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Genetic testing of railroad track workers with carpal tunnel syndrome

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Carpal tunnel syndrome (CTS) is the most common peripheral compression neuropathy with an estimated prevalence of 2.1%. It has a multifactorial etiology involving systemic, anatomic, idiopathic, and ergonomic factors (1–5). Work-related activities have been strongly associated with CTS (4–6). Some of the highest rates of CTS occur in occupations with high work demand or extensive manual exertion such as automobile assembly and meat processing. CTS also occurs in individuals with various health conditions such as rheumatoid arthritis, thyroid disease, diabetes, late pregnancy, and rapid weight loss. CTS often occurs as a result of two hereditary conditions: hereditary neuropathy with liability to pressure palsies (HNPP) and familial amyloidotic polyneuropathy (FAP). Occupations and medical conditions associated with CTS are shown in Tables 29.1 and 29.2, respectively.

In 2001, the Burlington Northern Santa Fe Railroad Co. settled Equal Employment Opportunity Commission (EEOC) and union lawsuits over the company's genetic testing of approximately 20 railroad track workers with CTS on-the-job injury reports or compensation claims (7). The testing was performed, without the knowledge and consent of workers, to detect mutations and deletions associated with HNPP and FAP. However, the extent to which the railroad company's actions were within the scope and practice of the Federal Employers' Liability Act or other workers' compensation statutes or were subject to the Americans with Disabilities Act prohibitions against medical examinations of current employees was not adjudicated. It is not the function of this chapter to address the ethical and legal issues. Rather, beyond the ethical and legal issues two scientific questions arose: are genetic risks likely to be important in these cases of CTS; and is there a scientific rationale for testing these workers? In this chapter, those questions are addressed.

Table 29.1 Some Occupations Associated with Carpal Tunnel Syndrome

Meat packers	Platers
Sewing machine operators	Frozen food factory workers
Ski manufacturers	Packaging machine workers
Poultry processors	Electrical component assembly
Automobile assembly	Rock drillers
Grinders	Grocery checkers

Source: NIOSH, 1997.

Background

CTS is a compression neuropathy of the median nerve of the wrist (14). In the United States, CTS occurs with an estimated prevalence of 2.1% and an incidence of 3.46 cases per 1000 person–years in the general population (8,9). A large percentage of these cases are work related (5,10). The costs associated with CTS are estimated to be more than $2 billion per year (11,12). CTS constitutes 3% of all Workers' Compensation Insurance claims. The costs are often higher than the average claim filed under workers' compensation. CTS results in one of the largest numbers of lost workdays among occupational conditions (13).

In many cases, the cause of CTS is unknown, and this is referred to as idiopathic CTS. However, there is strong evidence of a positive association between exposure to a combination of risk factors (e.g., force and repetition and/or force and posture) and CTS (15). CTS has been associated with numerous medical conditions (Table 29.2) such as rheumatoid arthritis, thyroid disease, diabetes, and late pregnancy (16), although many of the studies on which such a list is based did not control for occupation. CTS is not known to be a predominantly genetic condition; however, two hereditary diseases, HNPP and FAP are known to exhibit CTS in some cases. There are practically no epidemiologic studies that have assessed both environmental and genetic risk factors for CTS in the same study.

Table 29.2 Medical Conditions Associated with Carpal Tunnel Syndrome

Anatomic	Inflammatory
Ganglion	Tenosynovitis
Neuroma	Hypertrophic synovium
Lipoma	Rheumatoid arthritis
Myeloma	Gout
Neuropathic	Dermatomyositis
Diabetes	Scleroderma
Alcoholism	Systemic lupus erythematosus
Amyloidosis	Alteration of fluid balance
	Pregnancy
	Myxedema
	Obesity
	Long-term hemodialysis

Source: Adapted from Sternbach (1999).

Genetic testing for HNPP was part of a protocol that the railroad company used to evaluate workers who reported an on-the-job injury (17,18). The test for FAP involved detection of variants of the protein, transthyretin (TTR), and was added to the test battery by the laboratory performing the assays. Ultimately, the protocol was applied to approximately 20 workers (males) who had gone on to file injury reports—compensation claims for work-related CTS under the Federal Employers Liability Act. The company indicated that the testing was performed to assist the company medical officer to determine whether CTS was related to work or some other nonwork factor including a genetic disorder (19). In 2001, the U.S. Equal Employment Opportunity Commission filed suit against the employer and ultimately achieved an agreement that required the employer to stop further genetic testing and refrain from using any of the testing information obtained (7,18).

Hereditary Neuropathy with Liability to Pressure Palsies

CTS is a common manifestation of HNPP, which is part of a heterogeneous group of demyelinating polyneuropathies. HNPP generally develops during adolescence (20). HNPP was first reported in 1947 in a family digging potatoes (21). It was also known as "bulb diggers" palsy. Although there have been a number of case reports since 1947, the first population-based study of HNPP was not published until 1997 (22). The prevalence of HNPP was evaluated in 69 patients from 23 unrelated families (diagnosed between 1978 and 1995) in a population of 435,000 in southwestern Finland through family and medical history, clinical, neurologic, and neurophysiologic examinations and with documentation of a gene deletion (17p11.2). The prevalence of HNPP was estimated to be 16 in 100,000 (22).

In 1993, the genetic locus for HNPP was mapped to chromosome17p11.2-12, where it is often associated with a large 1.5 Mb (megabase pair) DNA deletion (20,23). In a study of 156 unrelated HNPP patients, 84% were found to have the 17p11.2 deletion and in 4.6% (6/131) of these, the deletion was de novo (24). However, higher frequencies of de novo deletions (25.6%) have been reported (25,26). The deletion of 17p11.2 appeared to be a reciprocal product of an unequal crossover involving Charcot-Marie-Tooth neuropathy type 1 (CMT1A) (23). The deletion at 17p11.2 includes the gene for peripheral myelin protein-22 (PMP22) (23,27). The gene for PMP22 spans approximately 40kb, and 27 distinct mutations have been identified in 35 unrelated patients (28). Of the 27 mutations, four were associated with HNPP phenotypes. Subsequently, investigators found deletions of 17p11.2 in patients in various countries (27,29–33).

The onset of HNPP is usually in childhood or adolescence. The clinical presentation of HNPP is broad and may range from clinically asymptomatic persons to those who present with recurrent palsies (20). HNPP usually occurs in the setting of a family history, indicating an autosomal dominant trait; however, sporadic cases have been described (24,34,35). Prior to 2001, the percentage of cases due to de novo deletion was not known. In 2001, a study of 14 consecutive unrelated index cases found that 3 (21%) were sporadic cases, due to a de novo deletion of 17p11.2

(25). There appears to be a direct relationship of gene dosage at the PMP22 locus with the phenotype palsies (20).

Animal models appear to exist for HNPP. Maycox et al. (36) found that transgenic mice expressing antisense PMP22 RNA showed modestly reduced levels of PMP22 together with a phenotype suggestive of HNPP. A striking movement disorder and a slowing of nerve conduction that worsened with age were observed in antisense homozygotes. Histologically, a subset of axons had thickened myelin sheaths and tomacula in young adult mice; significant myelin degeneration was observed in older animals (37). Nelis et al. (28) concluded that heterozygous mice correspond to HNPP patients with the 1.5 Mb deletion on 17p11.2. In both human and mouse, the myelin tomaculae are present, suggesting that the mice are useful animal models for HNPP (28).

Familial Amyloidotic Polyneuropathy

In addition to testing for PMP22, the laboratory marketing the genetic assay also used an assay for transthyretin (TTR), a plasma protein, on railroad track workers' blood specimens (38). Mutations in this plasma protein are observed in FAP. TTR is encoded by 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 (39–42). The hereditary amyloidoses have been classified into four subtypes, two of which, familial amyloid polyneuropathy type 1 and 2 (FAP1 and FAP2) are associated with CTS. The incidence of TTR amyloidosis is unknown (43). Amyloidosis occurs in about 8 of 1,000,000 people. At diagnosis, FAP1 patients often have undergone carpal tunnel surgery. In FAP2 patients, there is more frequent carpal tunnel manifestation (39). In the United States, the gene frequency for FAP1 and FAP2 is estimated to be 1 in 1,000,000 to 1 in 100,000 (44). Hence, the prevalence of CTS in people with FAP1 and FAP2 would be less than the gene frequency, because not all the people with the gene develop CTS.

Epidemiologic Findings

The epidemiology of CTS can be seen to have two focal areas: studies of occupational risk factors and studies of nonoccupational risk factors (generally involving arthritis, obesity, pregnancy, diabetes, thyroid disease, hormone replacement, and corticosteroid therapy) (45–50). Genetic factors (other than race and gender) generally have not been included in epidemiologic studies of CTS (50). However, there have been a few studies of familial occurrence (50,51).

One issue in the evaluation of epidemiologic studies has been the definition of carpal tunnel syndrome. There are differing opinions about what constitutes appropriate diagnostic criteria (1,52,53). The debate focuses on whether electrodiagnostic study findings alone or with symptoms is the best criterion and, if in the absence

of electrodiagnostic studies, specific combinations of symptom characteristics and physical examination findings are useful.

Occupational Studies

In a comprehensive review of more than 30 epidemiologic studies in the scientific literature in 1997, the National Institute for Occupational Safety and Health (15) concluded, and a committee of the National Academy of Sciences (54) subsequently confirmed, that there is strong evidence that a combination of workplace physical risk factors is associated with CTS. These included force and repetition and force and posture. Literature published since 1997 further supports this finding (5,45,55–57). Many of the studies in which a statistically significant association between individual or combinations of workplace physical factors was found controlled for potential confounders, such as age, sex, smoking, caffeine, alcohol, hobbies, body mass index (BMI), and medical conditions (8,15,55,58–61). Epidemiologic surveillance, nationally and internationally, has consistently indicated that the highest rates of CTS occur in occupations and job tasks with high work demands or extensive manual exertion (such as meat processors, poultry processors, and automobile assembly workers) (15); see Table 29.1 for some occupations associated with CTS. The prevalence of diagnosed carpal tunnel syndrome in U.S. workers has been estimated to be 53 per 10,000 (4).

Epidemiologic studies consistently link CTS to job tasks that involve a combination of risk factors (e.g., force and repetition, force and posture) (15). Railroad track maintenance is physically demanding and involves extreme manual exertion—the use of jackhammers and grinders, in some cases, for up to 14 hours a day. In one report, arising from tort litigation, that conflicts with much of the other literature, 900 railroad workers were randomly selected from a pool of 2500 Federal Employers' Liability Act (FELA) claimants, and their jobs were characterized into four categories previously described by Silverstein et al. (62). Jobs were classified into the following categories: I (low force/low repetition), 18.8%; category II (low force/high repetition), 20.7%; category III (high force/low repetition), 59.8%; category IV (high force/high repetition), 0.7% (14). The percentage of positive or borderline cases of CTS among all workers in each category (determined by an electrodiagnostic method of comparing median minus ulnar nerve digital latency differential) was as follows: category I, 47.9%; category II, 40.0%; category III, 43.4% and category IV, 50% (14). The report showed no association between occupational classification and CTS, but the investigators indicated that the small number of individuals in the most extreme job classification category IV (0.7%) may have obscured an occupational association. In other studies, it has been estimated that as much as 50% of all medically treated CTS is work-related (4,5,63). There is no published research that shows what portion of CTS is attributable to genetic factors. It is possible that gene–environment interactions are involved in the etiology of some CTS cases in the general population, but there are no data on this.

Nonoccupational Studies

Table 29.2 shows various medical conditions that have been associated with CTS. Additionally, older age and female gender have been identified as risk factors. Women in the general population have approximately three times the risk as men; men (8) and women in the same occupation appear to have similar risks (64). The strongest risk factor in one study of women was previous history of another musculoskeletal complaint for which consultation had been sought OR 1.98 (95% CI, 1.61–2.42). Autonomic disturbances have also been found in one study of CTS with increasing severity of electrophysiologic findings (65).

Familial CTS

Familial occurrence of CTS also has been documented (51,66–69). When carpal tunnel syndrome is inherited, it is often the manifestation of a systemic disease (70). Gossett and Chance (69) concluded that, in addition to linkage with familial amyloidosis and HNPP, patients may present with a familial CTS (McKusick number 115,430) (71). This familial CTS appears to be a rare but genetically distinct disorder. In a prospective study, a positive family history was predictive in 39.3% of cases with surgery for CTS who had median nerve slowing versus 13.3% of cases without these characteristics (51).

Risk Attributable to Genetic Factors

At the time of the testing, there were no published population data identified that confirmed that a genetic factor could explain the risk of CTS better than physical activities. In 2001, a study was published that examined 50 unrelated patients (age 18–76, mean age 50.5 years) diagnosed with CTS, all in need of surgical release, and none were found to have PMP22 deletions (72). Diagnosis of CTS was made by both clinical evaluation and electrodiagnostic methods. Exclusion criteria consisted of those with anatomic changes decreasing the available volume within the carpal tunnel; diagnoses that may result in the increased size of the carpal canal contents (including amyloidoses, rheumatoid arthritis, or edema); those diagnoses associated with soft tissue impingement (i.e., lipomas, hematomas, or urate crystal deposition); and other causes of peripheral mononeuropathies, such as diabetes mellitus. The authors calculated, based on their findings of no deletions, that the upper limit (95% confidence interval) of the prevalence of PMP22 deletion as a cause of CTS is approximately 6% (72). 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 2.5%. The authors (72) concluded that the prevalence of HNPP in idiopathic CTS is unknown, but using estimated CTS incidences of 1% to 3.8% (8,10,73) and HNPP (0.04%) (74), they calculated that HNPP could be responsible for 1% to 4% of CTS. DNA-based testing for individuals with a negative family

history for HNPP had been suggested (75,76) prior to the testing of railroad workers in 2000. The railroad company relied on the medical literature (e.g., 3,75) to support the contention that multiple causes of CTS, including HNPP, needed to be evaluated before determining work-relatedness.

Scientific Issues of Concern

The critical factors for evaluating predictive genetic tests are sensitivity, specificity, and predictive value (77) (see also Chapter 11). Other factors such as number needed to screen (NNS) and number needed to treat (NNT) are also useful. To assess these parameters, it is necessary to know the CTS risk for people with and without the genetic variant and particular exposure profiles. Prior to the testing of railroad track workers, no prospective studies have been published that assess the risk of CTS in people with 17p11.2 deletion, or TTR mutation. Until 2002, there were no population studies that assessed the relative risk or population attributable risk for genetic factors for CTS. In 2002, a study of twin women from the U.K. Adult Twin Registry (50) determined the relative genetic and environmental contributions to CTS. The genetic contribution was assessed using the variance component and regression methods and the heritability was adjusted for environmental confounders. The modeling resulted in a heritability estimate of 0.46 (95% CI, 0.34–0.58). The investigators reported that the study may have lacked the power to demonstrate that occupation in clerical and manual employment was a risk factor, since there were a small number of cases in these groups (50). There are no published data to establish the validity of susceptibility testing for CTS. Specifically, neither the positive nor negative predictive value has been established. The lack of data regarding the technical performance of the test and risk associated with a positive result would be a basis for rejecting the use of genetic testing except in the context of a research study. Further, in other examples where there is quantifiable risk corresponding with a genetic factor and occupational disease, authors have argued against screening on the basis of inadequate validation and poor predictive value (77–79).

For retrospective testing, this question then becomes analogous to the questions asked in historical cohort studies or in case-control studies. Like all cohort studies, historical cohort studies involve following groups with and without an exposure characteristic forward to determine if the risk for a health outcome is different in the two groups. The difference with historical cohort studies is that the start date of the study is in the past and determined retrospectively. In the case of the railroad workers, the question would be whether those with the 17p11.2 deletion or the TTR variant have a greater risk than those who do not. In a historical cohort study this would be assessed by the risk ratio. In a case-control study, cases of CTS and selected individuals without CTS would be cross-classified on the basis of the 17p11.2 deletion or TTR mutation. The association between the genetic variant and the disease would be assessed by using the odds ratio.

A search of the scientific literature prior to 2000 did not identify any studies of the risk ratio or odds ratio of 17p11.2 deletions or transthyretin mutations. The testing of approximately 20 railroad workers was not conducted as part of a case-control or prospective study, so there was no opportunity to calculate risk or odds ratios. The application of genetic tests to some cases, but not 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. The prevalence of HNPP and FAP1 and FAP2 are believed to be relatively rare on a population basis, so the likelihood of finding a genetic variant in 20, or even 150 workers is very low. It is not known whether a person with either of these conditions would be likely to be long-term railroad track worker. The extensive physical demands of the job could lead workers who were subject to self-limited episodes of peripheral neuropathy to seek other employment. However, people with HNPP can have mild or no symptoms, and thus their condition could have little effect on their ability to work (25).

Potential Contribution of Genetic Information to Improved Health Outcomes

In the railroad case, the use of genetic testing was not for the purpose of improving health outcomes but for clarifying the contributing factors to CTS in workers' compensation claimants. Medical tests, including genetic tests, may provide pertinent information about nonwork factors that may contribute to causing CTS. Employers have a legal right to identify work and nonwork factors that contribute to CTS and thereby attempt to apportion causation. Under workers' compensation statutes, this can be done in some states without informed consent about the specific tests. In contrast, 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 (80) discussed later. The example, described in this paper, where workers were not informed that they were tested, reinforces concerns that genetic testing will be used to discriminate against or otherwise disadvantage workers.

In some situations, prospective genetic testing for PMP22 or TTR could benefit workers by providing them information with which to make employment decisions. However, at present the lack of information on predictive value and attributable risk does not support such use.

Conclusions

A review of this case indicates that neither the scientific basis nor validity of the PMP22 or TTR assay for CTS were adequately established before their use on railroad workers in 2000. The prevalences of HNPP and FAP are exceedingly low and

unlikely to be a major contributory cause of work-related CTS. There are few data on the frequency of these variant genotypes in the population. The plan to use testing for these traits in the evaluation of railroad track workers with CTS is striking given the absence of evidence required to assess the use of the test in a workplace setting (e.g., absence of a database) to identify the role of genetic factors in CTS. There is no information indicating that equally exposed workers, with and without various genotypes, are at different risks of CTS. What data are available suggest that genetic factors play a very minor role, if any, in male railroad track workers. Ultimately, some genetic factors may be found that contribute along with occupational factors to CTS, but such information is not available at this time.

The role of genetic information in workers' compensation is an evolving question. Past practice has been that work-related disability could be generally compensated even when the source of the preexisting condition is not work related (81). There is no consistent record that demonstrates that the existence of genetic variants alone serve as pre-existing conditions; however, genetic information has been used in workers' compensation cases (82,83). State laws governing workers' compensation may provide an incentive for employers to use genetic screening tests. Iowa, New Hampshire, New York, and Wisconsin allow for consensual genetic testing for purposes of investigating workers' compensation claims. However, since 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 could be viewed as pre-existing conditions for CTS, extensive information would be needed. This includes: (*1*) the frequency of the variants, (*2*) the absolute and relative risk of the association of variants of HNPP and FAP, respectively, (*3*) the frequency 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. Almost all of this information is lacking. In the interim, guidance is available from the Task Force on Genetic Testing (84). The Task Force concluded that in regard to genetic testing, four features are important:

- Assessment of validity of test is necessary before use.
- Formal validation is needed for each intended use of a genetic test.
- Data to establish clinical validity must be collected under investigative protocols.
- Investigative protocols for validation of genetic tests need IRB approval (80).

Without the validation information, the mere existence of genetic characteristic is not an indication of the nature of its role in multifactorial diseases such as CTS. Technologic advances in detection have outrun the ability to interpret and use the information obtained. Until appropriate interpretive research is conducted, use of genetic tests (for PMP 22 deletion and TTR mutations) to impute causality in railroad track workers with CTS claims is not warranted.

The pressure to use genetic tests without population validation appears to be increasing. In the case described here, premature testing was based on a presumption of informativeness of the test that was unsupported by data (85). In order to enhance the utility of genetic tests, it would be helpful if those conducting such tests would provide information on the prevalence of the genetic trait, the predictive value, and other information about the test's validity. When information on any of these test properties is lacking, the evidence gap should be disclosed. This information could be useful to decisionmakers considering genetic testing. Such testing efforts still require, as prerequisite, attention to the ethical, social, and legal protections that have been advanced by the Task Force on Genetic Testing and various professional organizations (86,87).

References

1. Hadler NM. Occupational Musculoskeletal Disorders, second edition. Philadelphia, PA: Lippincott, Williams, and Wilkins, 1999.
2. Sternbach G. The carpal tunnel syndrome. J Emerg Med 1999;17:519–523.
3. Derebery VJ. Determining the cause of upper extremity complaints in the workplace. Review. Occup Med 1998;13:569–582.
4. Tanaka S, Wild DK, Seligman PJ, et al. Prevalence of work-relatedness of self-reported carpal tunnel syndrome among U.S. workers: analysis of the occupational health supplement data of 1988 National Health Interview Survey 1988 National Health Interview Survey Data. Am J Ind Med 1995;27:451–470.
5. Davis L, Wellman H, Punnett L. Surveillance of work-related carpal tunnel syndrome in Massachusetts 1992–1997: A report from the Massachusetts Sentinel Event Notification System for Occupational Risks (SENSOR). Am J Ind Med 2001;39:58–71.
6. Hagberg M, Morgenstern H, Kelsh M. Impact of occupations and job tasks on the prevalence of carpal tunnel syndrome. Scan J Work Environ Health 1992;18:337–345.
7. EEOC settles ADA suit against BNSF for genetic bias. http://www.eeoc.gov/press/4-18-01.html. Accessed November 30, 2001.
8. Atroshi I, Gummesson C, Johnsson R, et al. Prevalence of carpal tunnel syndrome in a general population. JAMA 1999;282:153–158.
9. Nordstrom DL, DeStefano F, Vierkant RF, et al. Incidence of diagnosed carpal tunnel syndrome in a general population. Epidemiology 1998;9:342–345.
10. Tanaka S, Wild DK, Seligman PJ, et al. The US prevalence of self-reported carpal tunnel syndrome: 1988 National Health Interview Survey data. Am J Public Health 1994; 84(11):1846–1848.
11. Levine DW, Simmons BP, Koris MJ, et al. A self-administered questionnaire for the assessment of severity of the symptoms and functional status of Carpal Tunnel Syndrome. J Bone Joint Surg Am 1993;75:1585–1592.
12. Palmer DH, Hanrahan LP. Social and economic costs of carpal tunnel surgery. Instr Course Lect 1995;44:167–172.
13. Kish J, Dobrila V. Carpal tunnel syndrome in workers compensation: frequency, costs and claim characteristics. National Council on Compensation Insurance, Inc. Research Brief 1996;3(3):1–11.
14. Cosgrove JL, Chase PM, Mask NJ, et al. Carpal tunnel syndrome in railroad workers. Am J Phys Med Rehabit 2002;81:101–107.

15. NIOSH. Musculoskeletal disorders and workplace factors. A critical review of epidemiologic evidence for work-related musculoskeletal disorders of the neck, upper extremity, and low back. 1997. U.S. Department of Health and Human Services DHHS (NIOSH) Publication No. 97–141.
16. Dawson DM. Entrapment neuropathies of the upper extremities. N Engl J Med 1993; 329:2013–2018.
17. U.S. District Court: EEOC v Burlington N. Santa Fe Railway Company, Civ No 01-4013 MWB, (N.D. Iowa, February 8, 2001) (EEOC's Memorandum in support of petition for a preliminary injunction).
18. U.S. District Court: for the Eastern District of Wisconsin Equal Opportunity Commission v Burlington N. Santa Fe Railway Company, Civ No 02-C-0456, May 6, 2002.
19. Rose M. Letter to all employees from BNSF President and CEP Matt Rose. BNSF Today. http://www.busf.com/media/articles/2001/03/2001-03-0-a.html. Accessed August 22, 2001.
20. Chance PF. Overview of hereditary neuropathy with liability to pressure palsies. Ann NY Acad Sci 1999;883:14–21.
21. DeJong JSY. Over families met hereditarie disposite tot het optreten van neuritiden gecorreleard met migraine. Psychiat Neurol Bl 1947;50:60–76.
22. Meretoja P, Silander K, Kalimo H, et al. Epidemiology of hereditory neuropathy with liability to pressure palsies (HNPP) in south western Finland. Neuromuscular Disorders 1997;7:529–532.
23. Chance PF, Alderson MK, Leppig KA, et al. DNA deletion associated with hereditary neuropathy with liability to pressure palsies. Cell 1993;72:143–151.
24. Nelis E, Van Broeckhoven C, De Jonghe P, et al. Estimation of the mutation frequencies in Charcot-Marie-Tooth disease type: 1 and hereditary neuropathy with liability to pressure palsies: a European collaborative study. Eur J Hum Genet 1996;4:25–33.
25. Infante J, Garcia A, Combarros O, et al. Diagnostic strategy for familial and sporadic cases of neuropathy associated with 17p11.2 deletion. Muscle Nerve 2001;24:1149–1155.
26. Bort S, Martinez F, Palau F. Prevalence and parental origin of de novo 1.5-Mb duplication in Charcot-Marie-Tooth disease type 1A. Am J Hum Genet 1997;60:230–233.
27. Mariman ECM, Gabreels-Festen AAWM, Van Beersum SEC, et al. Prevalence of the 1.5-mb 17p deletion in families with hereditary neuropathy with liability to pressure palsies. Ann Neurol 1994;36:650–655.
28. Nelis E, Haites V, Van Broeckhoven C. Mutations in the peripheral myelin genes and associated genes in inherited peripheral neuropathies. Human Mutat 1999;13:11–28.
29. Silander K, Halonen P, Sara R, et al. DNA analysis in Finnish patients with hereditary neuropathy with liability to pressure palsies (HNPP). J Neurol Neurosurg Psychiat 1994; 57:1260–1262.
30. Umehara F, Kiwaki T, Yoshikawa IT, et al. Deletion in chromosome 17p11.2 including peripheral myelin protein-22 (PMP22) gene in hereditary neuropathy with liability to pressure palsies. J Neurol Sci 1995;133(1–2):173–176.
31. Gonnaud PM, Sturtz F, Fourbil Y, et al. DNA analysis as a tool to confirm the diagnosis of asymptomatic hereditary neuropathy with liability to pressure palsies (HNPP) with further evidence for the occurrence of de novo mutations. Acta Neurol Scand 1995;92:313–318.
32. Sessa M, Nemni R, Quattrini A, et al. Atypical hereditary neuropathy with liability to pressure palsies (HNPP): the value of direct DNA diagnosis. Med Genet 1997;34:889–892.
33. Lenssen PPA, Gabreels-Festen AAWN, Valentijn LJ, et al. Hereditary neuropathy with liability to pressure palsies. Phenotypic differences between patients with the common deletion and a PMP22 frame shift mutation. Brain 1998;121:1451–1458.

34. Lopes J, Ravise N, Vandenbergher A, et al. Fine mapping of de novo CMT1A and HNPP rearrangements within CMT1A-REPs evidences two distinct sex-dependent mechanisms and candidate sequences involved in recombination. Hum Mol Genet 1998;7:141–8.
35. Verhalle D, Löfgren A, Nelis E, et al. Deletion in the CMT1A locus on chromosome 17p11.2 in hereditary neuropathy with liability to pressure palsies. Ann Neurol 1994; 35:704–708.
36. Maycox PR, Ortuno D, Burrola P, et al. A transgenic mouse model for human hereditary neuropathy with liability to pressure palsies. Molec Cell Neuro Sci 1997;8:405–416.
37. OMIM 162500. Neuropathy, hereditary with liability to pressure palsies; HNPP. Accessed June 6, 2002, from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=omim.
38. Athena Diagnostics product tests–test descriptions. Accessed February 13, 2001, from http://www.athenadiagnostics.com/site/product_search/test_description_template.asp?id=152.
39. Hund E, Linke RP, Willig F, et al. Transthyretin-associated neuropathic amyloidosis. Pathogenesis and treatment. Neurology 2001;56(4):431–435.
40. Buxbaum JW, Tagoe CE. The genetics of the amyloidoses. Ann Rev Med 2000;51: 543–569.
41. Izumoto S, Younger D, Hays AP, et al. Familial amyloidotic polyneuropathy presenting with carpal tunnel syndrome and a new transthyretin mutation, asparagine 70. Neurology 1992;42(11):2094–2102.
42. Saraiva MJM. Transthyretin mutations in health and disease. Hum Mutat 1995;5:191–196.
43. Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. New Engl J Med 1997;337:898–909.
44. Benson MD. Amyloidosis. In Scriver CR, Beaudet AL, Sly WS, Valle D eds. The metabolic and molecular basis of inherited disease. New York, NY, McGraw-Hill. 1995;4159–4191.
45. Giersiepen K, Eberle A, Pohlabein H. Gender differences in carpal tunnel syndrome? Occupational and non-occupational risk factors in a population-based case-control study. Ann Epidemiol 2000;10:481.
46. Tanaka S, Wild DK, Cameron LL, et al. Association of occupational and nonoccupatinal risk factors with prevalence of self-reported carpal tunnel syndrome in a national survey of the working population. Am J Ind Med 1997;32:550–556.
47. Nordstrom DL, Vierkant RA, DeStefano F, et al. Risk factors for carpal tunnel syndrome in a general population. Occup Environ Med 1997;54:734–740.
48. Solomon DH, Katz JN, Bohn R, et al. Nonoccupational risk factors for carpal tunnel syndrome. J Gen Intern Med. 1999;14:310–314.
49. Ferry S, Hannaford P, Warskyj M, et al. Carpal tunnel syndrome: a nested case-control study of risk factors in women. Am J Epidemiol. 2000;151:566–574.
50. Hakim AJ, Cherkas L, El Zayat S, et al. The genetic contribution to carpal tunnel syndrome in women: a twin study, Arthritis Rheum 2002;47:275–279.
51. Radecki P. The familial occurrence of carpal tunnel syndrome. Muscle Nerve 1994;17:325–330.
52. Nathan PA, Meadows KD. Neuromusculoskeletal conditions of the upper extremity: are they due to repetitive trauma? Occup Med. 2000;15:677–693.
53. Rempel D, Evanoff B, Amadio PC, et al. Consensus criteria for classification of carpal tunnel syndrome in epidemiologic studies. Am J Public Health 1998;88:1447–1451.
54. National Academy of Sciences. Work-related musculoskeletal disorders. Report, workshop, summary, and workshop papers. Washington, DC: National Academy of Sciences, National Research Council. 1999. [OSHA Exhibit No. 26–37].
55. Leclerc A, Franchi P, Cristofari MF, et al. Carpal tunnel syndrome and work organisation in repetitive work: a cross-sectional study in France. Occup Environ Med 1998;55:180–187.

56. Lalumandier JA, McPhee SD. Prevalence and risk factors of hand problems and carpal tunnel syndrome among dental hygienists. J Dent Hyg 2001;75:130–134.
57. Yagev Y, Carel RS, Yagev K. Assessment of work-related risks for carpal tunnel syndrome. Isr Med Assoc J 2001;3:569–571.
58. Frost P, Anderson JH, Nielson VK. Occurrence of carpal tunnel syndrome among slaughterhouse workers. Scand J Work Environ Health. 1998;24(4):285–292.
59. Latko WA, Armstrong TJ, Franzblau A, et al. Cross-sectional study of the relationship between repetitive work and the prevalence of upper limb musculoskeletal disorders. Am J Ind Med. 1999;36:248–259.
60. Gorsche RG, Wiley JP, Renger RF, et al. Prevalence and incidence of carpal tunnel syndrome in a meat packing plant. Occup Environ Med 1999;56:417–422.
61. Rossignol M, Stock S, Patry L, et al. Carpal tunnel syndrome: what is attributable to work? The Montreal study. Occup Environ Med 1997;54:519–523.
62. Silverstein BA, Fine LJ, Armstrong TJ. Occupational factors in carpal tunnel syndrome. Am Ind Hyg Assoc J 1987;11:343–358.
63. Cummings K, Maizlish N, Rudolph L, et al. Occupational disease surveillance: carpal tunnel syndrome. MMWR Morb Mortal Wkly Rep 1989;38(28):485–489.
64. McDiarmid M, Oliver M, Ruser J, et al. Male and female rate differences in carpal tunnel syndrome injuries: personal attributes or job tasks? Environ Res 2000;8:23–32.
65. Verghese J, Galanopoulou AS, Herskovitz S. Autonomic dysfunction in idiopathic carpal tunnel syndrome. Muscle Nerve 2000;23:1209–1213.
66. Lambird PA, Hartman WH. Hereditary amyloidosis, the flex or retinaculum and the carpal tunnel syndrome. Am J Clin Pathol 1969;52:714–719.
67. Danta G. Familial carpal tunnel syndrome with onset in childhood. J Neurol Neurosurg Psychiatry 1975;38:350–355.
68. Sparkes RS, Spence MA, Gottlieb NL, et al. Genetic linkage analysis of the carpal tunnel syndrome. Hum Hered 1985;35(5):288–291.
69. Gossett JG, Chance PF. Is there a familial carpal tunnel syndrome? An evaluation and literary review. Muscle Nerve 1998;21:1533–1536.
70. Stoll C, Maitrot D,. Autosomal dominant carpal tunnel syndrome. Clin Genet 1998;54: 345–348.
71. McKusick VA. Mendelian inheritance in man, catalogs of human genes and genetic disorders. 12th edition. Baltimore, MD: Johns Hopkins University Press, 1998.
72. Stockton DW, Meade RA, Netscher DT, et al. Hereditary neuropathy with liability to pressure palsies is not a major cause of idiopathic carpal tunnel syndrome. Arch Neurol 2001;58:1635–1637.
73. Stevens JC, Sun S, Beard CM, et al. Carpal tunnel syndrome in Rochester, Minnesota, 1961–1980. Neurology 1988;38:134–138.
74. Skre H. Genetic and clinical aspects of Charcot-Marie-Tooth's disease. Clin Genet.1974;6:98–118.
75. Bird TD, Hereditary neuropathy with liability to pressure palsies. GeneReviews. Initial posting: 28 September 1998; Last revision: 27 June 2001. Accessed September 18, 2002 from http://www.geneclinics.org.
76. Tyson J, Malcolm S, Thomas PK, et al. Deletions of chromosome 17p11.2 in multifocal neuropathies. Ann Neurol 1996;39:180–186.
77. Holtzman NA. Medical and ethical issues in genetic screening—an academic view. Environ Health Perspect 1996;104S5:987–990.
78. Vineis P, Schulte P, McMichael AJ. Misconceptions about the use of genetic tests in populations. Lancet 2001;357:709–712.
79. Peto J, Houlston RS. Genetics and the common cancers. Eur J Cancer 2001;37S8: S88–S96.

80. Holtzman NA. Promoting safe and effective genetic tests in the United States: Work of the Task Force on Genetic Testing. Clin Chem 1999;45:732–738.
81. Barth PS, Hunt HA. Workers' Compensation and Work-Related Illnesses and Diseases. Cambridge, MA: MIT, 1980.
82. Employee's Compensation Appeals Board Decisions/ECAB Table of Cases-Volume 48/Lambert Robert K 95-1002. Accessed November 30, 2001. http://www.nfoweb.com/cgi-bin/om_isapi.dll?clientID=10661&infobase-dol-32&jump=96.
83. Employee's Compensation Appeals Board Decisions/ECAB Table of Cases-Volume 49/Kreeger, Kim S 960142. http://www.nfoweb.com/cgi-bin/om_isapi.dll?clientID=10669&infobase=dol-38&jump=96. Accessed November 30, 2001.
84. Task Force on Genetic Testing. Promoting Safe and Effective Genetic Testing in the United States. Baltimore, MD: Johns Hopkins University Press, 1998.
85. Schulte PA, Lomax GP. Assessment of the scientific basis for genetic testing of railroad workers with Carpal Tunnel Syndrome. J Occup Environ Med 2003;45:592–600.
86. American College of Occupational and Environmental Medicine. Position Statements/Guidelines: Genetic screening in the workplace. October 24, 1994.
87. American College of Medical Genetics. Points to consider in preventing unfair discrimination based on genetic disease risk: a position statement of the American College of Medical Genetics. Genet Med 2001;3:436–437.

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