Genetic Discrimination: Perspectives of Consumers

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In a study of the perceptions of 332 members of genetic support groups with one or more of 101 different genetic disorders in the family, it was found that as a result of a genetic disorder 25 percent of the respondents or affected family members believed they were refused life insurance, 22 percent believed they were refused health insurance, and 13 percent believed they were denied or let go from a job. Fear of genetic discrimination resulted in 9 percent of respondents or family members refusing to be tested for genetic conditions, 18 percent not revealing genetic information to insurers, and 17 percent not revealing information to employers. The level of perceived discrimination points to the need for more information to determine the extent and scope of the problem.

The rapid advances in human genetics, largely fueled by the Human Genome Project (HGP), have resulted in the expansion of the number and range of genetic tests (*1*). These tests are capable of providing carrier and presymptomatic information including risk of future disease, disability, and early death. In addition, these tests may reveal genetic information not only about the health of the individual, but also about his or her family members (*2*).

Concern about access to genetic information by health insurers has historical support (*3*, *4*). In the early 1970s, several insurance companies discriminated against individuals who were carriers of sickle cell anemia, even though they were quite healthy (*5*). The use of genetic information to deny life insurance to individuals leaves their dependents more vulnerable to economic consequences than is the case with the 70% of adults who are covered (*6*). The use of genetic screening to identify workers who may be particularly sensitive to noxious environments has been the principal focus of concern about workplace genetic testing even when done for benevolent reasons (*7*). Issues of genetic discrimination in employment and insurance have become more urgent as a result of the genome project (*8*).

Overall concerns about privacy and confidentiality have led the Ethical, Legal, and Social Issues (ELSI) Branch of the National Center for Human Genome Research to identify this issue as a top priority with the goal of proposing legislation specifically designed to protect people against genetic discrimination (*9*). Additionally, several working groups and scholars are focusing on this issue and have developed background papers and policy recommendations about the use of genetic information in health insurance as well as other areas such as life insurance and employment (*10*, *11*). Despite these concerns about potential genetic discrimination and documentation of individual cases, there is little information about the incidence and range of the problem (*12*).

This report provides information on the experiences of 332 individuals with one or more family members with a genetic disorder who are affiliated with genetic support groups. The study was part of the Human Genome Education Model (HuGEM) Project of the Georgetown University Child Development Center and the Alliance of Genetic Support Groups. It was the first phase of the HuGEM Project with the aim of getting input from 300 consumers in order to develop, implement, and evaluate a collaborative education model for consumers and health care providers.

Participants were recruited primarily through the national, regional, and local genetic support groups affiliated with the Alliance of Genetic Support Groups. Notices were put in two issues of the monthly *Alliance Alert* and letters were sent to the directors of 101 genetic support groups (representing an estimated 585,800 members). The notices contained information about the study and requested volunteers that were at least 18 years old and with one or more persons in the family with a genetic disorder who would be willing to participate in a 30-min telephone interview to provide opinions on the ethical, legal, and social issues of the HGP as well as priority topics for education. Volunteers were assured confidentiality of their responses. Random sampling was considered and ruled out because of time, cost, and the primarily educational focus of the project. Thus, the findings are applicable only to this group. Support group leaders were requested to distribute the letter requesting volunteers at meetings and in newsletters. Persons interested in participating were to complete a form at the bottom of the letter or call a 1-800 number for more information.

As a result of information provided by the support groups to the members or through the *Alliance Alert*, a group of 483 persons (from 73 different groups) contacted the Alliance of Genetic Support Groups about the study. They were sent information about the study and about the Human Genome Project. Of these, 336 (70%) returned consent forms (*13*). From this group, four persons decided not to participate after the interviews started, 306 persons completed telephone interviews, and 26 requested and completed the questionnaire by mail, for a total return of 332 respondents from 44 states and the District of Columbia (*14*).

Respondents were primarily female, highly educated, married, and Caucasian (*15*)—characteristics believed to be typical of genetic support groups (*16*). Age categories ranged from the twenties through seventies with a median age in the forties. A range of religious preferences was reported (*17*). There was an average of 2.1 affected family members per respondent with a range of 1 to 12 affected members reported.

The study questionnaire was composed primarily of questions with multiple choice responses. Telephone interviews were conducted by four social workers, a genetic counselor, and a consumer administrator (*18*) and lasted an average of 40 min with a range of 29 to 90 min. The content covered five areas: demographic information; knowledge of the Human Genome Project (61% had heard about the HGP before volunteering to participate in the study, 74% considered the HGP very important to their families, and 81% considered it very important to society); personal and family experience in areas related to genetic testing and research; opinions on a range of ethical, legal, and social issues; and priority topics for education. The education priorities were used to develop and implement educational forums in the mid-Atlantic and Pacific Northwest regions and will be described elsewhere.

Respondents were asked whether they or other family members had encountered problems with health insurance, life insurance, and employment (*19*). The term "genetic discrimination" was not used in the survey. It is used in this report to describe prejudicial actions as perceived by the respondents that resulted from insurers' or employers' knowledge of an individual's genetic condition, carrier status, or presumed carrier status, based on observation, family history, genetic testing, or other means of gathering genetic information (*20*).

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Respondents reported 101 different primary genetic disorders. The 18% of families with two or more disorders were asked to select one for purposes of the study. Of the primary disorders 68% were single-gene disorders, 10% were chromosome disorders, 11% were multifactorial disorders, 11% were major malformation syndromes, and less than 1% were mitochondrial and endocrine diseases.

Data analysis included frequency responses and comparison of responses to the questions on genetic discrimination by education, religious preference, and health of respondent and they showed no statistically significant differences (Pearson value of $P < 0.05$ was considered significant). Gender and ethnicity showed no significant differences when controlled for sample size.

Consumer experiences with health insurers were deemed important because the availability of affordable health insurance often determines who does and who does not have access to health care (*4*). For many people with genetic disorders, health insurance may mean the difference between life and death (*21*).

Although considerable genetic information may already be available to insurers in medical records, 40% of the respondents recalled being specifically asked about genetic diseases or disabilities on their applications for health insurance (Table 1). It cannot be assumed that the remaining 60% had not been asked questions about genetic diseases and disabilities. Many of them volunteered the information that they had never applied for health insurance. Some were able to maintain the coverage they had prior to diagnosis of a genetic disorder. Others had not applied because they assumed the genetic condition in the family would result in being turned down. Whether or not this information was then used to deny insurance to these people based on their genetic condition is not known.

Twenty-two percent of the respondents (Table 1) said that they or a family member were refused health insurance as a result of the genetic condition in the family. Since insurers do not need to provide reasons for turning down applications, it might be argued that respondents may have subjectively assumed that the denials were made because of the genetic condition. In this study, however, 83% of those who were refused health insurance had also been asked about genetic diseases or disabilities on their applications. Looked at in another way, nearly half (47%) of those who were asked about genetic diseases or disabilities on an application for health insurance were subsequently turned down. As health and life insurers are primarily regulated by states and most states are just beginning to address genetic issues in legislation (*22*), it is not known how many insurers actually ask genetic questions on applications.

The 31% of respondents with health insurance coverage who were denied reimbursement for some service or treatment indicated reasons such as the treatments were considered experimental, and services such as physical or occupational therapy were not considered a medical necessity. Time limits for submitting claims were also an issue, with insurers not paying claims that were more than a year old even when they had been submitted within the year and returned for more information. In several instances, payment was denied even though preapproval for a treatment or service had been given.

The large majority (83%) of respondents (Table 2) said they would not want their insurers to know if they were tested and found to be at high risk for a genetic disorder. The rate decreased to 78% when a similar question was asked that added the condition, "if the insurer pays for the tests." Some of the respondents noted that they would pay for genetic tests themselves or not be tested if they wanted to keep their genetic information confidential. The fear of genetic discrimination, as shown in Table 3, resulted in 9% of the respondents or a family member refusing to be tested for a genetic condition. This fear eliminates the opportunities of individuals to learn that they are not at increased risk for the genetic disorder in the family or to make life-style changes to reduce the risks or seriousness of the condition. It may also affect the number of people willing to participate in scientific research (*10*). Fear also prevented 18% of the respondents from revealing genetic information to an insurance company.

Approximately 70% of adults in the United States have some form of life insur-

Table 1. Questions and responses about experiences of consumers in areas of health insurance, life insurance, and employment. The total number of respondents is 332.

Question	Responses (%)		
	Yes	No	Don't know
As a result of the genetic condition in your family, have you or a member of your family been—			
Asked questions about genetic diseases or disabilities on an application for health insurance?	40	55	5
Refused health insurance?	22	76	2
Refused insurance coverage of some service or treatment?	31	67	2
Refused life insurance?	25	70	6
Asked questions about genetic diseases or disabilities on a job application?	15	83	2
Denied a job or let go from a job?	13	85	2

Table 2. Questions and responses to opinions about genetic information in insurance and employment.

Question	Responses (%)		
	Strongly agree or agree	Disagree or strongly disagree	Not sure or don't know
Genetic testing should be part of pre-employment physical exams.	4	94	2
Health insurers should be able to get genetic information if they pay for the tests.	16	78	6
	Yes	No	Not sure
If you were tested and found to be at high risk for a genetic disorder with serious complications, which of the following would you want to know the results of the test?			
a. Your employers?	6	87	7
b. Your insurance company?	11	83	6

ance (23). It is widely available, and only 3% of those who apply for coverage are declined. Of the 97% accepted, 5% are required to pay higher than standard premiums (24). This may be compared to the respondents in this study in which 25% (Table 1) of the respondents or affected family member have been refused life insurance (25).

Two questions were asked about the employment experiences of the study population. As noted in Table 1, 15% of the respondents said that they or affected family members had been asked questions about genetic diseases or disabilities on job applications. This increased to 20% of affected respondents ($P = 0.006$). It is not clear how often this information was used to subsequently deny the job to the applicants but the possibility exists and was of concern to respondents. In this study, 87% of respondents (Table 2) would not want their employers to know if they were tested and found to be at high risk for a genetic disorder with serious complications.

Thirteen percent of all respondents (Table 1) reported that they or another family member had been denied a job or let go from a job because of the genetic condition in the family. This was true for 21% of affected respondents and 4% of unaffected respondents ($P = 0.00001$). The percent was reduced to 9% ($P = 0.006$) for those with an affected child, even though a higher proportion of these respondents were in the workforce than the total population.

During the course of the analysis, a question was raised as to whether the perceived problems encountered in job application or denial or dismissal emanated from an employer's perception of a visible disability. To approach this question, analysis was done for the 77 unaffected respondents whose only affected family member was a child of less than 16 years of age. It was found that 7% of this population was asked about genetic diseases or disabilities on a job application and 3% were denied or let go from a job. These numbers should only be used as a starting point for future analyses.

For the affected respondents, some specific examples highlight the kinds of problems experienced. A man with a sex chromosome disorder reported that he had been denied a job following a pre-employment physical exam after the doctor wrote the name of the possible disorder on his medical report. The employer, in this case, knew it was illegal to use the diagnosis in the hiring decision and told the applicant that he would deny the conversation in the future if asked. A woman with a skeletal disorder reported that she was given termination notice the day after she informed her employer of a genetic diagnosis. The notice was withdrawn after she sought legal counsel. Examples provided by other respondents focused on effects of the genetic condition that could come under the protection of the 1995 interpretations of the Americans with Disabilities Act (26). The dilemma for persons with genetic disorders is that they must show not only that they have a genetic defect but also that they were regarded as "disabled" by an employer and discriminated against because of that perception. This raises concerns about the privacy and confidentiality of genetic information in the workplace.

A total of 17% have not revealed genetic information to their employers (Table 3) for fear of losing their jobs or insurance coverage. This increased to 25% of affected respondents ($P = 0.00001$). Overall, 43% of the respondents reported that they or members of their family have experienced genetic discrimination in one or more of the three areas. This included health insurance only (9%), life insurance only (11%), employment only (6%), and more than one category (17%).

Additional studies of persons with genetic disorders are indicated to confirm or deny the perceptions of the consumers in this study. It is possible that members of genetic support groups who have experienced genetic discrimination may have been more motivated to volunteer for this study. On the other hand, persons with these resources of higher education and membership in support groups traditionally have the skills and means to work with and influence social systems and may have experienced less discrimination than other groups. With adequate funding, a random sampling of respondents from support group or clinic populations could be selected with probability methods and objective as well as subjective information could be gathered.

Another goal would be to design more detailed questions to elicit information on genetic discrimination from respondents. Distinctions between the implications of overt genetic disease and conditions on each person and the effects on unaffected family members, or persons who are carriers or do not overtly express the consequences of the genetic condition will require further study. Consumers may be willing to participate if confidentiality is assured and trust is established. In this study, it was also found important for the interviewers to have clinical as well as technical skills in interviewing to facilitate the comfort level of discussing sensitive issues. This would also be recommended for future studies.

Although the goal of the HGP (and other genetic testing and research) is to help people, it could also cause harm if the level of perceived discrimination is in fact true. Neither the authors nor the respondents (as indicated in earlier responses) are suggesting that the HGP should not continue. On the contrary, there is strong support to continue research and to find ways to deal with genetic discrimination including federal or state legislation, guidelines, and standards among insurers, employers, researchers, and health professionals, and citizen advocacy to establish protections.

Table 3. Percentage of respondents withholding information or refusing to be tested for a genetic condition as result of fear.

Question	Responses (%)		
	Yes	No	Don't know
As a result of a genetic condition, have you or a member of your family—			
Refused to be tested for a genetic condition for fear of your insurance coverage being dropped.	9	89	2
Not revealed genetic information to an insurance company.	18	79	3
Not revealed genetic information to an employer.	17	81	2

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12. See, for example, P. R. Billings *et al.*, *Am. J. Hum. Genet.* **50**, 476 (1992).
13. As the interviews progressed and it was apparent that few members of ethnic or racial minorities were volunteering, additional telephone outreach was made to support groups to increase awareness of the project and opportunities for volunteering. This was only partially successful as seen in the demographic data.
14. There were no statistically significant differences in the responses on the telephone and written interviews so they are reported here together.
15. Of the 332 respondents, 80% were female, 57% have at least a bachelors degree, and 90% were Caucasian. Other characteristics were: 75% were married and living with their spouses, 76% have children, and 63% work outside the home. Family relationship, whether or not the respondent or family members were affected, age of diagnosis, and current age were also recorded.
16. Precise data on the demographics of genetic support groups are not available. Impressions are from staff of the Alliance of Genetic Support Groups based on their conversations and communications with the member organizations and attendance at national, regional, and local meetings.
17. Religious preferences were Roman Catholic, 26%; Protestant, 41%; Christian-other, 9%; Jewish, 11%; other, 2%; and none, 12%.
18. The interviewers were trained in interview techniques by the principal investigator and participated in pretesting the questionnaire.
19. The questions on possible genetic discrimination were taken from a questionnaire developed by Dr. Dorothy C. Wertz, The Shriver Center, Waltham, MA, entitled, *Ethical Issues in Genetics, Part I*, p. 33, No. 34, and used with permission of Dr. Wertz (letter of 16 December 1993).
20. This definition of genetic discrimination differs from the one used by Billings *et al.* (*12*) as they did not include actions against persons who were symptomatic or visibly affected by their genetic disorders. The design of our questionnaire does not permit analysis according to the definition of Billings *et al.* (1993). Because the questions on discrimination ask about all family members at once, the questions do not distinguish among: (i) the direct consequences of ongoing genetic disease or conditions, (ii) the effect of genetic disease on other family members, and (iii) the consequences of genetic information gained through testing.
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25. Many respondents said they had never applied for life insurance because they assumed they would be turned down.
26. Since 1990, the Americans with Disabilities Act (ADA) has provided protection for persons with disabilities in the workplace. The ADA prevents employers from openly denying employment or firing an individual solely on the basis of a "disability" if there are "reasonable accommodations" that can be made in the work setting to allow the person to perform his or her job. In April 1995, the ADA was interpreted by the U.S. Equal Employment Opportunity Commission to include healthy people who are carriers of genetic disorders. Implementation in general relies on employers and employees knowing and similarly interpreting the law as well as having good faith efforts to comply.
27. We wish to thank the HuGEM Advisory Committee: N. A. Holtzman, F. Neal-Smith, E. O. Nightingale, K. H. Rothenberg, and L. Walters, for assistance in planning and carrying out the study. We also wish to thank L. Palinсsar, M. A. Wilson, S. Rennert, and M. Volner, for their assistance with the telephone interviews and M. J. Verdieck and M. O'Reilly for research assistance. Most of all, we wish to thank the consumers who provided the data. Funded by the National Institutes of Health at the National Center for Human Genome Research in the branch of Ethical, Legal and Social Issues, grant number RO1-HG00786-03. This support does not constitute an endorsement of the views expressed in this article.

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Kap104p: A Karyopherin Involved in the Nuclear Transport of Messenger RNA Binding Proteins

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A cytosolic yeast karyopherin, Kap104p, was isolated and shown to function in the nuclear import of a specific class of proteins. The protein bound directly to repeat-containing nucleoporins and to a cytosolic pool of two nuclear messenger RNA (mRNA) binding proteins, Nab2p and Nab4p. Depletion of Kap104p resulted in a rapid shift of Nab2p from the nucleus to the cytoplasm without affecting the localization of other nuclear proteins tested. This finding suggests that the major function of Kap104p lies in returning mRNA binding proteins to the nucleus after mRNA export.

Transport across the nuclear envelope occurs through nuclear pore complexes (NPCs) and is governed by the interaction of soluble transport proteins (karyopherins) with the transport substrate and the NPC (*1–12*). Most of our understanding of the mechanism of translocation comes from studying protein import in semipermeablized cells (*1*) of model karyophilic proteins that carry a nuclear localization signal (NLS) from either the SV40 large T antigen or nucleoplasmin (*2*). These classical NLSs are recognized by karyopherin α in a dimeric cytosolic complex with karyopherin β (*3–8*). The complex docks at the NPC through its interaction with nucleoporins that contain characteristic repeated peptide motifs (*6–11*). The small guanosine triphosphatase, Ran, and p10 are required for the subsequent translocation of the substrate (and karyopherin α) through the NPC (*11*, *12*).

Distinct saturable and noncompeting pathways for the import of different karyophiles have been uncovered through the use of microinjection studies in oocytes (*13–15*). Similarly, saturable noncompeting pathways exist for the export of macromolecules from the nucleus (*14*, *16*, *17*). The signals that mediate many of these processes are different from classical NLSs (*14*, *15*, *17–19*) and thus may use recognition factors other than karyopherin α and karyopherin β for nuclear transport. Here we characterize the first such factor, which we term Kap104p and which is required for the import of at least two yeast nuclear mRNA binding proteins.

The *Saccharomyces cerevisiae* proteins Kap60p and Kap95p are homologs of mammalian karyopherin α and karyopherin β (*20*). Sequence comparisons of Kap95p with the complete yeast genome database uncovered three additional proteins that are structurally similar to Kap95p; two of these, which we term Kap123p and Kap104p, have not been previously characterized (*21*), and the third, Pse1p, was identified as a multicopy enhancer of protein secretion (*22*). The sequence alignment of Kap104p with Kap95p is shown (Fig. 1A). The proteins bear substantial similarity over their entire lengths, and secondary structural predictions suggest that Kap95p and Kap104p share the same overall domain structure of HEAT motifs (*23*).

Deletion of *KAP104* resulted in a severe growth defect and temperature sensitivity (*24*). Immunofluorescence microscopy (*25*) with antibodies specific for Kap104p (in wild-type cells) showed that Kap104p was mainly cytosolic and was apparently absent from the nucleus (Fig. 1B). However, in *nup120Δ* cells, which cluster their NPCs to a region of the nuclear envelope opposite the nucleolus (*26*), Kap104p colocalized with the nucleoporin Nsp1p (*27*) (Fig. 1C). The ability to detect coincident staining of the nucleoporins and Kap104p under these conditions likely was due to an interaction of Kap104p with NPCs.

Subcellular fractionation (*28*) was consistent with the distribution of Kap104p detected by immunofluorescence. Kap104p was present mainly in the cytosolic fraction,

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