CME Article #2

Assessment of the Scientific Basis for Genetic Testing of Railroad Workers with Carpal Tunnel Syndrome

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Learning Objectives

- Evaluate the rationale used by those who would recommend genetic testing of railroad workers engaged in track management who have carpal tunnel syndrome (CTS).
- Describe the probable respective contributions of physical/environmental and genetic factors in railroad track workers with CTS.
- Discuss the medical, social, and ethical issues raised by testing railroad track workers for genetic mutations and deletions.

Abstract

In 2000, approximately 20 railroad track workers who filed injury reports or compensation claims for carpal tunnel syndrome were tested by their employer for two genetic traits to determine the work relatedness of the condition. The testing involved deletions, variants, or mutations in the genetic coding for peripheral myelin protein (PMP22) and transthyretin (TTR). This article is an assessment of whether there is a scientific basis for such testing. A review of the scientific literature indicated that neither the scientific basis nor the population validity of the PMP22 or TTR tests for carpal tunnel syndrome were adequately established before use on railroad track workers in 2000. Although ethical and legal issues may predominate in this case, the absence of a compelling scientific basis undermines the decision to conduct the tests. (J Occup Environ Med. *2003;45: 592–600*)

Carpal tunnel syndrome (CTS) is a common neurological condition that occurs in the general population with an estimated prevalence of 2.1% and an incidence of 3.46 cases per 1000 person years.[1,2] Although the condition has a multifactorial etiology,[3] a large percentage of cases are work related.[4–6] The costs associated with CTS are estimated to be more than $2 billion per year.[7,8] CTS accounts for 3% of all workers' compensation claims. This syndrome results in one of the largest numbers of lost workdays, and the costs are often higher than the average claim filed under workers' compensation.[9]

In 2000, a group of railroad track workers filed workers' compensation claims for CTS. They were not informed as part of the medical evaluation that they were tested for a genetic trait thought by the employer to explain whether or to what extent their condition was work related.[10,11] The workers performed railroad track maintenance. In 2001, the US Equal Employment Opportunity Commission (EEOC) filed suit against the employer and ultimately achieved an agreement that required the employer to stop further genetic testing and to refrain from evaluating, analyzing, or considering any gene test analysis previously performed on any of its employees. The basis for the EEOC suit was that the employer violated the Americans with Disabilities Act.[10–12] No violation of law was cited as part of the settlement agreement.

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Although the question of whether workers were informed of the genetic tests has received considerable attention, the issues in this regard remain unclear. Most workers' compensation statues, including the Federal Employer's Liability Act (FELA), permit medical testing, including genetic testing, to ascertain the medical condition of the claimant and the potential work-relatedness of the claim. However, the U.S. Task Force on Genetic Testing and other organizations, such as the American College of Medical Genetics, generally do not condone genetic testing without informed consent.[13–16]

The legal and ethical issues that arose in the EEOC suit were paramount concerns from the standpoint of occupational health practice but they are not the focus of this paper. Rather, it is useful to examine the scientific issues that arise in this case. Is there an underlying scientific rationale for such testing? This is important to ascertain since a test that is not scientifically valid is not likely to be ethically valid regardless of other ethical protections. Criteria for evaluating whether a genetic test was ready for clinical use were developed in 1998 by the Task Force on Genetic Testing.[13,17] The Task Force concluded that in regard to genetic testing, four features are important:

1. The validity of tests must be assessed before they are used.
2. Formal validation must be supplied for each intended use of a genetic test.
3. Data must be collected to establish clinical validity under investigative protocols.
4. Investigative protocols for validation of genetic testing need IRB approval.[13,17]

In this article, we examine the scientific rationale for testing workers with CTS for variants (duplications, deletions, sequence variants) related to the gene for peripheral myelin protein (PMP22) and for mutations in the gene for the protein transthyretin (TTR; Fig. 1). These proteins are related to neurologic conditions that sometimes have a clinical manifestation that includes CTS.[18–24] At issue is whether in 2000, there was sufficient information on the predictive value of these genetic tests for CTS and whether the genetic components of CTS were sufficiently understood to be considered in assessing causation.

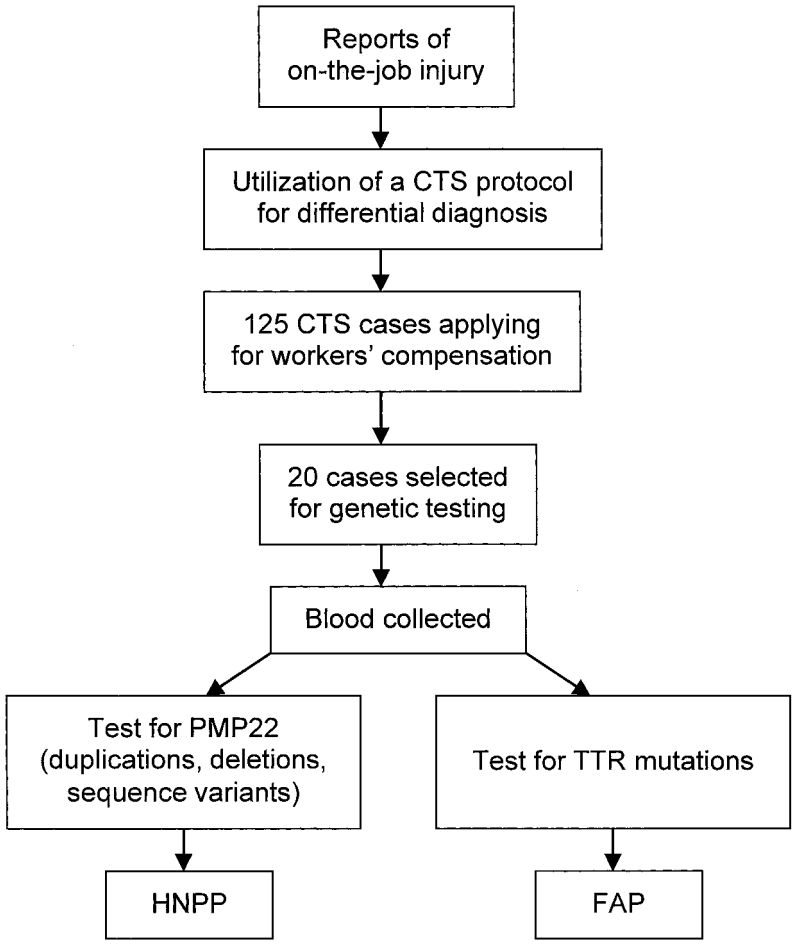

Fig. 1. Overview of genetic testing of railroad track workers.

CTS is a multifactorial compression neuropathy of the median nerve of the wrist.[3,21–23] When the cause is unknown, as it is in many cases, the condition is referred to as idiopathic CTS. However, strong evidence exists of a positive effect of force and repetition and/or force and posture.[22] CTS is also associated with numerous medical conditions such as rheumatoid arthritis, thyroid disease, diabetes, and late pregnancy.[3,23,24] Clearly, associated medical conditions need to be evaluated before determining work-relatedness of a disorder.

The genetic testing was part of a protocol that the railroad company used to make reporting decisions on an on-the-job injury or illness reporting form required by Federal Railroad Administration regulations.[10,11] The protocol was also used by the railroad claims department to make decisions on apportionment of causation based on work relatedness. The protocol included a request to the claimant to provide medical records for review, an ergonomic assessment of the claimant's individual job data and, if needed, a comprehensive medical examination to evaluate the presence of over 20 conditions known to be associated with CTS. The protocol also included a collec-

tion of blood specimens and laboratory testing for various factors including genetic ones.[10,11]

Although the tests used for the railroad workers were described by the laboratory conducting them[25] as tests for CTS, they are not. Rather, the tests are used to detect two conditions that can present with CTS—hereditary neuropathy with liability to pressure palsies (HNPP) and familial amyloidotic polyneuropathy (FAP). The tests are described by the marketing laboratory as ones that detect duplications, deletions, and sequence variants of the PMP22 gene involved in HNPP as well as mutations in transthyretin (TTR) involved in FAP. The tests were described in 2001 as follows:

> This profile should assist in the differential diagnosis of idiopathic CTS. It is important to distinguish genetic causes of CTS because they may require different long-term patient management strategies.[25]

The railroad company did not specifically include the TTR test in its protocol but that test was included in some test panels provided by the laboratory conducting the analyses.

Before the use by the railroad company, there was support in the medical literature for the contention that multiple causes of CTS, including HNPP, need to be evaluated before determining their relatedness to work.[3,18] DNA testing for individuals with a negative family history for HNPP had been suggested.[26]

To assess the scientific basis for using these assays on workers filing injury reports or compensation claims, we will review the relation of the genes PMP22 and TTR to the conditions they are associated with, HNPP and FAP respectively. We will then consider whether genetic testing using the PMP22 and FAP assays is warranted in railroad track workers by addressing two questions: (1) Is CTS a multifactorial disease that involves important genetic factors? (2) Is there a scientific rationale for testing railroad track workers for mutations or deletions involving PMP22 and TTR?

Hereditary Neuropathy with Liability to Pressure Palsies

CTS is a common manifestation of HNPP, which generally develops during adolescence.[19] HNPP was first reported in 1947 in a family digging potatoes;[27] it was also known as "bulb diggers" palsy. Despite case reports, the first population-based study of HNPP was not published until 1997.[28] The prevalence of HNPP was evaluated in 69 patients from 23 unrelated families in a population of 435,000 in Southwestern Finland. The patients were diagnosed between 1978 and 1995 through family and medical histories, documentation of a contiguous gene deletion (17p11.2), and clinical, neurological and neurophysiological examinations. The prevalence of HNPP was estimated to be 16 in 100,000.[28]

The gene deletion at 17p11.2–12 was first identified in 1993.[29] The frequency of the 17p11.2 deletion in HNPP cases was found to be 84% in a study of 156 unrelated patients.[30] In that study, 4.6% (6 of 131) had a de novo deletion. In contrast, other studies have shown rates for de novo deletions as high as 26.5%.[31,32] The deletion at 17p11.2 spans approximately 1.5 mb and includes the gene for PMP22.[19,29,33] The gene for PMP22 spans approximately 40 kb, and 27 distinct mutations have been identified in 35 unrelated patients.[34] HNPP usually occurs in the setting of a family history, indicating an autosomal-dominant trait; however, sporadic cases have been described.[30,35,36] Before 2001, the percentage of HNPP cases because of de novo deletion was not known. In 2001, a study of 14 consecutive, unrelated index cases found that 3 (21%) were sporadic cases resulting from a de novo deletion of 17p11.2.[31]

Familial Amyloidotic Polyneuropathy

The laboratory marketing the PMP22 genetic assay also had an assay for the gene coding for TTR, a plasma protein associated with neuropathic amyloidosis. The assay was used on some of the railroad track workers' blood specimens. Mutations in this plasma protein are observed in FAP, but the incidence of TTR amyloidosis is unknown.[37] TTR is encoded by a single gene on chromosome 18 (18q11.2-q12.1), of which more than 70 autosomal dominantly inherited point mutations (occurring at 51 different sites), have been described.[20,38] Hereditary amyloidoses have been classified into four subtypes, two of which are associated with CTS: familial amyloid polyneuropathy types 1 and 2 (FAP1 and FAP2). Amyloidosis occurs in about 8 per 1 million people.[39] In the United States, the gene frequency for FAP1 and FAP2 is estimated to be 1 per 1 million to 1 per 100,000.[39] Hence, the prevalence of CTS in people with FAP1 and FAP2 is likely to be less than the gene frequency, because not all the people with the gene develop CTS.

Genetic Testing and CTS

Genetic testing in the workplace can include at least three functions: genetic monitoring, genetic screening, and genetic testing for diagnoses. Genetic monitoring is the periodic assessment of DNA damage resulting from environmental and occupational exposures. Conceptually, genetic monitoring mirrors other forms of successful biological monitoring performed in the context of occupational disease prevention programs (eg, blood-lead testing and blood counts). Genetic monitoring can also detect endogenous DNA damage. Genetic screening is generally a one-time appraisal of asymptomatic individuals to assess a predisposition for a condition. Genetic screening has generally been discussed in terms of genetic testing to characterize an individual's future risk of disease. From the perspective of occupational health practice, the belief underlying all forms of predictive genetic testing is that early identification of damage or disease pre-

disposition will lead to reduced morbidity and mortality through targeted screening, surveillance, treatment, and prevention.[40] It should be emphasized that the clinical validity and utility of genetic screening related to workplace exposures remains uncertain, so no genetic tests have been authoritatively recommended for preventing work-related diseases.

In the case of the railroad track workers who filed an injury report or workers' compensation claims, a third use of genetic testing was employed, that is, genetic testing as part of obtaining the differential diagnosis. The railroad company initiated a protocol that included genetic testing for workers who reported an on-the-job injury. Ultimately, the genetic testing was applied to approximately 20 (males) of the 125 workers who filed injury reports or workers' compensation claims for CTS under FELA. Testing was used to provide information about nonwork factors that may contribute to causing CTS. The objective was to assist the company medical officer in determining whether CTS was related to work or to some other nonwork factor, including a genetic disorder.[41] In the context of a FELA compensation action, the employer has an economic interest in attributing injury to nonwork factors.

Is CTS a Multifactorial Disease That Involves An Important Genetic Risk Factor?

Various risk factors for CTS have been identified.[3,5,22,42,43] These include acquired, inherited, and systemic factors. CTS often occurs as a result of a variety of medical conditions.[3,23,24] Some cases of CTS are idiopathic. Nonetheless, in an extensive review of more than 30 epidemiologic studies in the scientific literature in 1997, the National Institute for Occupational Safety and Health[22] concluded—and a committee of the National Academy of Sciences[43] subsequently confirmed—that there is strong evidence that a combination of workplace physical risk factors is associated with CTS. These factors included force and repetition and force and posture. Literature published since 1997 further corroborates this finding.[6,44–49] Many of the studies finding a statistically significant association between individual or combinations of workplace physical factors controlled for potential confounders such as age, sex, smoking, caffeine, alcohol, hobbies, body mass index, and medical conditions.[1,22,47–51] Nationally and internationally, epidemiologic surveillance has consistently indicated that the highest rates of CTS occur in occupations involving job tasks with high work demands or extensive manual exertion (such as meat processors, poultry processors, and automobile assembly workers).[22] Railroad track maintenance can involve extreme manual exertion—the use of jackhammers and grinders for long time periods. The prevalence of diagnosed carpal tunnel syndrome has been estimated at 53 per 10,000 US workers.[4]

Familial occurrence of CTS also has been documented.[52–57] When CTS is inherited, it is often the manifestation of a systemic disease.[58] Gossett and Chance[57] concluded that in addition to linkage with FAP and HNPP, patients may present with a familial CTS.[59] This familial CTS appears to be a rare but genetically distinct disorder. In a prospective study, a positive family history was predictive of a median nerve abnormality or prior surgery at the carpal tunnel.[56] When confirmed cases (defined by median nerve slowing in the carpal tunnel or prior CTS surgery) were compared with cases with no confirmed CTS, family history accounted for 39.3% in the former versus 12.3% in the latter. Before 2000, no prospective studies had been published assessing the risk of CTS in people with PMP22 or 17p11.2 deletion.

Before 2000, no population studies have been identified that assess the relative risk, population-attributable risk, or attributable fraction for genetic factors for CTS. Also, no published data establish the validity of susceptibility testing for CTS. Specifically, neither the positive nor the negative predictive value of the PMP22 nor the TTR tests were identified. The population distribution of PMP22 is not known. The lack of published data regarding the technical performance of the test and the risk associated with a positive result form a basis for rejecting the use of genetic testing except in the context of a research study. Furthermore, in other examples involving quantifiable risk corresponding with a genetic factor and occupational disease, authors have argued against screening.[60–62]

At the time of the railroad workers' testing, no published data confirmed that a genetic factor could explain the risk of CTS remotely as well as physical activities. It has been estimated that as much as 50% of all medically treated CTS is work-related.[4,6,63] Although it is not possible to rule out the potential for gene–environment interactions in some CTS cases in the general population, the exposure to known CTS risk factors in railroad track workers supports the conclusion that CTS risk in this population is more likely related to workplace exposure than to other factors. In 2002, a study of twin women was published that found that the strongest risk factor for CTS was genetic (heritability estimate 0.46; 95%CI 0.34 to 0.58) even after adjusting for age, body mass index, physical activities, and hormonal/reproductive factors.[64] However, the investigators reported that the study of may have lacked power to demonstrate that clerical and manual employment were risk factors given the small number of cases in these groups.

In 2001, a study was published describing 50 unrelated patients (aged 18 to 76, with a mean age of 50.5 years) diagnosed with CTS, all in need of surgical release; none

were found to have PMP22 deletions.[65] Diagnosis of CTS was made by both clinical evaluation and electrodiagnostic methods. Exclusion criteria consisted of (1) anatomical changes decreasing the available volume within the carpal tunnel; (2) diagnoses, including amyloidoses, rheumatoid arthritis, and edema, that might result in an increased size of the carpal canal contents; (3) diagnoses associated with soft tissue impingement (ie, lipomas, hematomas, or urate crystal deposition); and (4) other causes of peripheral mononeuropathies, such as diabetes mellitus. The actual sampling frame from which case were selected was not specified nor were the numbers excluded. On the basis of their findings of no deletions, the authors calculated that the upper limit (95% confidence interval) of the prevalence of PMP22 deletion as a cause of CTS is approximately 6%.[65] This analysis appears to assume a binomial distribution and uses a one-sided confidence interval that includes all 5% in the upper bound instead of only 2.5%. These researchers concluded that the prevalence of HNPP in idiopathic CTS is unknown; but using estimated CTS incidences of 1% to 3.8%[1,4,66] and HNPP of 0.04%,[67] they calculated that HNPP could be responsible for 1% to 4% of CTS.[65] This analysis appears to assume that HNPP always causes CTS.

If the PMP22 mutation occurs with a prevalence similar to HNPP, which is estimated at 16/100,000, then proportionally, less than 1 person (0.003) would be found with the PMP22 deletion in a random sample of 20 people (X/20 = 16/100,000). However, the actual population prevalence of PMP22 has not been assessed. Clearly in this case, the assay was not used in a predictive sense in a random sample but to aid in evaluating reports of injury or claims of workers.

Generally, epidemiological studies (other than family studies with small numbers of cases) have not addressed the possibility of significant hereditary factors in the occurrence of CTS.[56,64] However, in studies on worker populations in certain industries compared with the general population, the prevalence and incidence rates of CTS were much higher in the worker populations than in the general population.[1,2,50,68] The rate of mutations and subsequent diseases that present with CTS is much less than the rate of occurrence of CTS, especially in working populations. Although a possibility of gene–environment interaction may exist, the strong association between environmental risk factors and CTS and the apparent low prevalence of gene mutations (for PMP22 and TTR) in the general population suggests the contribution of these genetic components is low in the population of railroad CTS claimants.

Is There a Scientific Rationale for Testing Railroad Track Workers for Mutations or Deletions Involving PMP22 and TTR?

The critical factors for evaluating predictive and diagnostic genetic tests are sensitivity, specificity, and predictive value.[13,17] To assess these parameters, it is necessary to know the CTS risk for persons with and without the genetic variant and particular exposure profiles. For retrospective testing, this question then becomes analogous to the questions asked in historical prospective epidemiologic studies or in case–control studies. Like all prospective studies, historical prospective studies involve the following forward in time of groups with and without an exposure characteristic to determine whether the risk for a health outcome is different in the two groups. The difference with historical prospective studies is that the start date of the study is in the past and determined retrospectively. In the case of the railroad track workers, the question would be whether those who have the 17p11.2 deletion or the TTR variant are at a greater risk than those who do not. In a historical prospective epidemiologic study, this risk would be assessed by the risk ratio. In a case–control study, cases of CTS and selected subjects without CTS would be cross-classified on the basis of the 17p11.2 (or PMP22) deletion or TTR mutation. The association between the genetic variant and the disease would be assessed using the odds ratio.

No studies of the risk ratio or odds ratio of 17p11.2 (or PMP22) deletions or TTR mutations were found in the literature before 2000. The testing of approximately 20 railroad track workers was not conducted as part of a case–control or prospective study, so there was no opportunity to develop risk or odds ratios. The application of genetic tests to some cases but not to others apparently was not defined in any identified research protocol or experimental design. The rationale provided by the company was that a case management protocol of CTS cases was developed, and it included genetic testing of some workers. Had testing occurred with informed consent in the context of a reviewed and approved study intended to evaluate the potential benefit of testing, the apparent ethical issues would be greatly diminished. Although genetic testing has been used diagnostically in some cases of HNPP and FAP,[31,69] the prevalence of HNPP and FAP1 and FAP 2 appear to be rare (see Table 1), so the likelihood of finding a genetic variant in 20 workers is very low. It is not known whether a person with those conditions would be a long-term railroad track worker in a job involving extensive physical demands, because the vulnerability of such a worker to self-limited episodes of peripheral neuropathy could lead him or her to seek other types of work. However, people with HNPP can have mild or no symptoms that may not cause them to stop working.[31] In conclusion, the absence of a knowledge base on important aspects of the prevalence, attributable risk, relative

TABLE 1
Available Frequency Estimates for Conditions and Genes Involved in Railroad Track Worker Testing

Condition or Gene	Estimated Frequency
Prevalence of CTS (general population)*	2,100/100,000†
Prevalence of work-related CTS	530/100,000 workers‡
Prevalence of HNPP	16/100,000[28]
Prevalence of all amyloidoses	0.8/100,000‖
Gene frequency FAP	0.1–1/100,000
Prevalence of PMP22 deletion	16/100,000¶
Prevalence of PMP22 in 50 unrelated people with CTS	0/50[65]
Frequency of 17p11.2 del in 156 unrelated people with HNPP	84%[30]

* CTS, carpal tunnel syndrome; HNPP,
† Reported as 2.1%.[1]
‡ Reported as 53 per 10,000 U.S. workers.[4]
§ Reported as 8 per 1,000,000 people.[39]
‖ Reported as 1 per 1 million to 1 per 100,000.[39]
¶ Assumed prevalence of PMP22 deletion is similar to prevalence of HNPP.

risks, and predictive value of PMP22 and TTR related to CTS indicates that in 2000 these tests were not appropriate for use on railroad claimants with CTS.

Discussion

There are a number of scientific issues in this case that are arguable. First is the issue of whether genetic testing is useful in assessing the work-relatedness of musculoskeletal disorders. Apart from any ethical or legal issues is the fact that the value of genetic testing will be affected by the state of the science. Increasingly, more genetics tests are becoming important tools in the differential diagnosis of individual diseases. As research is conducted and information obtained, tests that may be predictive in asymptomatic workers may be diagnostic or contribute to making the differential diagnosis in workers or patients with signs and symptoms. In assessing the work-relatedness of a disease there is a need to have not only a complete description of work factors, but also an assessment of non-work factors that might be important. However, to actually use genetic information requires appropriate assessment of the prevalence, predictive value, relative, and attributable risks in weighing the importance of the information. It is also important to consider a plausible mechanism of action or interaction between genetic, work and other risk factors. Merely identifying a genetic factor in a particular person is not sufficient to assess causality.

A second issue is whether genetic information is of a unique nature that it should be treated distinctly from other medical information. This has been referred to as "genetic exceptionalism."[70] As applied to the case of railroad workers, is it appropriate to obtain genetic information on a person filing an on-the-job injury report or a claim for compensation of an injury allegedly caused by work? Clearly, genetic information in medical records has long been used in medical assessment of workers and patients. Why would information obtained from a genetic test be treated differently? If not enough is known about a test, that is, if it is not validated on a population basis, it is not useful. However, if it is validated in that way, the question becomes one of how society weighs the role of genetic factors compared with work factors in a disease "obtained" by working. Should nonwork factors, including genetic factors, be used to apportion causation? Routinely, some nonwork factors, such as medical conditions, are used to apportion causation. Are genetic factors obtained through valid testing any less informative? Genetic factors could be at least as informative as other predisposing factors, but whether and how to use that information to apportion causation is still a debated subject in need of ethical review and methodological development.[71,72]

Separate from the science is whether society will sanction the use of genetic characteristics, over which a worker has no control, as predisposing factors in assessing a work-related injury. Such a practice would appear to be contrary to US occupational safety and health practices as defined in the Occupational Safety and Health Act (PL 91–596), but not necessarily excluded under various workers' compensation practices and state laws.[73,74] States such as Iowa, New York, New Hampshire, and Wisconsin allow consensual genetic testing for purposes of investigating workers' compensation claims. Moreover, workers' compensation statutes routinely allow independent medical examinations including medical and genetic tests. Given the rapid development of genetic tests, thoughtful deliberation should be applied to the appropriate role of such testing in the context of occupational health policy and workers' compensation.

Molecular genetics provide important tools that can be used in support of occupational disease prevention.[75–77] However, retrospective testing, outside a research study, has limited potential for morbidity or mortality reduction. This limited potential is in sharp contrast to the potential benefits of mechanistic assessments, prospective genetic screening of asymptomatic workers and ongoing monitoring of workers exposed to a putative hazard. Conceivably, retrospective testing could provide an injured worker with information about a chemical sensitivity (eg, toluene diisocyanate) that could help prevent future exposures. In the

specific case described in this article, the genetic tests were not used to foster health benefits but to aid in the apportionment of causation. The fact that claimants were not informed of genetic tests as part of the medical examination does not appear to be illegal, but the conduct of genetic tests without informed consent is not condoned in any guidelines for genetic testing and in fact conflicts with the guidelines of the Task Force on Genetic Testing[13] discussed earlier. The example described here reinforces concerns that genetic testing will be used to discriminate against or otherwise disadvantage workers.

This case illustrates a concern about differential applications of genetic information depending on social activity.[78] In the context of a FELA claim, the question is whether ad hoc data derived in a nonscientific manner may be used to apportion causation of an injury. In larger terms, can genetic testing serve the socially sanctioned practice of apportionment when compensation is based on the percentage of injury attributed to work as opposed to other life factors? The role of genetic and environmental factors in CTS has not been adequately established to support the conclusion that the finding of a genetic mutation, related to PMP22 or TTR, in an "exposed" worker diminished a work-relatedness claim.

Conclusion

Neither the scientific basis nor the population validity of the PMP22 or TTR assay for CTS was adequately established before its use on railroad workers in 2000. Few data exist on the frequency of the variant genotypes in the population. The plan to use testing for these traits when evaluating workers with CTS is striking given the absence of evidence required to assess the use of the test in a workplace setting—that is, the absence of a strong database to identify the role of genetic factors in CTS. No information indicated that equally exposed workers, with or without various genotypes, have different risks of CTS. The available data suggest that genetic factors (genes for PMP22 or TTR) play a very minor role. Additionally, there is a lack of information on a mechanism by which these genetic factors and environmental factors could interact.

The utility of genetic information as an indicator of pre-existing conditions in workers' compensation has not been widely examined. Past practice has been that work-related disability can be generally compensated even when the source of the pre-existing condition is not work related.[79] Because the predictive value of PMP22 and TTR for CTS has not been demonstrated, these genotypes are not useful for retrospective assessment of causality in occupational populations. Before PMP22 and TTR variants can be viewed as pre-existing conditions and contributory for CTS, extensive information is needed. This information includes (1) the frequency of the variants; (2) the absolute and relative risk of the association of the variants with HNPP and FAP, respectively; (3) the frequency (and attributable fraction) with which HNPP and FAP are related to CTS; (4) the predictive value of the tests; (5) the interaction between work-related factors, and genetic factors in the risk for CTS; and (6) the factors influencing the penetrance of the genetic factors in HNPP and FAP. Nearly all of this information is lacking. In the interim, guidance is available from the Task Force on Genetic Testing.[13,17]

The mere existence of genetic characteristics in claimants is not an indication of its role in multifactorial diseases such as CTS. In most instances, technological advances in genotype detection have outrun the ability to interpret and use the information obtained. Until appropriate interpretive research is conducted, the use of genetic tests (for PMP22 and TTR) to impute causality in railroad workers with CTS claims is not warranted.

This case illustrates the inappropriate use of a test based on the faulty assumption that the test would be informative about the relative role of genetic factors in the causation of CTS. To enhance the utility of genetic tests, it would be helpful if those marketing such tests would provide information about the prevalence of the genetic trait, the predictive value, and other information about validity of the test. This information would enhance transparency and contribute to a more complete scientific evaluation of a particular test.

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