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Genetic Counseling for *DAPK1* Mutation in a Chronic Lymphocytic Leukemia Family

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Abstract

Genetic counseling has become the clinical bedrock of hereditary cancer. Countless advances in molecular genetics contributing to the identification of cancer-causing germline mutations have increased its importance. We report perhaps the world's first genetic counseling experience involving a family with hereditary chronic lymphocytic leukemia and the cancer-causing mutation in the death-associated protein kinase 1 (*DAPK1*) gene. This hereditary disorder currently lacks any preventive or curative interventions for mutation carriers.

This family has been under our investigation for a decade, during which time genealogy, cancer of all anatomic sites, medical and pathology records, and, whenever possible, slides and tissue blocks were reviewed. Family attendance at three Family Information Services provided intensive education about this disease. Blood and skin fibroblasts were obtained for molecular genetic studies of DNA leading to the discovery of the *DAPK1* mutation in the family. Their intellectual and emotional reaction to its presence or absence in them was assessed.

This family serves as a model for genetic counseling in disorders where life-saving intervention is not yet possible.

Keywords

chronic lymphocytic leukemia (CLL); *DAPK1* gene; genetic counseling; natural history; hereditary cancer; familial cancer; molecular genetics; family history; linkage analysis

Introduction

The incidence of chronic lymphocytic leukemia (CLL) in the United States in 2008 is estimated at 15,110, with a mortality of 4,390 [1]. It is the most common form of leukemia and shows a

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high frequency of familial aggregation [2], which in some families appears to be consonant with an autosomal dominant mode of genetic transmission [3,4]. Multiple primary cancers and lymphoproliferative disorders, including cancer of the lung, brain, melanoma, renal cell, and non-melanoma skin cancers, and secondary lymphoproliferative disorders, have been previously reported as showing an excess in CLL [5–9].

However, unlike several classical hereditary cancer-prone syndromes, such as familial adenomatous polyposis (FAP), which harbor well-defined hereditary cancer-causing germline mutations and thereby are amenable to DNA-based mutation screening and management [10], there is very little we can offer patients at high genetic risk for CLL, inclusive of available educational information to be given them at the time of genetic counseling. This pertains to those CLL family members in this report who are carriers of the death-associated protein kinase 1 (*DAPK1*) mutation [8]. This therapeutic quandary is comparable to the severe limitations of lifesaving measures we can recommend during the genetic counseling sessions for patients at high risk for such hereditary cancer syndromes as the familial atypical multiple mole melanoma (FAMMM) and pancreatic cancer syndrome (FAMMM-PC) with the *CDKN2A* (*p16*) mutation [11]. In the non-cancer realm, one of the better known hereditary disorders lacking medical benefit through genetic counseling and knowledge of its causal mutation is Huntington's Chorea [12].

DAPK1 is a Ca^{2+} /calmodulin-dependent serine/threonine kinase that acts as a positive regulator of apoptosis in part via phosphorylation of *p53*. *DAPK1* appears to be regulated in part by autophosphorylation as well as by the RAS/RAF/MAPK pathway via phosphorylation after activation of ERK (RAS-extracellular signal kinase). Loss of *DAPK1* function in humans has been associated with cancer of solid organs (bladder cancer, ovarian and endometrial cancer) and hematological cancers (lymphomas of T, NK cells as well as B cell origin, treatment-related myelodysplasia, and leukemia).

Raval et al. [8] have shown that lost or reduced expression of *DAPK1* predisposes to heritable CLL; furthermore, its epigenetic silencing by promoter methylation occurs in most sporadic CLL cases. In the large family reported herein, we "...defined a disease haplotype, which segregates with the CLL phenotype... *DAPK1* expression of the CLL allele is downregulated by 75% in germline cells due to increased *HOXB7* binding. In the blood cells from affected family members, promoter methylation results in additional loss of *DAPK1* expression." It was, therefore, concluded that reduced expression of *DAPK1* is a crucial event in causing or contributing to the CLL phenotype which may result from germline predisposition as well as epigenetic or somatic causal events.

Caporaso et al. [13] note that the familial aspect of CLL, while speculated upon for decades, has only recently begun to be clarified as a result of the confluence of advances in molecular and genetic technologies, in concert with extensive international collaborative network efforts. They prudently call attention to studies which show that the risk for CLL is strongly increased in relatives of CLL cases. Moreover, risk of familial CLL, as mentioned, is also increased in the presence of other lymphoproliferative (LP) malignancies. Furthermore, these co-aggregations of LP malignancies are not necessarily due to referral bias; rather, they indicate the "...sharing of at least some genes that contribute to the risk for multiple LPs. This means that linkage and association studies in each of these malignancies will need to be closely examined for common elements that might reveal common mechanisms." In summary, CLL may exhibit one of the strongest familial tendencies of any malignancy [14].

Our purpose is to describe our genetic counseling experience with a large CLL family. The molecular findings in this family do not lend themselves to a definitive assessment of risk in individual family members. We refer to the "mutation" in *DAPK1* for simplicity while the more

detailed facts are as follows [8,15]. The germline involvement of *DAPK1* is based on cosegregation of a ~700 kb haplotype containing *DAPK1* with the disease phenotype (linkage). Nevertheless, individual IV-9 who was diagnosed with CLL at age 58 and died at age 71 did not carry the “affected” haplotype nor the “mutation.” We tentatively consider individual IV-9 to represent a phenocopy. The total absence of CLL in her extensive branch of the family supports this assumption. The “mutation” is an A→G single nucleotide change located 6.5 kb upstream of exon 1 of *DAPK1*. It is present in all individuals with the “affected” haplotype. Experimentally it was shown that the A→G change (the “mutation”) leads to enhanced binding of HOXB7, which in turn leads to transcriptional downregulation of *DAPK1*. The ~75% downregulation of transcription occurs in the “affected” allele in germline cells (fibroblasts) of affected family members, thus tying it to the hereditary predisposition. Of note, the “mutation” is rare or almost unique, having been seen in a single sporadic CLL patient from Sweden, but in none of 263 other familial and sporadic CLL patients and in none of 383 controls. All four brothers in generation IV have CLL and carry the “affected” haplotype and the “mutation.” However, in generation V there are 4 individuals with the “affected” haplotype and mutation, only one of whom has CLL to date. Because of the uniqueness of the genetic change in *DAPK1* in this family we are unable to estimate the actual risk of CLL conferred by the haplotype and “mutation.” These somewhat complicated and technical caveats have been explicitly explained to the members of the family.

Material and Methods

This study was approved by Creighton University’s Institutional Review Board. The family history was compiled in accord with Creighton’s family history protocol, which has been in use and continually modified over the past several decades. This CLL family was ascertained through the University of Nebraska lymphoma resource. Careful attention was given to the pathology documentation of CLL in concert with diverse hematologic malignancies or solid tumors in the family.

The proband, after initially consenting almost a decade ago, was intensively interviewed, giving particular attention to his personal as well as his family history of CLL, inclusive of cancer of all anatomic sites. Standardized questionnaires that asked about family history and personal history of each family member were then sent to all consenting family members. This included permission forms for the release of medical and pathology records, inclusive of slides and tissue blocks when available, for each affected individual or deceased legal next of kin. Once information about the high rate of CLL in the family was documented, a Family Information Service (FIS) [16] was arranged at a location that was most convenient for the family.

In 2001, Creighton investigators conducted the first of three FISs for the family. This included education of approximately 25 family members, which included detailed information about the objectives of our study. Blood was drawn at this meeting for complete blood counts, enzymes, and DNA for formal linkage analysis contributing to the *DAPK1* findings [8]; cytogenetics and molecular genetics were performed (WS). Subsequently, slides and tissue blocks were obtained for pathology review (DW) and molecular genetics. Buccal cells and skin biopsies were also obtained [8]. Each individual who provided tissue sample(s) for the research study, was asked to indicate on the consent form signed at the time of tissue retrieval whether he/she wanted to be notified of results that could pertain to his/her health.

The initial version of this family’s pedigree was published in 2002 [7], following which a second FIS was conducted in 2005. This FIS provided updated information to family attendees relevant to our progress which was underway for the discovery of the *DAPK1* germline mutation. At the conclusion of our second FIS in 2005, we told each family member that we

would provide them with detailed follow-up in a further FIS session once evidence of significant progress was made in our understanding of CLL's etiology and pathogenesis in their family. This included any implications for its prevention and/or management.

The family has been extremely supportive of each other and the research team. Once the mutation was identified [8], the family membership was re-contacted and the plan for a third FIS was arranged. The proband was contacted through a Creighton University IRB-approved letter indicating that new research genetic test results and information regarding the significance of these results, as well as genetic counseling, were available. A tentative FIS date was proposed to the proband; he then confirmed availability of himself and his family members. The proband and family members were then sent another IRB-approved letter with an attached response form, which asked about the level of interest in receiving their genetic research results.

The third FIS provided the attendees additional education about the *DAPK1* discovery, including its clinical limitations and the continuous aspects of our research efforts. This was presented to the family because we had promised them that any progress on our research of CLL in their family, inclusive of the potential discovery of the deleterious mutation, would be discussed with them in detail (HTL). We also educated the family members about all facets of CLL's natural history (SDT). The genetic counselor (KMF) advised participants in detail about DNA testing and its implications, such as its potential emotional impact as well as their concern about insurance and employment discrimination; this information had also been covered in the IRB-approved consent form that needed to be signed by each participant prior to releasing the test result. Following the didactic coverage, each member in attendance who had signed the necessary consent form was independently counseled and advised as to whether he/she was a carrier of the mutation, and was advised in detail regarding what this meant. Two family members who did not attend the FIS were counseled via telephone conference. The pinnacle finding from our study which emerged in their family, namely, the discovery of a germline mutation in the *DAPK1* gene [8], appeared to have made the family pleased with their participation in this accomplishment.

Results

This third FIS included an update of our research progress on the family by our international clinical and molecular genetics team. We expressed our gratitude for all of the help that the family provided us through their sharing of their medical histories, pathology records, slides and tissue blocks (when available), and biological specimens (inclusive of blood, serum, and skin fibroblasts). They were told how this important material enabled us to contribute knowledge about CLL and, in particular, our discovery of the *DAPK1* mutation in their CLL family [8]. We then discussed our particular involvement with those most salient educational and genetic research findings in the project, using lay language whenever possible. Approximately 3 hours was devoted to this educational session. (See the pedigree of this CLL family, Figure 1).

The proband (IV-2), as the family patriarch, contacted several family members and ascertained their interest in another FIS. Each family member who participated did so of his or her own free will without coercion, and signed the above-mentioned IRB consent forms to receive mutation research results.

We then met with individual V-10, a 39-year-old male who had CLL at age 34. His diagnosis of CLL ensued following our initial FIS in 2001; through the cytogenetic and molecular workup of his biologic samples obtained at that FIS, a clonal CLL population with a deletion of 13q14 was found in his peripheral blood. When this report was received by the oncologist/medical

geneticist (HTL), he telephoned individual V-10, explained the finding, and advised him to see an oncologist/hematologist regarding the results.

When discussing the mutation, this individual took the position that since his father (IV-4) and his grandfather (III-1) had CLL, it was his belief that it would be "...only a matter of time that he would become affected." However, when told that he had the CLL causal germline mutation, he stated that "...the whole world closed in on him." He became emotionally distressed. He then began realizing that his father and grandfather had survived many years with CLL and these facts appeared to make him feel marginally better.

Individual IV-4 is a 71-year-old man who, at age 54, was diagnosed with CLL and is currently under therapy for this disease. He was convinced that he would be told that he had the mutation, attributing this reasoning to the fact that his son (V-10) had CLL at age 34 and was known to have been positive for the mutation. When we told him of his positive mutation status, he was accepting of these results. He has continued to be extremely helpful throughout our research.

Individual (IV-3) is also a 71-year-old male, the identical twin brother of IV-4, who was certain he would be told that he had the mutation. He had developed CLL at age 56. He appeared to have adjusted quite well to the presence of CLL. He was fully knowledgeable that his identical twin brother was also affected with CLL. When told that he had the deleterious *DAPK1* mutation, he fully accepted this finding.

Individual V-5 is a 43-year-old male who has been an extremely active participant in our CLL project. He works in a health-related field. Because of the family's CLL situation, he has become exceedingly knowledgeable about the disorder. We discussed the results with him during a telephone conference. He steadfastly stated his belief that a 50/50 Mendelian inheritance-type pattern for the germline mutation was the crucial variable to his knowledge and expectation as to whether he would be told if he did or did not have the germline mutation. He had reviewed all of the educational materials we had made available to him and he hoped that he would not have the deleterious gene. However, he freely kept the issue open, stating that he realized that it could "go either way, but I will be at peace either way." He has not had any advice about CLL from a physician other than the feedback he has received from his family, his own research pursuit, and his past participation in the 2005 FIS.

He stated that if told he was found to be positive for the mutation that he would likely make lifestyle changes, particularly involving his nutrition and exercise patterns. He indicated that, as far as he can determine, he has not had any sequelae of CLL. It appeared to us that he was thinking more favorably about his risk status, in that at age 43 he was still free of any CLL manifestations and that, perhaps, this would be a "good sign" indicating that he did not have the mutation. He also stated that, knowing he would be told the result, this would not have an emotional impact upon him. We then told him that he, in fact, had inherited the deleterious mutation. He was quite objective and accepting. We then discussed, at length, the medical and genetic aspects of CLL. We emphasized that, at this time, we don't have any prospective information about lifestyle changes, medications, or any other medical or preventive advice that will change the course of this in him. He kept probing us for any preventive measures but we steadfastly told him that, at this point in time, proven information that is available on prevention of CLL simply doesn't exist; but we let him know that we are holding out hope that knowledge of CLL's molecular aspects may prove therapeutically helpful in the future. We reinforced the cancer prevention strategies recommended for the general public (healthy diet including fruits, legumes, reduced use of meat; physical fitness; healthy body weight; and tobacco avoidance). We recommended an annual complete blood count with differential and early hematology consultation for significant peripheral blood lymphocytosis (>5000), unexplained anemia or thrombocytopenia. Finally, he wondered whether our research could

ultimately, through advancing knowledge, help him and his family. We told him that this was our fervent hope but that, unfortunately, we were not able to provide any level of certainty about such scientific advances at this time. However, it was comforting to him to know that our entire international research team was steadfastly pursuing every possible lead toward the better comprehension of CLL's etiology, ultimate management, and prevention.

He then became quite concerned about the risk to his children. We told him that should a predisposition to CLL exist in his children that we would not, at this time, change anything that we would do for them from a medical standpoint. We also told him that we would prefer not to test his children until they are 18 years of age or older, have become knowledgeable about the disease, and are consenting, given the fact that we cannot provide them at this time with any medical benefit through DNA testing. He understood this fully and was aware that each child would have a 50% risk for inheriting the deleterious mutation. When discussing implications of test results to children, the genetic counselor reviewed that, as in other hereditary cancer syndromes, an individual inheriting a mutation does not mean they will necessarily develop the disease. We reviewed the age of onset of CLL in his pedigree (range 34 to 56 years) pertinent to the question raised regarding gene testing on his minor children.

Individual V-1 is a 55-year-old male. During a telephone disclosure of results with him, he was objective and fully recognized that his CLL risk was quite high. However, he had difficulty understanding the significance of a genetic 50/50 basis for his risk for the mutation. While recognizing that his risk was high, he didn't appear to be bothered emotionally about that fact. However, we wondered whether this was a psychological defensive mechanism.

He had seen a physician on several occasions about his CLL risk, has had blood drawn, and realizes that one of the first telling signs of the disease would be an increased white count. He did not appear to have any heightened emotional response knowing that his results would be divulged to him in our counseling session. However, we were surprised when midway through our conversation he stated "Well, now I am moderately concerned." During the telephone result disclosure, he stated that he believed that he was going to be a mutation carrier, having realized that his father and uncle had received this news. We then told him that he, in fact, did inherit the deleterious mutation. There was no blatant emotional response and when directly asked if it impacted upon his emotions, he answered abruptly "Not really."

He then wondered whether this was more a "male disease," at least in his family. We answered by discussing the Mendelian inherited autosomal dominant features of CLL in his family, emphasizing that females are likely at equal risk but perhaps due to as-yet-unknown mitigating endogenous or exogenous factors, and possible interaction among them, there may be a male predominance for unknown reasons. The absence of any proven preventive medicine measures was discussed, as were the general recommendations for health and specific follow-up mentioned above.

The next family member to be counseled (V-7), is a 39-year-old female who reasoned that she would be negative for the mutation because of the complete absence of women being affected with CLL in the family. She was told that she was, indeed, negative for the mutation. The Mendelian inheritance probabilities were discussed with her, particularly the issue surrounding the excess of males being affected in her family versus the likelihood that this was possibly a chance phenomenon.

Family member (V-8) is a 44-year-old male who was very proactive and who stated that he did not have any anxiety or apprehension about receiving the pending result of his mutation status. He stated that he was well prepared and wanted to continue participating with our research in the interest of helping his family. He steadfastly stated that he believed he was negative for the mutation because his brother, who is positive, had been told about this earlier

on. We then told him that he did not inherit the deleterious mutation. His rationale for his strong belief of a mutation negative finding was his stated conviction that had he been positive, we would have told him immediately. His wife was present during the counseling session and she stated the same thing, namely that had he been positive, we would have shared that information with him “immediately.” They each stated that they would have continued assisting us even if he had turned out to be positive.

We then counseled three family members (two women and one man) together, at their request (V-3, V-4, and V-6). Each of the women inferred that she would be told that she was negative for the mutation based on the fact that no females in the family had been affected with CLL, and the belief that if she had been positive for the mutation she would have already been advised of that fact. In the case of the male (V-3), his reasoning was also based on the idea that had he been positive for the mutation, he would have been told his test result much earlier. (Indeed, this reasoning has repeatedly been voiced throughout our experience with countless genetic counseling sessions.) Each was told that he/she did not inherit the *DAPK1* mutation, and because of their reasoning they displayed very little emotional affect about the “good news.”

Discussion

We are living in an age of veritably explosive discoveries in molecular genetics which, in the hereditary cancer field, constitutes its golden age. Although it is exceedingly important for common hereditary cancer traits such as *BRCA1* and *BRCA2* in the case of hereditary breast-ovarian cancer (HBOC) syndrome, and mismatch repair mutations in *MLH1*, *MSH2*, and *MSH6* for the Lynch syndrome, we must also consider how molecular genetics will impact on exceedingly rare disorders such as the Hutchinson-Gilford progeria syndrome [17]. For example, 15 children between 1 and 17 years of age made up a cohort which represented half of the world’s known population of Hutchinson-Gilford progeria syndrome. Still, rare as it is, it offers unique opportunities to investigate the sequelae of aging which, in turn, is one of the most significant factors correlating with the onset of cancer. Korf [18] describes how the rarest of conditions may teach us about the pathophysiologic mechanisms involved in the genesis of the more common conditions associated with age. In the case of CLL, which constitutes the most common form of leukemia, and wherein our CLL-prone family exhibits the first evidence of a causal mutation (*DAPK1*) [8], we have the unique opportunity to one day determine its pathophysiology which, so far as we can determine, has been described for the first time in a single family. However, we can certainly hypothesize that it will impact not only this family but possibly other CLL families, as well as having the potential of adding to our understanding about the diverse universe of leukemias and lymphomas.

But what about the patient? Clearly, the answer for every experimental mission is the need for genetic counseling, which requires informed consent, and which appropriately has become the standard of care for most hereditary disorders, thereby imposing upon the physician an obligation to inform the consenting patient of risks, benefits, and alternatives to any proposed course of DNA testing and treatment. This obligation is not limited to those disorders for which treatment has been proven to be effective, such as prophylactic total colectomy in an individual with FAP and an *APC* germline mutation. Identification of the *RET* proto-oncogene in a mutation carrier enables life-saving protection against medullary thyroid carcinoma through prophylactic total thyroidectomy by age five [19]. These compare with disorders where curative intent is not currently possible, as in our mentioned risk for pancreatic cancer in the FAMMM-PC syndrome with the *CDKN2A* germline mutation, or the hereditary non-cancer example, Huntington’s Chorea. Indeed, failure to subscribe to this communication dictum may expose the physician to malpractice liability [20–24]. Consequently, these concerns have become the bedrock of a communication issue commensurate with the many advances that have arisen through the Human Genome Project; in short, these advances have provided new

genomic tools wherein a family history has become highly relevant toward determining who needs DNA testing [25,26]. Failure to provide genetic counseling, regardless of potential benefit to the patient, poses a disservice to the patient's "right to know" his/her genetic status for a particular disorder.

This paper reports the first documented experience, so far as we can determine, of genetic counseling being provided for a CLL germline mutation affected family. The importance of genetic counseling in virtually all hereditary disorders, inclusive of cancer, is crucial and, indeed, mandatory for high-risk and/or affected patients in the interest of their medical and psychological welfare. Genetic counseling has reached the pinnacle of clinical importance, spurred on by the veritably explosive advances in genomic medicine. This is particularly evidenced by the discovery of a potpourri of cancer-causing germline mutations. In many cases, such mutations have made it possible to identify the patient's susceptibility to the "family disease" at an extremely early stage so that, in some of these disorders, appropriate screening and management might be effective.

The *DAPK1* mutation in CLL fits the category of disorders wherein a germline causal mutation may be clinically available but yet preventive methods are wholly lacking. So what do you tell the patient from a CLL family, such as the one reported herein, where the *DAPK1* disease-causing mutation has been identified and is, with the exception of the phenocopy (IV-9) already mentioned, co-segregating with CLL throughout the family? The answer is a vexing one given the absence of any frame of reference based upon empirical evidence since our experience indicates that this is the first and, currently, the only CLL family known to have the *DAPK1* mutation. Therefore, we have outright declared these facts while counseling our CLL family members.

We have described several pertinent responses to disclosure of the presence or absence of the *DAPK1* germline mutation in this CLL family. Responses include total objectivity in the case of individual V-10 who recognized that his father (IV-4) and his grandfather (III-1), had CLL and thereby reasoned that he would likely be told that he harbored the deleterious mutation but, yet, when he received that information he became devastated. Subsequently, he appeared to be somewhat heartened by the fact that both his grandfather and father had survived for more than a decade with CLL. Individual IV-4 had manifested CLL at age 54 and now at age 71 reasoned that he would certainly be told that he had the mutation since he was aware of its presence in his son (V-10) who had manifested CLL at the age of 34. Individual IV-3, a 71-year-old male with CLL who had an identical twin with CLL and the mutation, was also certain that he himself had the mutation. This individual was fully knowledgeable about these facts, and clearly indicated that he essentially had to have the mutation, based upon facts emanating from the genetics of identical twinning.

Individual V-5 is a health educator who had read extensively about CLL and appeared to be objective about the matter, had a high level of intellectual insight, and recognized his high 50/50 risk status; yet when told he was a *DAPK1* mutation carrier he immediately began wondering about preventive measures, including changes in lifestyle (nutrition and exercise). The paradox is that he was fully knowledgeable that preventive action was not yet available for CLL. Thus, we see a disparity between intellectual insight and emotional response to a perceived threat.

A very telling assessment of risk status among female members of the family emanated from the fact that, to date, only male members were affected with CLL in this family. This finding contributed to their rather firm belief that female family members would not be at risk for inheriting the *DAPK1* mutation since, for whatever reason, females in the family were not affected with CLL, as opposed to their CLL-affected male relatives.

While not evidenced-based, given the fact that this is the first family with CLL in the world, so far as we can determine, where a causal mutation has been identified [8], we share this genetic counseling experience.

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Pedigree drawn by Toni Richardson-Nelson, B.G.S.

Figure 1.

This is a pedigree of a chronic lymphocytic leukemia (CLL) family showing the disease present in three generations. A + indicates the presence of the *DAPK1* mutation, which is segregating with CLL. Patient IV-9 has CLL but lacks the *DAPK1* mutation and is considered to be a phenocopy.