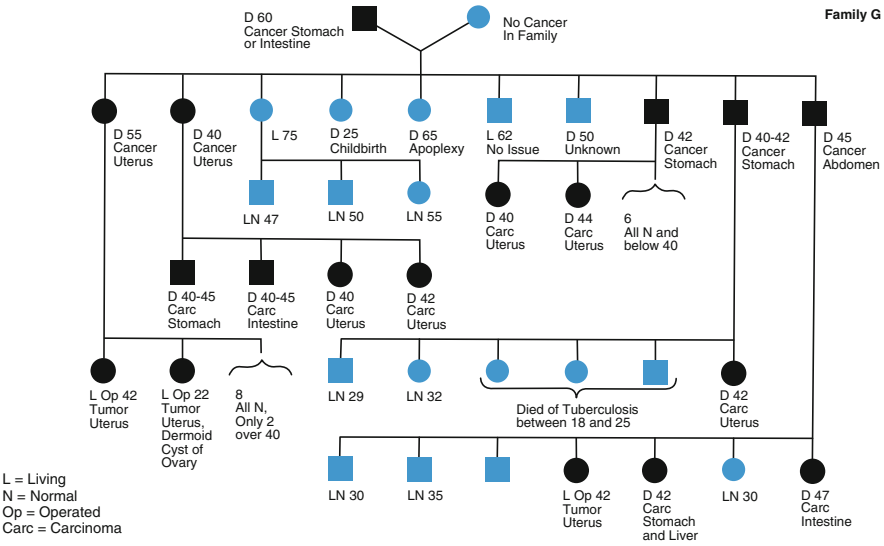

Fig. 1 Pedigree of Family 'G': By courtesy of Ca—A Cancer Journal for Clinicians (Copyright 1985)

have entered into the annals of medicine as an exemplary case of a multiple family occurrence of cancer in the Michigan area.[8]

In 1913, the Family G made its first appearance in medical literature as part of one of the most extensive early statistical studies of the influence of heredity on cancer. Out of 1600 cases of cancer, Warthin claimed that 15 % had a history of multiple family cancers. Family G was presented by Warthin as the first of four families with complete records of the descendants of a cancerous grandparent, and this stood out prominently because of the striking proclivity of cancer shown in two generations (see Fig. 1). Of the 48 descendants of the cancerous Pioneer G, apparently 17 had died or were operated on for cancer of the uterus or stomach. This family 'tendency', apparently present in the family line before the surname beginning with G, was introduced by marriage, and Warthin argued that it was so striking that Family G showed a so-called inherited susceptibility to cancer. In addition, Warthin pointed out a marked association between susceptibility for cancer and tuberculosis. The two susceptibilities seemed to run together and were believed to indicate a progressive degenerative inheritance and were associated with the development of an 'inferior stock'.[9,10]

Motivated by studies on heredity and disease, and the vogue for eugenics in the wake of the excitement over the rediscovery of Gregor Mendel's laws of

[8]Warthin 1914; Krush 1971; Remini 2001, 257.

[9]Warthin 1913.

[10]Lynch 1985.

inheritance in 1900, one would have expected strong scientific support for Warthin's study.[11] Only a few years before Warthin published his study, the internationally known cancer expert William Roger Williams quite plainly stated, 'those pathologists whose horizon does not extend beyond cells and microbes, have overlooked the chief factor in the cancer problem—that is to say, predisposition'.[12] And did not the highly reputed New York pathologist Isaac Levin (1874–1945) almost simultaneously announce that he was about to revise his view on the hereditability of the dreaded disease from 'no' to 'yes'?[13] The question of a possible familial susceptibility to cancer also excited lively interest from a new field of research—experimental animal breeding. The American researchers Ernest Tyzzer (1875–1965), Clarence C. Little (1888–1971) and the famous 'mouse lady' Maud Slye (1869–1954) pioneered efforts to trace Mendelian characteristics of cancer heritability in experimentally created lines of inbred mice.[14] If not for purely scientific reasons, Family G might have been selected as supporting the gospel of eugenics by serving as an exemplary case of a degenerative stock to be used during a eugenics exhibit.[15] After all, Warthin was a rising star within the American medical establishment and had become part of John Kellogg's (1852–1943) eugenic priesthood in Michigan.[16] However, none of these likely scenarios materialized. By 1914, the cancer research and treatment landscape was changing dramatically and so was the 'susceptibility' for cancer theory in scientific news on heredity and cancer.

3 Heredity, Eugenics and the Organized Fight Against Cancer: Family G Revisited

However promising as part of the emerging field of Mendelian genetics, medical support for the cancer hypothesis on hereditability waned. By the turn of the twentieth century, some surgeons argued that the popular belief in cancer as a hereditary disease could have negative health consequences of its own. For

[11]Rushton 1994, 59–84.

[12]Williams 1908, 374.

[13]Levin 1912.

[14]Mc Coy 1977.

[15]Eugenics can be seen as a biological theory of human improvement that was informed and vitalized by revolutionary developments in biology and medicine at the end of the nineteenth and early twentieth century. These scientific insights seemed to promise a new cure not only for a wide range of diseases but also for social problems. The social applications of the biological sciences have initiated debates about social differentiation, scientific responsibility, medical ethics, reproductive autonomy and human rights that resonate until the present day. Eugenics can equally be regarded as a social and cultural philosophy of individual and collective identity within the context of modernity; Kevles 1985.

[16]Lynch 1985; Robbins 1914 and 1915.

example, a presumed, but not proved, hereditary disposition to cancer could lead to depression and so cause cancer.[17] Twenty years later, with the rise of the organized fight against cancer, notions of hereditary cancer would become a major object of medical, social and political concern.[18]

With the support of the American Society for the Control of Cancer (ASCC), new cancer hospitals and research institutes and their specialists spread the message of *Do Not Delay*: cancer is curable, if and when detected early.[19] Within this context, we see attempts at a transformation of the responsible healthy citizen into a 'sentry patient' or 'homo medicus'—a patient ever watchful for the first signs of the dreaded disease.[20] The cancer idiom of heredity that was associated with shame, fatalism and stigmatization became regarded as counterproductive to the 'Do Not Delay' message.[21] The 'cancer prevention propagandists', as Warthin rather cynically called them, strongly believed that one of the major reasons for laymen to delay seeking medical attention was the creation of cancer-phobic states of mind by unfounded notions of hereditary and a predestination to certain doom.[22] Not surprisingly, in the propaganda literature of the ASCC, little, if any, attention was paid to a hereditary factor in the aetiology of cancer.[23] According to ASCC protagonist, the clinical pathologist James Ewing (1866–1943), in the interests of the American public, this hereditary doctrine ought to be combatted. Yes, people might pass on a liability for cancer, but cancer was not expressed until other factors were brought into play. A major building block for Ewing's anti-hereditary argument was statistical evidence from life insurance companies. Why bother with a theory of susceptibility to cancer when these companies had found no statistical evidence to pay serious attention to a history of 'cancer in the family'?[24]

The 'hereditary factor' might have been deleted completely from the 'Do Not Delay' campaign script, but did this mean that cancer and heredity were no longer up for medical debate? As Robert Proctor has shown in the interwar period, ethnic or geographic differences in cancer rates were commonly discussed in terms of racial or constitutional predispositions.[25] Given the unproblematic nature of these discussions, it is of interest to trace possible changes in the appreciation of Warthin's ongoing medical research on family cancers.

[17]Snow 1885.

[18]Patterson 1987, 38.

[19]Aronowitz 2001, 356.

[20]Pinell 2000 and 2002.

[21]Patterson 1987, 38; Aronowitz 2007, 144–162.

[22]Childe 1906, 144; Warthin 1926, 838.

[23]Bloodgood 1914; Special Committee for the control of cancer 1920, 10–11; Council on health and public instruction of the American Medical Association 1924; American Society for the Control of Cancer 1940.

[24]Ewing 1928, 109–114.

[25]Proctor 1995, 221.

In 1925, Warthin published a further study of the 'cancer' Family G.[26] In the introduction, he regrets that his first report met with little favour among the Alliance against Cancer. However, apparently the animal investigations of Maud Slye, Clarence Little and others had encouraged him to continue his research of cancerous grandfather G's offspring, which stood out as the best documented family with cancer and cancer fraternities identified in his previous study. Once again with the cooperation of the seamstress Pauline—who despite her regular visits to Warthin's department and awareness of the importance of early detection died of cancer prematurely—Warthin created a follow-up pedigree chart of the by then 144 descendants (three generations) of the original German settler and his wife. Out of the 146 individuals, 28 known cases of cancer had reportedly occurred, which was an incidence of 19.2 %. The accumulation of cancer cases was argued to be significantly in excess of the expected 10 % according to the law of probability for the whole population. According to Warthin, these findings suggested a recessive familial susceptibility to develop cancer and shown in females in the generative organs and in males in the gastrointestinal tract. He also noted (as in the case of the seamstress) a marked tendency to the sudden development and rapid course of the disease. However dramatic in terms of the presentation of clinical and statistical findings, once again, Warthin's writings on heredity, cancer and medical family research did not meet with much acclaim.

First, genealogy as a scientific method for studies on human heredity was increasingly put up for debate. The excessive popular use of pedigrees at eugenics exhibits and growing criticism against explaining human heredity in simple Mendelian terms undermined the authority of medical family research.[27] Moreover, animal and twin research had emerged as new standard methods of genetic research. Second, Warthin's public accusations of the ASCC's neglect of a hereditary factor for cancer did not help his cause.[28] And third, the 'Do Not Delay' supporters continued to keep doctors and lay people away from the perceived fatalistic associations between cancer and heredity in individuals and families.

Even in his position as editor of the Annals of Internal Medicine and president of the American Association for Cancer Research, Warthin was unable to distinguish himself from a voice crying in the wilderness. Although highly regarded as an internationally distinguished pathologist, Warthin's views on the influence of heredity on cancer in individuals and families remained controversial. Ultimately, however, Warthin was undeterred and was not influenced by his peers.

Shortly before Warthin's death in 1930, his eugenic manifest, *The Creed of a Biologist*, pleaded for the eugenic measure of marriage restrictions for those with a demonstrated heritable cancer susceptibility.[29] Warthin was especially concerned

[26]Warthin 1925.

[27]Kevles 1985.

[28]Warthin 1926; George A. Soper to Aldred Scott Warthin, letter dated 7 December 1926, Bentley Historical Archives, Warthin Papers Box 1.

[29]Warthin 1930.

about the reproduction of so-called *durchschlag* families like his Family G with a marked unhealthy family susceptibility for cancer and an associated predisposition to tuberculosis.[30] In Warthin's opinion, his new category of cancer families could only survive by breeding with individuals from families with no history of cancer and by avoiding all known extrinsic cancer-causing agents. 'He should not smoke; he should not engage in any industry in which...irritating products are used. He should not expose himself to irradiation'.[31] Given a proper and healthy regimen, the burden of cancer could be reduced even in cancer families like Family G. Although Warthin's views on the nature and magnitude of the hereditary factor differed from the mainstream, ironically he shared the optimistic and plastic nineteenth-century notion of coping with the natural history of cancer with his fierce opponents in the Alliance Against Cancer. Despite the development of new biological and medical theories in the first part of the twentieth century, doctors in the consulting room continued to regard health and disease as malleable states of being.

4 Conclusion

In my chapter, I have shown that the American cancer community was far less receptive to associations between heredity and cancer than might have been expected from the general popularity of debates on heredity, disease and behaviour in the nineteenth century. The translation and understanding of the hereditary risk factor in cancer medicine and the specific consequences for prophylaxis and treatment depended as much on the medical as on the socioeconomic and political contexts of doctoring cancer. My hypothesis is that the specific American resistance against an association between heredity and cancer in individuals and families has its origin in the rather radical translation of the 'Do not Delay' ideology by the ASCC. As part of the ASCC's economic struggle for existence, its leaders chose a straightforward and aggressive message: early detection and surgery were the only means to fight the dreaded disease. Anything that might hinder the circulation of this message was regarded as offensive, even if this implied resistance against the attractive world of brave new biology. ASCC's behaviour was in line with the curative focus that met the immediate needs of twentieth-century patients in American medicine.[32] ASCC was the leading force in the American war against cancer and was dominated by hospital doctors and entrepreneurs who shared a preference for private and technical forms of medical prophylaxis and treatment as part of a 'Do not Delay' ideology. This approach seems to be more significance in the rejection of eugenic measures than a general disapproval of eugenic measures in

[30]Warthin 1931.
[31]Warthin 1931, 696.
[32]Burnham 2015.

the face of a dreaded disease. In her book *Eugenic Nation*, Alexandra Stern has convincingly argued that the fear of disease could just as well have fuelled eugenic thinking and measures.[33] But, in the ideas and concepts across medicine and society, cancer has always been a possible, but not a necessary, outcome of a presumed hereditary or genetic predisposition, and this has created the flexibility that enabled interest groups (including Family G members) to explain and use hereditary and genetic 'at-risk' factors to their own advantage.

I also showed that in circulating between various realms, the pedigree of Family G began to take on a life of its own between 1895 and 1931 from the age of Weismannism to the age of a brave new biology. I argue that as part of this process, identity formation went both ways; as Family G changed, so did its handlers. In being 'revisited' in the medical literature in 1936 (four generations/305 descendants), 1971 (five generations/more than 650 descendants) and 2005 (seven generations/more than 929 descendants), the visibility, meaning and legitimacy of 'Family G' as a 'high-risk' cancer family continued to change.[34]

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Epilogue

Following the early scientific paper trail of Family G does not do justice to the pain, hardship, sorrow and stigma the family members had to endure throughout the twentieth century right into genomic age in coping with their genealogical disease burden and their role as objects of research. The long-term process of collecting family history data has involved intensive and emotional discussions with researchers and relatives about health, disease, death and other related aspects of personal biographies. The major question for the expanding Family G continues to be: How might the 'new' knowledge that is generated by participating in medical research benefit them?

For more than a century, scientific ideas circulated within the family about the aetiology of their disease burden from a recessive familial susceptibility (1930s), a cancer-susceptible genotype with a possible underlying viral oncogene mechanism (1970s), hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome associated with a possible genetic mechanism (1980s) to germline mutations in DNA mismatch repair (MMR) genes (1990s).[35] The understanding of those ideas

[33] Stern 2005.

[34] Hauser 1936; Lynch 1971; Douglas 2005.

[35] Lynch et al. 2004; Boland 2013; Necochea 2007.

within Family G circles was always associated with the hope for a cure, but, at the same time, the knowledge that their close cooperation with scientists had not yielded major therapeutic benefits or a dramatic change in the family's biography.

Following a frantic race, the headline news in 1994 that researchers had cloned the specific disease genes associated with Lynch syndrome and development of a genetic test was imminent was hailed as a victory within Family G. Predictive genetic medicine was believed to succeed where other medical approaches had failed, and the promise for an all-in-one cure for their genealogical misfortunes seemed more tangible than ever. President Bill Clinton exemplified this optimism when he announced the 'first draft' of the human genome in June 2000. Clinton claimed that for our children's children, cancer would only be known as a constellation of stars.[36]

However, in approximately 2001, the first results of the genetic tests were shared among Family G members, and their optimism quickly dwindled due to the development of disruptive family disputes over the issue of testing status. Those family members who had tested positive were confronted with complex preventive monitoring (e.g. colonoscopy) and surgical trajectories. They felt excluded by those family members who had tested negative and had no immediate medical obligation and the other way around. The professional writer Ami Mckay and Family G member, who lives in Canada, wrote and produced a most insightful radio documentary for CBC Radio 'Daughter of Family G' concerning the rather difficult decision to undergo genetic testing, what it meant to be tested and how she and other family members tried to cope with their test results. I would like to encourage all readers to learn more about this penetrating radio documentary. You will find a direct link to it here: http://www.mutantme.com/daughter-of-family-g/.[37]

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[36] http://www.thehumangenome.co.uk/THE_HUMAN_GENOME/Cancer.html.

[37] See for more information on Ami McKay's ongoing activities as public gatekeeper and Family G reporter: http://www.mutantme.com/daughter-of-family-g/.

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