Background/Aims: Adult-type hypolactasia (primary lactose malabsorption) affects most of world’s human population and limits the use of fresh milk due to lactose intolerance. The diagnosis of adult-type hypolactasia has been difficult to establish because of unsatisfactory diagnostic methods. C/T,13910 single nucleotide polymorphism residing 13910 base pairs from the 5’ end of the lactase gene has been shown to be associated with lactase persistence. The aim of the study was to assess the applicability of the C/T,13910 variant as a diagnostic test for adult-type hypolactasia during childhood.

Methods: Intestinal biopsies were obtained from 329 children and adolescents of African, Finnish, and other White origins aged 0.1–20 years undergoing upper gastrointestinal endoscopy because of abdominal complaints. The biopsies were assayed for lactase, sucrase, and maltase activity and genotyped for the C/T,13910 variant using polymerase chain reaction minisequencing.

Results: The frequency of the C/C,13910 genotype defining lactase non-persistence was well in agreement in this study with published figures for the prevalences of adult-type hypolactasia in Africans and Whites. The C/C,13910 genotype was associated with very low lactase activity (<10 U/g protein) in the majority of children tested at 8 years of age and in every child older than 12 years of age giving a specificity of 100% and sensitivity of 93% for the genetic test. The decline of lactase activity was somewhat earlier in African compared with Finnish children with C/C,13910 genotype (p<0.03).

Conclusions: Genetic test of C/T,13910 polymorphism can be used as a first stage screening test for adult-type hypolactasia.

A bdominal pain and symptoms related to gastrointestinal function are common both in children and adults and are a challenge for clinicians in everyday practice.1–3 Studies tracing back to the 1970s have shown that lactose malabsorption has a significant role in recurrent abdominal pain.4–6 The impact of adult-type hypolactasia on abdominal complaints has been difficult to study because of the variability of clinical symptoms and inaccurate diagnostic laboratory tests.7 The diagnosis of adult-type hypolactasia is by definition based on the measurement of lactase, sucrase, and maltase activities and the lactase to sucrase (L:S) ratio in intestinal biopsies.8–10 This invasive technique is not suitable for primary screening of abdominal complaints. The diagnosis is usually based on the lactose tolerance test (LTT) for which specificity has been reported to range from 77–96% and sensitivity from 76–94%. For the breath hydrogen test the specificity is observed to be 89–100% and sensitivity 69–100%.11 Data are scarce for the reliability of the routine diagnostic tests of lactose malabsorption during childhood. The incidence of false positive results in LTT in children has been reported to be as high as 30% reducing its value in clinical use.12 In adulthood, 11–32% of lactose malabsorbers report no symptoms from lactose containing milk products13,14 whereas up to 57% of subjects who experience symptoms of lactose intolerance may have normal lactase activity.14–16 These data imply that an improvement in the diagnostic testing of adult-type hypolactasia is needed.

Adult-type hypolactasia is inherited as an autosomal recessive trait leading to downregulation of lactase activity in the intestinal mucosa.17 It is the most common enzyme deficiency in humans with a varying age of onset ranging from 1–20 years in different ethnic populations. The condition is most prevalent in Asian and African countries with 1–18%.18 We have identified a single nucleotide polymorphism (SNP), a C to T change residing 13910 base pairs upstream of the lactase phosphorizin hydrolase (LPH) gene at chromosome 2q21–22 that shows complete association with the lactase non-persistence/persistence trait.19 The genotype C/C,13910 is associated with adult-type hypolactasia and genotypes C/T,13910 and T/T,13910 with lactase persistence. These three genotypes perfectly correlate with the level of the lactase activity in intestinal biopsy samples and their lactase:sucrase (L:S) ratio in several populations including Italians, Germans, and Finns.20–23 Furthermore, molecular epidemiological studies have shown that the prevalence of the C/C,13910 genotype is consistent with previously published figures of adult-type hypolactasia in several populations (for example, Koreans and African Americans).24 Additional molecular epidemiological studies on the frequency of the C/C,13910 genotype in >40 populations (>1300 individuals studied) is in full agreement with the previously published epidemiological data (unpublished data).

There is evidence that the C/T,13910 variant has a functional role in the expression of the LPH gene. Individuals with the persistent T,13910 allele show several times higher mRNA content of the LPH in their intestinal mucosa compared with that found in individuals with the non-persistent C,13910 allele, suggesting regulation of the LPH gene at the transcriptional level.25 This is in agreement with recent in vitro studies reporting greater increase in lactase promoter activity by the T,13910 variant.26 Another single nucleotide polymorphism, G/A,2018 residing about 8 kb telomeric to C/T,13910 has also been found to associate with the adult-type hypolactasia.

Abbreviations: CLD, congenital lactase deficiency; LM, lactose malabsorption; LPH, lactase-phlorizin hydrolase; LTT, lactose tolerance test; L:S, lactase: sucrase; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism.
hypolactasia genotype G/G -22018 indicating lactase non-persistence in 98% of cases.14 However, its induction of LPH promoter activity has recently been shown to be minimal.18 19

To investigate the applicability of the C/T -13910 variant in the diagnosis of adult-type hypolactasia we compared the C/C -13910, C/T -13910, and T/T -13910 genotypes to lactase activities and L:S ratios from intestinal biopsy specimens of 329 children representing several ethnic groups. The variant G/A -22018 was also analysed in order to further determine its role as a possible coregulator of the lactase activity.

**MATERIALS AND METHODS**

**Participants**

Intestinal biopsy specimens of 329 children undergoing upper gastrointestinal endoscopy because of abdominal complaints at the Hospital for Children and Adolescents, University of Helsinki between October 2001 and June 2003 were analysed for this study. Children receiving chemotherapy and children with gastrointestinal anomalies or a villous height to crypt depth ratio of less than 2:1 were excluded from the analysis. At the time of endoscopy, the families were asked to complete a questionnaire concerned with milk consumption and possible milk related symptoms.

The group consisted of 252 Finnish children (mean age 9 years; range 0.6–20.2 years; females, 127), 65 children of African origin (mean age 6.9 years; range 0.1–15.6 years; females, 34) and 12 children classified as other Whites (mean age 6.9 years; range 1.9–10.9 years; females, 6). All the children lived in Finland. Figure 1 shows the age distribution of the children in different ethnic groups. The study was approved by the Ethic Committee of the Hospital for Children and Adolescents, University of Helsinki. The families/children gave their informed consent.

**Assay of intestinal disaccharidases**

The activities of lactase, sucrase, and maltase were determined by a method based on that of Messer and Dahlqvist.16 All disaccharidase measurements were carried out at the Scientific Laboratory of the Hospital for Children and Adolescents, University of Helsinki. Samples with maltase activity <100 U/g protein were excluded as having low overall activities. We used a cut off point of 10 U/g protein for lactase activity and 0.2 for L:S ratio.15 16 Pathologists’ reports were reviewed in every case of lactase <20 U/g protein.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Finnish, n (%)</th>
<th>African, n (%)</th>
<th>Other White, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/C</td>
<td>37 (14.7)</td>
<td>62 (95.4)</td>
<td>9 (75.0)</td>
</tr>
<tr>
<td>C/T</td>
<td>137 (54.4)</td>
<td>3 (4.6)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>T/T</td>
<td>78 (31.0)</td>
<td>0 (0)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Total</td>
<td>252 (100)</td>
<td>65 (100)</td>
<td>12 (100)</td>
</tr>
</tbody>
</table>

**Table 1** Prevalence of the adult-type hypolactasia associated genotype C/T -13910 in African, Finnish, and other White children

**Genotyping**

DNA was isolated from intestinal biopsy specimens by phenol-chloroform extraction.21 The DNA fragments spanning the C/T -13910 and G/A -22018 variants, respectively, were amplified using one biotinylated (5’-CCTCGTAAATA CCCCAGCCTA-3’ for C/T -13910 variant and 5’-TGCTCA GGACATGCTGATCAA-3’ for G/A -22018 variant) and one unbiotinylated (5’-GTCACCTTGATATGAGGAGCA-3’ for C/T -13910 variant and 5’-TACCCATCGATAAGCCCTA-3’ for G/A -22018 variant) primer. The polymerase chain reaction (PCR) amplifications were carried out in a 50 µl volume with genomic DNA (100 ng), primers (20 ng each), dNTPs (200 µM) and 0.5 U of Taq polymerase in a standard buffer (Dynazyme, Finnzymes, Espoo, Finland). The PCR cycle conditions were as follows: an initial round of denaturation at 94˚C, then 35 cycles at 94˚C for 30 seconds, 53˚C for 30 seconds, 72˚C for 75 seconds, and a final extension of 72˚C for 10 minutes. Ten µl of the PCR product was captured in a streptavidin coated microtiter well (Thermo Electron, Helsinki, Finland); two parallel minisequencing reactions were carried out for each PCR product. The wells were washed and the bound DNA denatured. The minisequencing reaction contained 10 pmols of the corresponding minisequencing primer for the variant in question (5’-GGCAATGCTGATCAAAC-3’ for C/T -13910 and 5’-AAAAACAGCATCTCAGCTGGGC-3’ for G/A -22018). 0.1 µl of tritium labelled dNTP (Amersham Biosciences, Buckinghamshire, UK), and 0.05 U of DNA polymerase (Dynazyme II, Finnzymes, Finland). The microtiter wells were incubated for 15 minutes at 56˚C (reaction for C/T -13910 variant) versus 51˚C (reaction for G/A -22018), and finally the wells were washed. The detection primer was eluted, and the eluted radioactivity was measured in a liquid scintillation counter (Rackbeta 1209, Wallac, Finland).21

![Figure 1](http://gutjnl.com)
Table 2  Lactase activity and lactase: sucrase (L:S) ratio in Finnish children with T/T-13910, C/T-13910, and C/C-13910 genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Lactase activity (U/g protein)</th>
<th>L:S</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>T/T (n)</td>
<td>77 (99%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>C/T (n)</td>
<td>134 (98%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>C/C (n)</td>
<td>11 (92%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>0–5 years</td>
<td>6 (38%)</td>
<td>10 (63%)</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>0 (0%)</td>
<td>9 (100%)</td>
</tr>
</tbody>
</table>

Haplotype analysis of suspected congenital lactase deficiency patients was performed using 14 microsatellite markers covering approximately 5 cM of the critical CLD region on 2q21. Primer sequences of the analysed microsatellite markers are available upon request.

RESULTS

The prevalence of lactase genotypes in Finnish and non-Finnish children are shown in table 1. Among the 252 Finnish children, the prevalence of the genotype C/C-13910 defining adult-type hypolactasia was 14.7%. All but two of the children with the C/C-13910 genotype were also G/G homozygous for the G/A22018 variant. One of the two children heterozygous for the G/A22018 variant had low lactase activity (5 U/g protein) at the age of 10 years; the other had high lactase activity at the age of 5 years. In the other White children (n = 12) the prevalence of genotype C/C-13910 was 75.0%. In the African children, the prevalence of C/C-13910 genotype was 95.4%. The African children included 61 children of Somali origin, two Moroccans, one child from Cameroon, and one from the Congo. Among these 65 African children, only three (4.6%) had C/T-13910 genotype and none had T/T-13910 genotype.

In this study population, including Finnish and non-Finnish children, the mean lactase activity in children with the C/C-13910 genotype was 13.8 U/g protein, in children with the C/T-13910 genotype 33.1 U/g protein, and in those with the T/T-13910 genotype 50.4 U/g protein (p<0.0001, Kruskal-Wallis). The majority of children with the C/C-13910 genotype tested after the age of 8 years (40/43) had a lactase activity under 10 U/g protein. One African child with the C/C-13910 genotype had a lactase activity above 20 U/g protein (fig 2) and two Finnish children had enzyme activities within 10–20 U/g protein when tested after 8 years of age (fig 3). Among the children with the C/C-13910 genotype tested before the age of five, 67% (16/24) of Africans had lactase activities under 20 U/g protein compared with 25% (3/12) of the respective Finnish children (p<0.033, Fischer’s exact test), and 13% (3/24) had lactase activities under 10 U/g protein compared with 8% (1/11) of Finnish children (p value not significant). In the other White children with the C/C-13910 genotype (n = 9), the lactase activity had already dropped below 20 U/g protein at the age of 3 years in all but one child and below 10 U/g protein at the age of 6 years in every child (data not shown).

Lactase activities and L:S ratios in Finnish children with the C/T-13910 and T/T-13910 genotypes are shown in table 2. Three out of 142 children (2%) with C/T-13910 genotype and one of 79 with T/T-13910 genotype had lactase activity <10 U/g protein and normal histological examination of the villous architecture. One child of 14 months of age with T/T-13910 genotype had a very low lactase activity of 3 U/g protein and was diagnosed to have congenital lactase deficiency (CLD), which was confirmed by haplotype analysis in the CLD region (data not shown). An 11 year old girl with C/T genotype and unspecified abdominal pain had a very low lactase activity of 3 U/g protein and lactose intolerance (confirmed in LTT). Although her clinical history excluded CLD her haplotype on the CLD region was analysed. She was found to be a carrier of the Finnish major haplotype for CLD. The other two children with C/T genotype and low lactase (9 U/g protein) had continuous abdominal symptoms when on a low lactose

Table 3  Sensitivity, specificity, and predictive values for the C/C-13910 genotype defining low lactase activity in a series of 329 children. Lactase activity below 10 U/g protein was used as a cut off point for low enzyme activity

<table>
<thead>
<tr>
<th>Age group</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years (n = 109)</td>
<td>80.0</td>
<td>94.6</td>
<td>93.3</td>
<td>96.8</td>
</tr>
<tr>
<td>6–11 years (n = 142)</td>
<td>65.4</td>
<td>81.9</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>&gt;12 years (n = 78)</td>
<td>10.0</td>
<td>64.8</td>
<td>100.0</td>
<td>98.4</td>
</tr>
</tbody>
</table>

Table 4  Milk related symptoms and milk consumption in Finnish children with different genotypes of the C/T-13910 variant

<table>
<thead>
<tr>
<th>Genotype</th>
<th>C/C-13910</th>
<th>C/T-13910</th>
<th>T/T-13910</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lactase absorber n (%)</td>
<td>Lactose absorber n (%)</td>
<td>Lactose absorber n (%)</td>
</tr>
<tr>
<td>Answers</td>
<td>7 (10%)</td>
<td>42 (59%)</td>
<td>22 (31%)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>3 (43%)</td>
<td>13 (31%)</td>
<td>9 (41%)</td>
</tr>
<tr>
<td>from milk</td>
<td>1 (14%)</td>
<td>1 (2%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Verified milk allergy</td>
<td>1 (7%)</td>
<td>1 (2%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Suspicion of lactose intolerance</td>
<td>3 (18%)</td>
<td>5 (12%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Drinks milk</td>
<td>2 (29%)</td>
<td>25 (60%)</td>
<td>12 (55%)</td>
</tr>
<tr>
<td>&gt;2 dl/day</td>
<td>1 (14%)</td>
<td>16 (38%)</td>
<td>9 (41%)</td>
</tr>
<tr>
<td>1-2 dl milk/day</td>
<td>4 (57%)</td>
<td>1 (2%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Never drinks milk</td>
<td>1 (57%)</td>
<td>1 (2%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

*Compared with non-milk drinkers.
†Milk drinkers versus non-milk drinkers.
‡Lactose malabsorption confirmed in lactose tolerance test in two children.

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containing diet. The other boy aged 10 years was considered to have cow’s milk protein sensitive enteropathy and the other boy aged 14 years had unspecified episodic pain possibly related to food allergy.

With a reference value of 10 U/g protein, the sensitivity of the genetic test was 93% and specificity 80% in this group of 329 children. Lactase activity was decreased below 10 U/g in most children with C/C-13910 genotype at 8 years of age, and at this age the specificity was 97%. In children older than 12 years, the specificity was 100%. The sensitivity and specificity of the genetic test in different age groups are presented in table 3. The positive predictive value ranged from 10% in children <5 years of age to 65% in the age group of 6–11 years, and finally to 100% in children >12 years. The negative predictive value varied between 97–98% (table 3).

With an alternate cut off point of 20 U/g protein for low lactase activity the specificity of the genetic test is unaltered at the older age groups (data not shown).

Milk related symptoms and milk consumption in Finnish children with different genotypes are shown in table 4. The questionnaire about milk consumption and possible milk related symptoms was completed by 28% (71/252) of the Finnish families and a total of 35% of the children reported having symptoms caused by milk products. Children with the C/C-13910 genotype did not report significantly more symptoms from milk than children with the C/T-13910 or T/T-13910 genotypes. Lactose malabsorption had been diagnosed by lactose tolerance tests in two of these children, both with the C/C-13910 genotype. It is notable that no difference between genotype groups was seen in the numbers of the children for whom their parents suspected lactose intolerance but for whom the diagnostic work up had not been done (table 4). There was a significant difference in milk drinking habits between children with C/C-13910 or non-C/C-13910 genotypes (p<0.001, Fischer’s exact test). The majority, 57% (4/7) of the children with C/C-13910 genotype, reported that they never drank milk whereas only 3% (2/64) of children with C/T-13910 or T/T-13910 genotype did not drink milk at all (table 4). No data concerning milk consumption and milk related symptoms were available from non-Finnish speaking children.

**DISCUSSION**

Analysis of the C/T-13910 variant in 329 intestinal biopsy sample specimens representing several human populations showed 100% specificity and 93% sensitivity for the detection of adult-type hypolactasia in children >12 years of age. The results confirm our original findings and show the applicability of the C/T-13910 variant as a screening test for adult-type hypolactasia over age 12 years.

The prevalence figures for adult-type hypolactasia obtained in this study do not differ significantly from those reported in earlier studies. The frequency of 14.7% for C/C-13910 genotype in this study is somewhat lower compared with the population prevalence of 18% in anonymous Finnish blood donors. The prevalence of adult-type hypolactasia in Africans (95%) is well in agreement with the earlier published figures of 70–90% from Africa, as well as the prevalence in other Whites (75%) in this study with the
figures of 60–70% in the Mediterranean area from where the majority of the other Whites originate.26

Wide ethnic variation in the age of onset has been reported in adult-type hypolactasia.27–31 In black populations adult-type hypolactasia has been shown to manifest between 1–8 years of age, whereas in White populations low lactase levels are rarely seen in children under 5 years of age.27–31 Previous studies of the Finnish population, based on the lactose tolerance test, have shown adult-type hypolactasia to manifest up to 20 years of age.27 In most children with the C/C\_13910 genotype tested at 8 years of age and in all children tested at 12 years of age lactase activity had declined to <10 U/g protein in this study. The decline of the lactase activity in African children occurred somewhat earlier compared with Finnish children. The regulatory mechanisms for ethnic differences in timing of the downregulation of lactase activity are poorly understood. Interestingly, a fairly late downregulation of lactase activity in a subset of the African children is noticeable suggesting that the differences among genetically diverse populations (Africans and Finns) are smaller than previously reported.

Analysis of the C/T\_13910 variant was excellent in grouping the tested individuals according to the level of lactase activity in the intestinal mucosa—that is, lactase was low in those with the C/C\_13910 genotype and high in those with the T/T\_13910 genotype. The one child with a T/T\_13910 genotype and very low lactase activity (<10 U/g protein) was confirmed to have CLD. This rare autosomal recessive disorder enriched in the Finnish population is characterised by an earlier onset of the symptoms and an almost total lack of lactase activity, and is caused by an uncharacterised gene defect in the immediate vicinity of the lactase gene at 2q21–22.23 24

Three children with C/T\_13910 genotype had lactase activities of <10 U/g protein and normal villous structure. In two of these children, lactase activity was borderline (9 U/g protein) as well as the L:S ratio (0.21 and 0.22, respectively) and in one child the lactase activity was very low (3 U/g protein). This child with low value was a carrier of the Finnish major haplotype for CLD (unpublished results). The T\_13910 allele has been observed to be associated with the CLD haplotype (unpublished results), hence it can be assumed that the C\_13910 allele associated with developmental downregulation of lactase could underlie the very low lactase activity in this case.

In the diagnosis of adult-type hypolactasia, cut off points of 20 U/g, 10 U/g, and 8 U/g protein for lactase activity and 0.3 or 0.2 for L:S ratio have been used.4 15 20 21 Based on the results of this study all children with the C/C\_13910 genotype, regardless of ethnicity, had lactase activities below 10 U/g protein and an L:S ratio below 0.2 at 12 years of age. This is in agreement with our recent studies in the adult population where the lactase activity in subjects with the C/C\_13910 genotype varied from 4–9 U/g protein and L:S ratio from 0.05–0.18.31 In addition, in the present study the specificity of this genetic test was 100% with either a cut off point of 10 U/g or 20 U/g protein for low lactase activity in children >12 years of age. These data suggest that 20 U/g of lactase activity for diagnosing adult-type hypolactasia would be too high.

In addition to the C/T\_13910 variant we also assessed the other variant, G/A\_22018. Shown to be associated with lactase persistence,16 17 in all but two children with genotype C/C\_13910, this other variant was G/G\_22018. In these two children the genotype was G/A\_22018. One of them had high lactase activity at the age of 5 years. As the child was of Finnish origin, it is likely that the downregulation of lactase activity appeared later. The other child with G/A\_22018 genotype, aged 10 years, had a very low lactase activity, These cases together with the in vitro expression studies18 19 support the idea that C/T\_13910 is the only variant underlying adult-type hypolactasia, and G/A\_22018 residing only 8 kb from the C/T\_13910 variant is only in linkage disequilibrium with it.

A question frequently asked by parents and clinicians is: what is the amount of lactose tolerated in adult-type hypolactasia? We did not find any significant difference in symptoms from milk between children with the C/C\_13910 genotype and those with the non-C/C\_13910 genotype according to the results of a questionnaire survey. Children with the C/C\_13910 genotype, however, consumed significantly less milk compared with children with the non-C/C\_13910 genotype. These preliminary data reflect the complexity of abdominal complaints caused by milk seen also in earlier studies.12–14

Genetic testing of adult-type hypolactasia is a clinical aid in diagnosis of abdominal complaints in populations like those of Northern Europeans where the prevalence of adult-type hypolactasia is relatively high and consumption of dairy products common. In such populations genetic testing is of most value when the decline in lactase level is complete—for example, in Finnish children from 10–12 years onwards. In younger children, genotyping may help to exclude adult-type hypolactasia as a cause of abdominal symptoms. It should be noted that if parents are aware that their child has a C/C\_13910 genotype at a time when their lactase activity is high and/or when there are no symptoms of lactose intolerance this may have an undesired effect on the child’s nutrition.22

In conclusion, our results highlight the applicability of the genetic test for C/T\_13910 variant in the diagnosis of adult-type hypolactasia. This test is easily performed with a semi-automated analysis from a drop of peripheral blood without fasting,22 making this test suitable not just for diagnostic purposes at the individual level but also as a screening method for population studies. In our study parents had a positive attitude towards genetic testing of adult-type hypolactasia in their children and only a few refused to participate in the study. This further supports the usefulness and acceptance of this test as a first stage screening method for adult-type hypolactasia.

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A genetic test which can be used to diagnose adult-type hypolactasia in children


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