Phenotypic Variation in Heterozygous Familial Hypercholesterolemia

A Comparison of Chinese Patients With the Same or Similar Mutations in the LDL Receptor Gene in China or Canada

Simon N. Pimstone, Xi-Ming Sun, Christele du Souich, Jiri J. Frohlich, Michael R. Hayden, Anne K. Soutar

Abstract—Familial hypercholesterolemia (FH) is caused by mutations in the LDL receptor (LDLR) gene and is usually associated with hypercholesterolemia, lipid deposition in tissues, and premature coronary artery disease (CAD). However, individuals with heterozygous FH in China exhibit a milder phenotype despite having deleterious mutations in the LDLR gene (X.-M. Sun et al, Arterioscler Thromb. 1994;14:85–94). Nineteen Chinese FH heterozygotes living in Canada were screened for the 11 mutations that had been described in FH patients living in China. One Chinese Canadian carried one of these mutations (Trp462Stop), 2 carried a previously unreported single-base substitution (Cys163Arg), and 1 carried a mutation observed in French-Canadian patients (Glu207Lys). Twelve additional carriers of these mutations were identified in the families of the index patients. Significantly higher LDL cholesterol concentrations were observed in FH heterozygotes with defined mutations living in Canada (mean ± SD, 7.46 ± 1.29, n = 16) than in those living in China (4.35 ± 1.09, n = 18; P < .0001). Six of the 16 FH heterozygotes residing in Canada had evidence of tendon xanthomata and 4 had a history of premature CAD, whereas none of those in China had tendon xanthomata or CAD. Complete segregation between hypercholesterolemia and inheritance of a mutant allele was observed in 3 Canadian Chinese FH families. Thus, Chinese FH heterozygotes living in Canada exhibit a phenotype similar to that of other FH patients in Western societies. The difference between patients living in Canada and those living in China could be ascribed to differences in dietary fat consumption, showing that environmental factors such as diet play a significant role in modulating the phenotype of heterozygous FH. (Arterioscler Thromb Vasc Biol. 1998;18:309-315.)

Key Words: familial hypercholesterolemia ♦ Chinese ♦ LDL receptor ♦ environment ♦ dietary fats

Heterozygous FH is caused by mutations in the LDLR gene and affects approximately 1 in 500 persons worldwide. Inheritance of a single defective LDLR gene generally results in significant hypercholesterolemia, lipid deposition in peripheral tissues, and premature CAD. Fifty percent of men and 20% of women with heterozygous FH will have clinical evidence of CAD by 45 years of age. Persons with mutations affecting both alleles of the LDLR gene, ie, homozygous or compound-heterozygous FH, usually have cholesterol concentrations approximately four to five times normal, with cutaneous xanthomata appearing in early childhood and CAD before 30 years of age.

In a small proportion of patients, mutations in the gene for the LDLR are associated with a milder phenotype. Both genetic and environmental factors may be contributing to this. For example, the effect of an unidentified, dominant, cholesterol-lowering gene has been observed in one family with FH. In addition, it has been shown that different environmental factors may moderate the phenotype in heterozygous FH. Strict adherence to a low-fat, low-cholesterol diet with a high ratio of polyunsaturated to saturated fat may reduce LDL-C concentrations by 15% to 20%, and smoking significantly increases the risk for developing CAD, particularly in males. However, despite this clinical variability, the penetrance of LDLR mutations is >90% in heterozygous persons living a Western lifestyle.

On the other hand, we have shown that individuals heterozygous for mutations in the LDLR gene who are living in China do not have a markedly elevated concentration of LDL in plasma, do not exhibit evidence of tendon or skin xanthomata, and apparently do not have any increased risk of CAD. Indeed, Chinese individuals with heterozygous FH are recognized only by virtue of their being parents of offspring with mutations in both alleles of the LDLR gene. Unlike their heterozygous parents, the Chinese homozygous FH patients are as severely affected as those elsewhere and carry the same
range of deleterious mutations in the LDLR gene as in other populations.

In this study, we investigated whether the milder phenotype of FH in China was mainly due to genetic, environmental, or a combination of both factors. To do this, we identified mutations in the LDLR gene in heterozygous FH patients of Chinese origin who are now living in Vancouver, Canada, and compared their clinical phenotype with individuals with the same or similar mutations living in China.

Methods

Study Subjects

A total of 19 apparently unrelated index cases of Chinese ancestry (province of Canton) with heterozygous FH were identified from the St Paul's Hospital Lipid Clinic in Vancouver, Canada. A diagnosis of FH was made if subjects satisfied at least two of the following criteria: (1) LDL-C concentration >95th percentile, corrected for both age and sex (2) premature CAD in a first-degree relative <60 years of age; and (3) tendon xanthomata in the index patient, a first-degree relative, or a pediatric relative with an LDL-C level >95th percentile, corrected for age and sex. The criteria for CAD included the presence of angina or myocardial infarction, angiographically proven disease, or a history of coronary artery bypass surgery. BMI was calculated as body weight in kilograms divided by the square of the height in meters. The percentages of dietary fat and cholesterol intake were calculated from 3-day food recall and analyzed by dietitians in the lipid clinic. In addition, 12 family members from three of the four index cases with identified mutations (families FH-6, FH-40, and FH-258) were recruited for LDLR genotype analysis and evaluation of phenotype. No family members from family FH-37 were available for the study. Signed consent was obtained from all study participants. Eighteen FH heterozygotes residing in China were recruited from family studies of Chinese homozygous FH subjects as described in detail elsewhere.

Selected Abbreviations and Acronyms

- BMI = body mass index
- C = cholesterol
- CAD = coronary artery disease
- FH = familial hypercholesterolemia
- LDLR = LDL receptor
- LDL-C = low-density lipoprotein cholesterol
- CAD = coronary artery disease
- BMI = body mass index

Canadian Chinese normolipidemic control subjects consisted of 30 non-FH subjects recruited from family studies of Chinese FH families in Vancouver. Six of these individuals were from three of the FH families discussed in this article. The remaining 24 control subjects were non-FH subjects from other Chinese FH families not described in this study but were from families in which other functional LDLR defects had been described that had clearly segregated with the FH phenotype in affected individuals (data not shown).

Laboratory Methods

Venous blood was collected from all subjects after an overnight fast of 12 to 14 hours. EDTA/plasma was separated from cells and was either analyzed immediately or frozen at −70 °C. Total plasma cholesterol, triglycerides, and HDL-C (determined after precipitation of apolipoprotein B-containing lipoproteins with heparin/MnCl₂) were measured by standard enzymatic techniques. LDL-C concentration was calculated with the Friedewald formula. None of the subjects had fasting triglyceride concentrations >4.5 mmol/L. Lp(a) was measured by radioimmunoassay (Apo(a)RIA kit, Mercodia AB).

Screening for Mutations in the LDLR Gene

Genomic DNA prepared from whole-blood samples from the index patients and their relatives was sent to London, UK, for genetic analysis. Fragments of the LDLR gene were amplified by polymerase chain reaction and analyzed for the presence of known mutations in the Chinese population by single-strand conformational polymorphism, restriction enzyme digestion, nondenaturing gel electrophoresis (to detect heteroduplexes), or automated nucleotide sequencing, all as described previously. Any samples that yielded either the mutant or an unexpected pattern during screening were subjected to nucleotide sequencing to confirm the suspected base change(s).

Statistical Analysis

Differences between Canadian and Chinese FH cohorts in mean values for lipid concentrations, age, and dietary and anthropomorphic parameters were assessed by an unpaired t test using StatView (Abacus Concepts). Differences in the incidence of CAD and tendon xanthomata between the two FH cohorts were assessed by Fisher’s exact two-tail probability test. The nonparametric Kruskal-Wallis test was used to determine differences in lipid and other parameters between the Canadian FH subjects with and without CAD.

Results

Identification of Mutations

Genomic DNA from 19 apparently unrelated individuals of Chinese ancestry who now reside in Canada was screened for the presence of the 11 known mutations in the LDLR gene that have been previously observed in Chinese FH patients and their parents living in the Nanjing area of southeastern China (Table 1). Four of these 19 subjects were found to carry identical or similar mutations in the LDLR gene (and only these four subjects, together with their 12 available family members, were included for phenotype analysis). One individual (subject III-1 in family FH-40) was found to have lost the BanHI site in exon 10, suggesting that the patient was heterozygous for the Trp462Stop mutation. This was confirmed by nucleotide sequencing (sequencing data not shown).

Another patient (subject III-2 in family FH-6) was found to have lost the Dde I site in exon 4, suggesting that the patient was heterozygous for the Glu207Stop mutation previously observed in Chinese patients. However, nucleotide sequencing showed that the loss of the Dde I site was due to a different base substitution in codon 207, G to A, which was predicted to cause substitution of Lys207 for Glu. In two other patients (subject III-2 and subject 37.33 from families FH-258 and FH-37, respectively), an unusual pattern of fragments was observed after Dde I digestion of the polymerase chain reaction.
product of exon 4. Nucleotide sequencing revealed the presence of the same new mutation (T to C) in codon 163 in these two patients and was predicted to cause substitution of Arg for Cys163. This mutation destroys a site for the restriction enzyme Eco47III in exon 4. Thus, of 19 unrelated FH individuals, one was found to carry a mutation that had been previously identified in Chinese patients (Trp462Stop). Two patients carried a previously unreported single-base substitution (Cys163Arg), and one patient carried a mutation in the same codon (Glu207Lys) as the one described previously in Chinese patients. This mutation has been previously observed in patients of diverse origin.10 Because this study was aimed at identifying phenotypic differences between Chinese FH heterozygotes residing in China versus those living in Canada but carrying the same or similar mutations in the LDLR gene, only these patients and their families formed the basis for this study.

Genomic DNA from the 12 available family members of these three patients (families FH-6, FH-40, and FH-258) was screened for the presence of the mutation found in the relevant index patient by restriction enzyme digestion of the appropriate amplified fragment (Fig 1). As shown in the family pedigrees in Fig 2, there was complete cosegregation between hypercholesterolemia and inheritance of a mutant allele in the family members tested. No members of the family of FH 37.33 were available for study.

**Haplotype Analysis**
The origin of the Canadian family (FH-40) with the Trp462Stop mutation in the LDLR gene is the village of Chung Han in Canton Province. The Chinese FH family with the Trp462Stop mutation in the LDLR gene is from the environs of the city of Nanjing in Jiang-su Province.5 Haplotype analysis was undertaken to determine whether the mutation in both families was likely to have been inherited from a common ancestor. The haplotype of the Trp462Stop allele, based on four informative common polymorphisms that span the region containing the mutation, is the same in family FH-40 and the Chinese FH patient previously described (Table 2). This finding is compatible with but not conclusive evidence for the mutant allele’s having been inherited from a common ancestor.

**Comparison of Phenotypes of FH Patients in China and Canada**

**Lipoprotein Phenotype**
In addition to the index patients studied from Canada, all of their relatives in Canada who were found to be heterozygous for an LDLR mutation had a pretreatment concentration of LDL-C in plasma that was above the age-corrected limit specified for a diagnosis of FH.1 The mean value in these Canadian heterozygous patients and family members with defined mutations in the LDLR gene was 7.46±1.29 mmol/L (n=16). This value is in marked contrast to our previous observations in obligate heterozygous FH patients living in China as shown in Table 3, wherein the mean LDL-C concentration was significantly lower (4.35±1.09 mmol/L, n=18; P<.001). There was no significant difference in the mean age of the two groups. In particular, comparison of lipid levels between the Canadian and Chinese families with the same Trp462Stop mutation revealed considerably higher total cholesterol and LDL-C concentrations in each affected member of the Canadian FH family, two of whom were of similar age to the FH heterozygous individuals living in China (Table 4). The total cholesterol and LDL-C concentrations in the Canadian cohort (Table 3) are similar to those reported for Canadian FH patients of European origin.4,15 No significant difference was observed in mean HDL-C or triglyceride concentrations between the FH cohorts from Canada and China.

The mean concentration of Lp(a) in the Chinese Canadian FH heterozygote population (mean±SD, 947.5±613.7 U/L, n=7) was considerably higher than the values reported for other Chinese non-FH populations, whose levels do not differ significantly from those in other general populations.16 However, no differences in Lp(a) concentrations were observed between the FH and non-FH individuals from the Canadian Chinese families participating in this study (data not shown). 

---

**Figure 1.** Identification of mutations in the families of index patients. Fragments of genomic DNA from each available family member of the index patient was amplified by polymerase chain reaction and digested with restriction enzymes, as indicated in the diagrams. Fragments were separated by electrophoresis on agarose gels and stained with ethidium bromide. Individuals are identified by a number, as indicated on the pedigrees shown in Fig 2, and the genotype at the position of the mutation shown below. + Indicates mutation present; −, mutation absent.
Clinical Phenotype

The observed difference in lipoprotein phenotype was accompanied by a significantly higher proportion of Chinese Canadian heterozygous FH patients with tendon xanthomata and premature CAD. As shown in Table 3, 7 of 16 Canadian subjects (43.75%) had tendon xanthomata compared with 0 of 18 in China \( (P = .006) \), and 4 of 16 Canadian subjects (25%) had CAD compared with 0 of 18 in China \( (P = .039) \). Of the 4 Canadian individuals presenting with premature CAD, 2 were females from the same family (FH-40), and both had suffered an MI before 37 years of age and were nonsmokers. The other two Chinese Canadians with CAD were male and were from different families (subject III-2 from family FH-258 and subject II-4 from family FH-6).

Anthropomorphic, Dietary, and Risk Factor Assessment

BMI levels in the Chinese Canadian FH cohort were considerably lower than those reported for a general, age-matched population from British Columbia, Canada. Males in the Chinese Canadian FH cohort had a mean BMI of 22.9 ± 3.6 kg/m² in contrast to a value of ≈26 kg/m² for age-matched males living in British Columbia, Canada \( (n = 275) \). In addition, Chinese Canadian FH females had a mean BMI of 19.3 ± 2.1 kg/m², in marked contrast to a mean BMI of 25.5 kg/m² in a cohort of age-matched women residing in British Columbia, Canada \( (n = 307) \). Although no BMI measurements were available for the Chinese FH cohort, all the subjects who participated in the study were lean.

Comparison of the diet of the Canadian FH cohort at the time of diagnosis with a typical diet in China revealed that a significantly higher percentage of calories were obtained from fat in the Canadian diet. The mean percentage of calories consumed as fat by the Chinese Canadian FH cohort was 33.5 ± 9.0%. Although no dietary data were available for the Chinese FH cohort at the time they were known to reside in poor rural areas around Nanjing and to be consuming a typical Chinese diet (L.-M. Fan and X.-M. Sun, unpublished observations, 1993) that includes ≈20% of calories as fat, with a high polyunsaturated to saturated fat ratio. When one individual in the Canadian cohort (II-3 in family FH-6) consumed a low-calorie, very-low-fat diet for 3 months (975 calories/d, 13% of calories as fat), his LDL-C concentration fell by 21.1% (from 5.77 to 4.55 mmol/L). Surprisingly, despite this response to diet, no significant change in the patient’s BMI was noted. Two subjects from the Canadian FH cohort were smokers. One of these individuals (family FH-6, II-4) had a 56-pack-year history and had suffered a myocardial infarction at the age of 43 years. This subject also had the highest presenting cholesterol levels in this family (Fig 2C). None of the other three patients with a history of premature CAD were smokers. None of the FH cohort from mainland China smoked.

It was also noted that none of the Canadian FH cohort undertook significant aerobic exercise, as defined by any form of aerobic activity for at least 20 minutes more than twice weekly.

Discussion

In this study, we sought to determine whether 11 LDLR mutations previously described in individuals with FH living in China were also present in Chinese patients with FH who had migrated to Canada. Of the 19 Chinese FH heterozygotes screened, one individual was found to carry a mutation identical to one described previously in Chinese patients \( (\text{Trp462Stop}) \), and another carried a mutation \( (\text{Glu207Lys}) \) that occurred in the same codon as one described previously in Chinese patients \( (\text{Glu207Stop}) \). One other mutation identified in the remaining two subjects has not been reported previously \( (\text{Cys163Arg}) \). It is likely that the Trp462Stop mutation was inherited from a common ancestor, but overall, these results suggest that single founder mutations are unlikely to account for a large proportion of patients with FH in China. The Chinese population residing in Vancou
ver originates mainly from the province of Canton in southern China, whereas the FH cohort previously described from China were all from Nanjing in Jiang-Su Province, ~1000 miles north of Canton. However, Canton, Nanjing, and Shanghai form the commercial center of the Chinese economy, and there has been considerable movement between these areas. It is perhaps surprising, therefore, that only one common mutant allele was identified, but relatively small numbers were studied in each group.

In the Canadian patients studied, there is no doubt that the observed mutations are responsible for their clinical disorder. The Trp462Stop mutation is predicted to produce a truncated protein that is unlikely to reach the cell surface, and the Glu207Lys mutation results in an LDLR protein with normal activity in cultured cells. This mutation has been observed in French Canadians living in the Montreal area, but it is an uncommon cause of FH in this population, with an allele frequency of 2% in a group of 130 unrelated patients. It is perhaps surprising, therefore, that only one common mutant allele was identified, but relatively small numbers were studied in each group.

TABLE 2. Haplotype of the Trp462Stop Allele of the LDLR Gene in Chinese FH Patients in China and Canada

<table>
<thead>
<tr>
<th>Polymorphism in LDLR Gene (Location)</th>
<th>Frequency in Chinese† (CH 6 Ref)</th>
<th>Chinese*</th>
<th>Canadian Chinese FH Family 40*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Htz)</td>
<td></td>
<td>III-1 (Hz) II-1 (Hz) II-3 (Nor)</td>
</tr>
<tr>
<td></td>
<td>(Nor)</td>
<td></td>
<td>III-2 (Hz) II-3 (Nor)</td>
</tr>
<tr>
<td>Hha I (intron 9)†</td>
<td>0.17 (-)</td>
<td></td>
<td>Hha - Bsm A - Avi II + Nco I +</td>
</tr>
<tr>
<td>BsmAI (exon 10)‡</td>
<td>0.28 (+)</td>
<td></td>
<td>Hha - Bsm A - Avi II + Nco I +</td>
</tr>
<tr>
<td>Avi II (exon 13)†</td>
<td>0.27 (+)</td>
<td></td>
<td>Hha - Bsm A - Avi II + Nco I +</td>
</tr>
<tr>
<td>Nco I (exon 18)†</td>
<td>0.26 (-)</td>
<td></td>
<td>Hha - Bsm A - Avi II + Nco I +</td>
</tr>
</tbody>
</table>

†Frequency of rare allele (+ indicates presence and - absence of cutting site) in 18 unrelated individuals from Nanjing area.

short region, especially at CpG dinucleotides, have recurred in different populations. Thus, it is very unlikely that the Gln207Lys mutation has been inherited from a common ancestor in patients of Chinese, French, and Mexican origin. The Cys163Arg mutation occurs in the part of exon 4 that codes for one of the disulfide-rich repeats that is critical for full ligand binding activity. It involves a cysteine residue that is conserved between all species in which the sequence is known and forms a disulfide bond that is critical for ligand binding.

Phenotypic variation in persons of the same ethnic origin with the same genetic disease but living in different cultures allows one to assess directly whether other factors limited to a particular environment will influence the clinical characteristics and course of the disease under study. It is clear from this study that despite the same or similar LDLR defects, a significantly milder biochemical and clinical phenotype is observed among FH heterozygotes of Chinese ancestry residing in China than in FH heterozygotes residing in Canada. It may be argued that these phenotypic differences are due solely to the different selection process of the two FH cohorts, because the mainland Chinese FH cohort was recruited from family studies of FH homozygotes, whereas the Canadian index cases were selected from a high-risk lipid clinic setting. However, because the majority of Canadian FH heterozygotes included in the phenotyping studies (12/16) were family members of these index cases and were not attending a lipid clinic, both cohorts represent FH heterozygotes obtained from family studies of high-risk index cases.

All the evidence from this study shows that the difference in lipid phenotype is not due to variation in the nature of the mutations in the LDLR gene, as suggested by the difference between the Chinese and Canadian FH families who shared an identical mutant LDLR allele. This apparent protection of heterozygous FH individuals against premature CAD is not restricted to China, as it has also been observed that the parents of homozgyous FH patients in Tunisia do not suffer from an increased incidence of CAD. We conclude that environmental or genetic factors unrelated to the LDLR gene must make a major contribution to the variability of the phenotype in these patients.

The most likely environmental factor is the nature of the diet consumed by the two groups. The occurrence of a significantly lower mean plasma cholesterol concentration in rural mainland China than in Western populations has been
well documented, and this is thought to correlate with the lower reported incidence of CAD in China, which is 10% that of Western countries. With increased urbanization, however, there is a tendency to higher cholesterol concentrations in Chinese populations. This has been observed in Chinese populations within mainland China and with immigrant Chinese populations in other geographic locations.

Dietary differences but that FH heterozygotes may be more sensitive to different urban settings may not produce marked cholesterol concentrations observed between Chinese populations in Canadian Chinese population study. This may suggest that the dietary differences observed between Chinese populations in urban areas. The mean values are higher in Taipei and Hong Kong (3.07) and Hong Kong (3.27). Although differences for males only are illustrated in Table 5, a similar trend is observed in females. The cholesterol concentrations of control Chinese Canadian subjects from this study were markedly higher than those of control subjects from rural mainland China but did not differ significantly from those of urban mainland Chinese, from Chinese control populations in Hong Kong or Taiwan, or from a yet-unpublished general Canadian Chinese population study. This may suggest that the dietary differences observed between Chinese populations in different urban settings may not produce marked cholesterol differences but that FH heterozygotes may be more sensitive to such dietary changes in terms of their cholesterol response.

We observed that the diet of the immigrant Chinese living in North America differs from the typical mainland Chinese diet, in that the percentage of calories obtained from fat is significantly higher. Further evidence that diet can have a significant effect on lipoprotein levels in FH comes from the marked reduction of LDL-C to within the normal range that occurred in one male FH heterozygote from the Chinese Canadian cohort when he consumed a very-low-fat (13% fat as calories) diet, which is comparable to a typical rural Chinese diet. These results suggest that strict restriction of caloric intake and reduction of dietary fat without pharmacological therapy may be sufficient to reduce cholesterol concentrations in other FH patients to the levels observed in FH heterozygotes residing in China.

Another environmental factor that could influence the difference in FH phenotype between the two FH cohorts is physical activity. None of the 16 Chinese FH patients studied in Canada were undertaking any form of significant exercise at the time of presentation, and it has been previously observed that Chinese residing in North America have significantly lower levels of physical activity than do those living in China. Despite their physical inactivity, the mean BMI levels for FH heterozygotes of Chinese ancestry living in Vancouver was lower than the mean values reported for other subjects with FH residing in Vancouver and for the general population residing in British Columbia, Canada. Significantly lower BMI levels have also been observed in individuals living in China compared with Western populations, and all the Chinese FH patients in China were lean. It is unlikely therefore that differences in BMI are a major contributing factor underlying the difference in FH phenotype observed in Chinese subjects from Canada and China.

The prevalence of CAD was significantly higher in the Chinese Canadian FH cohort. Four of the 16 Chinese FH heterozygotes residing in Canada had evidence of premature CAD (25%). In contrast, none of the FH heterozygotes living in China had CAD (0%, P = .039). Apart from the significantly elevated cholesterol concentrations in the Chinese Canadian FH cohort, other traditional risk factors for CAD were assessed. Smoking did not appear to be a significant risk factor in the Chinese Canadian FH cohort, as only 2 of the 16 subjects from the four families studied were smokers. Hypertension was not a significant factor associated with CAD in the Canadian cohort. Only 1 of the Canadian cohort was taking medication for reduction of blood pressure (FH-258, 220).

### Table 5: Baseline Data for Male Chinese Normolipidemic Subjects Residing in Canada, Mainland China, Taiwan, and Hong Kong

<table>
<thead>
<tr>
<th>Residence</th>
<th>Study Year</th>
<th>Age, y</th>
<th>Number</th>
<th>TC, mmol/L</th>
<th>LDL-C, mmol/L</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural</td>
<td>Beijing</td>
<td>1983–1984</td>
<td>35–39</td>
<td>125</td>
<td>4.37±0.95</td>
<td>2.34±0.87</td>
</tr>
<tr>
<td></td>
<td>Guangzhou</td>
<td>1983–1984</td>
<td>35–39</td>
<td>216</td>
<td>4.00±0.80</td>
<td>2.38±0.69</td>
</tr>
<tr>
<td>Urban</td>
<td>Canada</td>
<td>1997</td>
<td>27.2±17.1</td>
<td>11</td>
<td>4.71±0.85</td>
<td>2.77±0.67</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>1993</td>
<td>51.6±16.1</td>
<td>711</td>
<td>4.96±0.98</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Beijing</td>
<td>1983–1984</td>
<td>35–39</td>
<td>183</td>
<td>4.66±0.96</td>
<td>2.81±0.92</td>
</tr>
<tr>
<td></td>
<td>Guangzhou</td>
<td>1983–1984</td>
<td>35–39</td>
<td>374</td>
<td>4.59±0.78</td>
<td>2.84±0.71</td>
</tr>
<tr>
<td></td>
<td>Taipei</td>
<td>1993</td>
<td>49.3±6.3</td>
<td>209</td>
<td>4.97±0.82</td>
<td>3.07±0.77</td>
</tr>
<tr>
<td></td>
<td>Hong Kong</td>
<td>1993</td>
<td>25–34</td>
<td>317</td>
<td>5.09±1.01</td>
<td>3.27±0.92</td>
</tr>
</tbody>
</table>

TC indicates total cholesterol; NA, not available.

---

**TABLE 4. Comparison of Plasma LDL-C Concentration and Clinical Phenotype in Individuals of Chinese Origin Who Are Heterozygous for the W462X Mutation in the LDLR Gene**

<table>
<thead>
<tr>
<th>Place of Residence</th>
<th>Age, y</th>
<th>LDL-C, mmol/L</th>
<th>TX</th>
<th>CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancouver</td>
<td>67</td>
<td>6.76</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Vancouver</td>
<td>31</td>
<td>7.60</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vancouver</td>
<td>37</td>
<td>7.03</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>45.0 (19.3)</td>
<td>7.13 (0.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nanjing</td>
<td>34</td>
<td>5.44</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nanjing</td>
<td>35</td>
<td>5.68</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

TX indicates tendon xanthomata.
III–1), and none of the remaining 15 subjects were hypertensive on physical examination.

The possible influence of genetic factors other than variation at the LDLR gene locus could not be examined fully in this relatively small sample. Allelic variation in the genes for apoE, apo(a), angiotensin-converting enzyme, and apoB have been reported to affect lipoprotein concentrations and predisposition to premature CAD in subjects with FH, but these effects are relatively small. Data for the apo(a) and apoE phenotypes/genotypes were not available for the original Chinese FH patients, but it is unlikely that variation in these genes alone is a cause for the highly significant difference in phenotype observed in this study between the Chinese FH heterozygotes living in Canada and China, the data from this study would suggest that this variability in phenotype is most likely secondary to significant environmental differences between these two groups. In particular, dietary factors are likely to have a major influence, and these data provide further evidence supporting the initiation of dietary counseling for FH subjects at an early age.

Acknowledgments

This work was supported in part by grants from the British Heart Foundation (AKS grant No. 93/005) and the British Columbia Heart and Stroke Foundation (to M.R.H.).

References

Phenotypic Variation in Heterozygous Familial Hypercholesterolemia: A Comparison of Chinese Patients With the Same or Similar Mutations in the LDL Receptor Gene in China or Canada

Simon N. Pimstone, Xi-Ming Sun, Christele du Souich, Jiri J. Frohlich, Michael R. Hayden and Anne K. Soutar

doi: 10.1161/01.ATV.18.2.309

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/18/2/309