

Replication of the Recessive STBMS1 Locus but with Dominant Inheritance

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PURPOSE. Strabismus is a common eye disorder with a prevalence of 1% to 4%. Comitant strabismus accounts for approximately 75% of all strabismus, yet more is known about the less common incomitant disorders. Comitant strabismus is at least partly inherited, but only one recessive genetic susceptibility locus, on chromosome 7p, has been identified in one family. The purpose of this study was to determine the frequency of STBMS1 as a cause of primary nonsyndromic comitant esotropia (PNCE).

METHODS. Twelve families were recruited within the UK Hospital Eye Service as children attended for treatment of PNCE. All consenting persons were clinically assessed, and DNA was sampled. Chromosome 7 microsatellite markers were genotyped in all 12 families, and LOD scores were calculated under recessive and dominant models.

RESULTS. One family was linked to STBMS1; in three, linkage was significantly excluded; and the remainder were uninformative. Twenty-six members from three generations of the linked family were analyzed further. Five family members were defined as affected; two had esotropia with an accommodative element; and three underwent strabismus surgery and appeared to have had an infantile/early-onset esotropia. A maximum LOD score of 3.21 was obtained under a dominant mode of inheritance; a recessive model gave an LOD score of 1.2.

CONCLUSIONS. This study confirms that PNCE can result from sequence variants in an unknown gene at the STBMS1 locus. However, this locus accounts for only a proportion of cases, and other genetic loci remain to be identified. In contrast with

the previously reported family, the pedigree described in this study is consistent with dominant rather than recessive inheritance at the STBMS1 locus. (*Invest Ophthalmol Vis Sci.* 2009; 50:3210–3217) DOI:10.1167/iovs.07-1631

Strabismus, synonymous with heterotropia, squint, and tropia, is a common eye disorder with a prevalence of 1% to 4%.^{1–3} Strabismus can be subclassified into comitant and incomitant deviations whereby the angle of deviation is constant or the angle of deviation varies with either the position of gaze or the fixing eye. The most common form of strabismus is of the horizontal, comitant type.^{1,4,5} However, although comitant strabismus accounts for approximately three-quarters of all cases,¹ more is known about the underlying causes of the less common incomitant form. Genes and loci have been identified for incomitant deviations such as Duane syndrome, chronic progressive external ophthalmoplegia, and congenital fibrosis of the extraocular muscles.^{6,7} In contrast, for the more common comitant strabismus, only one recessive susceptibility locus has been identified, in a single family, on chromosome 7p.^{6,8}

Nevertheless, there is considerable evidence of a genetic basis for comitant strabismus. Clinically, it is readily observed that strabismus clusters within families. Hippocrates is often quoted as the first to describe a familial tendency in the inheritance of strabismus, with transmission from parent to child.^{9–14} Several studies have cited heredity as a risk factor for strabismus, specifically for accommodative esotropia,¹¹ intermittent and constant exotropia,¹⁵ and accommodative and partially accommodative esotropia.¹⁵ A large collaborative project reported that the odds of a sibling having esotropia more than doubled when another sibling was affected, but if a child had exotropia, a sibling was at risk for exotropia only if the children were from the same multiple birth.¹³ Twin studies have demonstrated increased monozygotic concordance of esotropia in a Caucasian female cohort in the United Kingdom (Hammond CJ, et al. *IOVS* 2002;43:E-Abstract 1465) and of accommodative esotropia and intermittent exotropia in a Japanese cohort.¹⁶

Furthermore, strabismus type has been noted to vary with race. A short report from the 1970s based on a Hawaiian cohort recorded that esotropia was more common in Caucasians, exotropia was more common in Asians, and esotropia and exotropia were approximately equally distributed in the racially mixed group.¹⁷ This early description regarding the racial distribution of strabismus is further supported by more recent studies, such as one in a Hong Kong Chinese population in whom exotropia was more prevalent than esotropia¹⁸ and another by Chew et al.¹⁹ who described being white as a risk factor for esotropia.

However, it is also evident that environment plays a significant role. The prevalence of strabismus is usually quoted as less than 5%, but when ascertaining a cohort that has been subjected to altered conditions during development, the prevalence of strabismus increases. Numerous authors have re-

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ported abnormalities in pregnancy²⁰⁻²⁴ and delivery,¹⁵ prematurity,^{25,26} low birth weight,²⁷ cortical insult,^{28,29} and craniofacial synostosis³⁰ as risk factors for strabismus. Furthermore, strabismus is frequently observed as a syndromic feature in which the prevalence may be as high as 50%.³¹⁻³⁵

To date there have been only two reported whole genome linkage screens for nonsyndromic strabismus. One, by Fujiwara et al.,³⁶ screened markers in a clinic-based series of 30 strabismic sibling pairs. However, this study was underpowered and revealed only a series of insignificant linkage peaks with no definite linkage. The second study, undertaken by Parikh et al.,⁸ identified potential strabismic families with multiple affected members. Strabismus status was construed from telephone conversations and retrospective analyses of medical records. Subjects were considered to be affected if they had obvious strabismus, underwent strabismus surgery, occlusion, or orthoptic exercises, or received a diagnosis of strabismus or amblyopia. This study,⁸ like the previous one,³⁶ did not distinguish between esotropia and exotropia. DNA of seven large families of European ancestry was sampled, with phenotypes recorded primarily by self-report, and family members underwent whole genome linkage analysis. One family, treated by the same clinician and whose affected members had esotropia that developed in infancy or childhood, demonstrated linkage of strabismus to chromosome 7p under a recessive model of inheritance. This locus was designated STBMS1. The remaining families showed no significant linkage to this or any other locus.

To determine the frequency of STBMS1 as a cause of primary nonsyndromic comitant esotropia (PNCE), we recruited and sampled 12 families with multiple members affected with PNCE. In these we tested 21 microsatellite markers regularly distributed along chromosome 7. Herein we report replication of the STBMS1 locus but with a dominant pattern of inheritance in a Northern Irish family with PNCE.

SUBJECTS AND METHODS

Subjects

Genomic DNA samples from 12 families with diagnoses of PNCE were analyzed in this study. Informed consent was obtained from all subjects tested; the research adhered to the tenets of the Declaration of Helsinki. Ethical approval was obtained from the Leeds East Research Ethics Committee, and the study received National Health Service, Research and Development consent.

As we sought to investigate the inheritance of PNCE, exclusion criteria were established before subjects were included in this study. These criteria were intended to minimize the genetic heterogeneity of the cohort by excluding potential environmental causes of strabismus. Exotropic strabismus was an exclusion criterion because it is not yet known whether the underlying mechanism is the same as that for esotropia. The other exclusion criteria were any incomitant deviation, any exotropia (except consecutive exotropia, in which the primary deviation was esotropia), any consecutive esotropia, esotropia secondary to another eye abnormality, esotropia secondary to brain or other neurologic abnormality, esotropia secondary to trauma, esotropia secondary to craniofacial/orbit anomalies, esotropia secondary to gestation less than 36 weeks, esotropia secondary to birth weight less than 1500 g, esotropia secondary to traumatic circumstances at birth, and syndromic esotropia.

All participants, affected and unaffected, were clinically assessed by one of the authors (AR or JH) with the exception of 16 persons for whom clinical reports were sought from the optometrist or orthoptist, original hospital records were consulted, or childhood photographs of those with esotropia that had been taken before strabismus surgery were examined.

Linkage Analyses

Genotyping was performed using fluorescently tagged microsatellite markers. PCR reactions were carried out in a 25- μ L volume with 50 ng genomic DNA, 20 pmol each primer (a fluorescent and an unlabeled primer in each pair), 200 μ M each dATP, dCTP, dGTP, dTTP, 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM MgCl₂, 0.01% gelatin, and 1 U *Taq* DNA polymerase (Invitrogen, Carlsbad, CA). After the initial denaturation step at 96°C for 3 minutes, the samples were processed through 35 cycles of 92°C for 30 seconds, 50° to 60°C for 30 seconds, and 72°C for 30 seconds. A final extension step was performed at 72°C for 10 minutes. After amplification, PCR products were resolved by capillary sequencing (ABI 377; Applied Biosystems, Foster City, CA) and were analyzed with appropriate software (GeneScan 2.0.2 and Genotyper 1.1.1; Applied Biosystems).

Haplotypes were constructed using pedigree drawing/genotype database software (Cyrillic version 2.1.3; Cherwell Scientific Publishers, Oxford, UK). LOD scores were calculated under recessive and dominant models, as detailed in Results. Linkage was undertaken with the programs GENEHUNTER and LINKMAP within the Genetic Linkage User Environment (GLUE) as hosted by the Laboratory for Interdisciplinary Technologies in Bioinformatics (LITBIO; <http://www.litbio.org/main.htm>). Marker-allele frequencies were based on 41 unrelated Caucasian persons of UK descent. The deCODE genetic map³⁷ was used for the selection of markers and to determine the genetic distances.

RESULTS

Linkage Analyses

Twelve UK families who had multiple members affected with PNCE were analyzed. To determine whether PNCE in any of these families showed linkage to STBMS1, 21 markers spanning chromosome 7 were tested for linkage, with multipoint LOD scores generated using the program GENEHUNTER. Markers (deCODE location) used were as follows: 7ptel-D7S2477 (0 cM)-D7S1819 (9 cM)-D7S2200 (20 cM)-D7S3051 (32 cM)-D7S1802 (35 cM)-D7S1808 (43 cM)-D7S817 (52 cM)-D7S2846 (59 cM)-D7S1818 (71 cM)-D7S3046 (82 cM)-D7S2204 (91 cM)-D7S820 (98 cM)-D7S821 (106 cM)-D7S1799 (113 cM)-D7S3061 (126 cM)-D7S1804 (138 cM)-D7S2202 (149 cM)-GATA104 (152 cM)-D7S3070 (166 cM)-D7S3058 (175 cM)-MFD442 (183 cM)-7qtel.

By observation, the mode of inheritance of nonsyndromic comitant esotropia within the pedigrees appeared dominant. However, the STBMS1 locus was reported under a recessive mode of inheritance.⁸ Multipoint analyses were therefore undertaken under both recessive and dominant models. To define appropriate parameters for dominant and recessive inheritance for PNCE, we made the assumption that STBMS1 accounted for approximately 20% of PNCE but that mutations at other unidentified loci accounted for the remainder of the trait. This estimate was based on the results of Parikh et al.,⁸ who reported linkage to STBMS1 for 1 of 7 families analyzed after whole genome scanning but did not clarify whether the remaining families significantly excluded, or were merely uninformative for, the STBMS1 locus. We further assumed that strabismus in this population had a prevalence of approximately 4% and that PNCE accounted for approximately 70% of strabismus in Caucasians,³⁸⁻⁴⁰ giving an overall prevalence for PNCE of approximately 2.5% in Caucasians. We estimated that sequence variants at the STBMS1 locus cause strabismus in approximately 0.5% of the Caucasian population. A dominant STBMS1 allele (or alleles) would thus be expected to have a frequency of approximately 0.0025, whereas a recessive allele would have a frequency of approximately 0.07. For dominant and recessive inheritance models, the phenocopy rate was

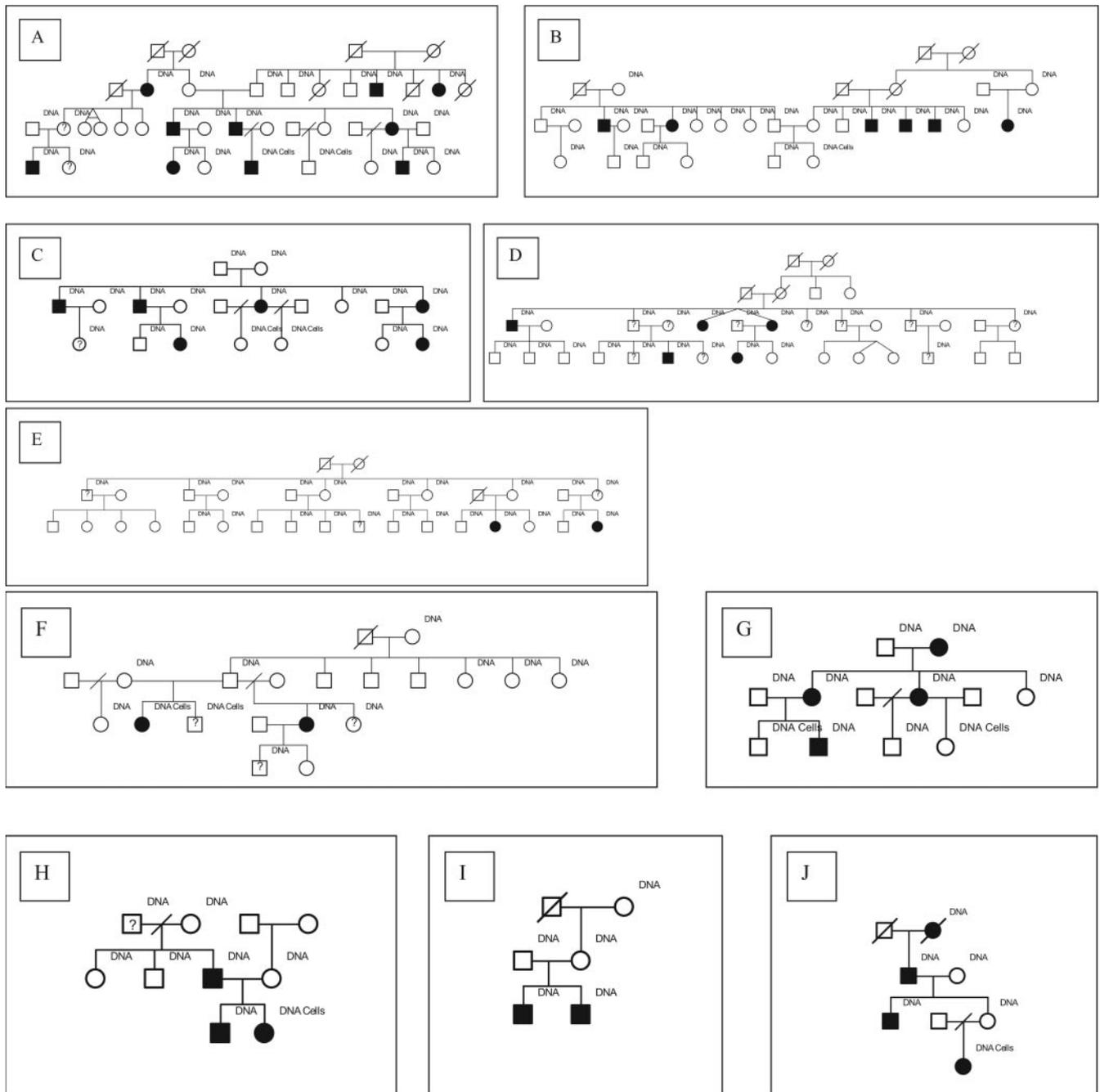


FIGURE 1. The 11 pedigrees (pedigrees A–J) included in the study in which no evidence of linkage to chromosome 7p was observed; pedigree B is an amalgamation of two pedigrees that were recruited separately. *Solid symbols*: individuals confirmed to be affected with PNCe. *Open symbols*: individuals confirmed to be unaffected. *Question marks*: individuals whose status was uncertain. All participants were Caucasian except for three of mixed race. DNA, DNA extracted from whole blood; DNA cells, DNA extracted from a buccal sample.

assumed to be 2%. Parikh et al.⁸ assumed a penetrance of 90% in their analysis, and we used the same figure of 90% penetrance in both models.

In 11 of the 12 families, no evidence of linkage to chromosome 7p was observed using the dominant model of inheritance described; these families are shown in Figure 1. Linkage to STBMS1 was significantly excluded in three of these families (families A, B and G; the power for exclusion in family B came from the right/maternal side of the family). LOD scores in the remaining families were not significant. Family C had an LOD score of 0.5; families D, H, I, and J had nonsignificant negative LOD scores; and families E and F were completely uninforma-

tive in the STBMS1 region. Only one family of Northern Irish origin demonstrated possible linkage to STBMS1 (LOD score 2.1). To confirm these findings, five additional microsatellite markers flanking the reported STBMS1 locus were genotyped in all 12 families, including five additional members of the putative STBMS1-linked family (Fig. 2). Markers (deCODE location) were 7ptel–D7S513 (23 cM)–D7S2557 (29 cM)–D7S2508 (31.37 cM)–D7S507 (31.51 cM)–D7S503 (34 cM)–7qtel.

Using data from all microsatellite markers analyzed, the maximum LOD score obtained for the pedigree with the program GENEHUNTER was 1.13 at 25 cM (Fig. 3) under a recessive mode of inheritance and 2.17 at 31 cM with a dominant

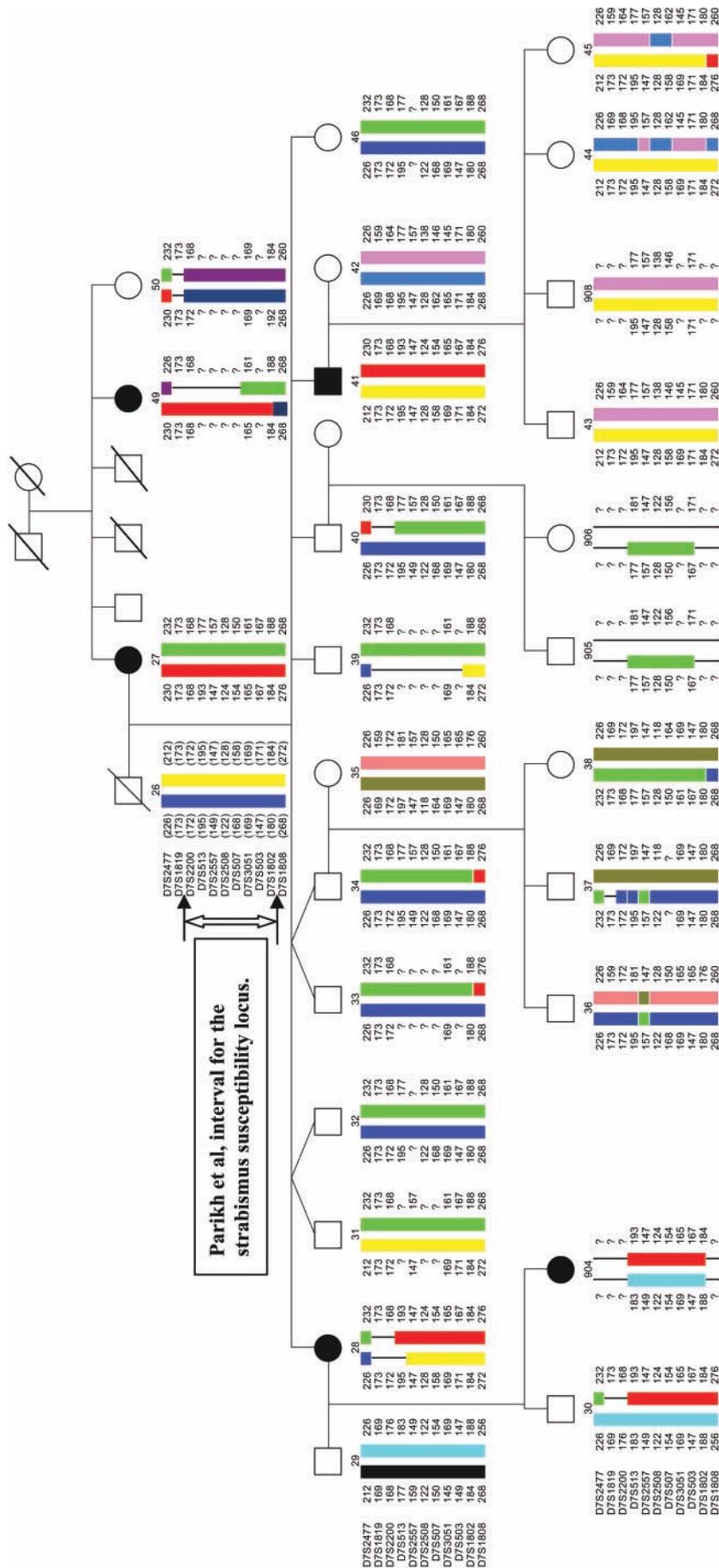


FIGURE 2. Pedigree of the autosomal dominant Pnce family analyzed in this study. *Solid symbols:* individuals confirmed to be affected with Pnce. *Open symbols:* individuals confirmed to be unaffected. Haplotypes spanning the STBMS1 locus are shown below each symbol. Each haplotype block is represented by a different color. The black line within the haplotype bars represents and 50 were genotyped for the first set of markers covering the whole of chromosome 7, but there was insufficient DNA to refine the genotyping in the second marker set within the STBMS1 locus.

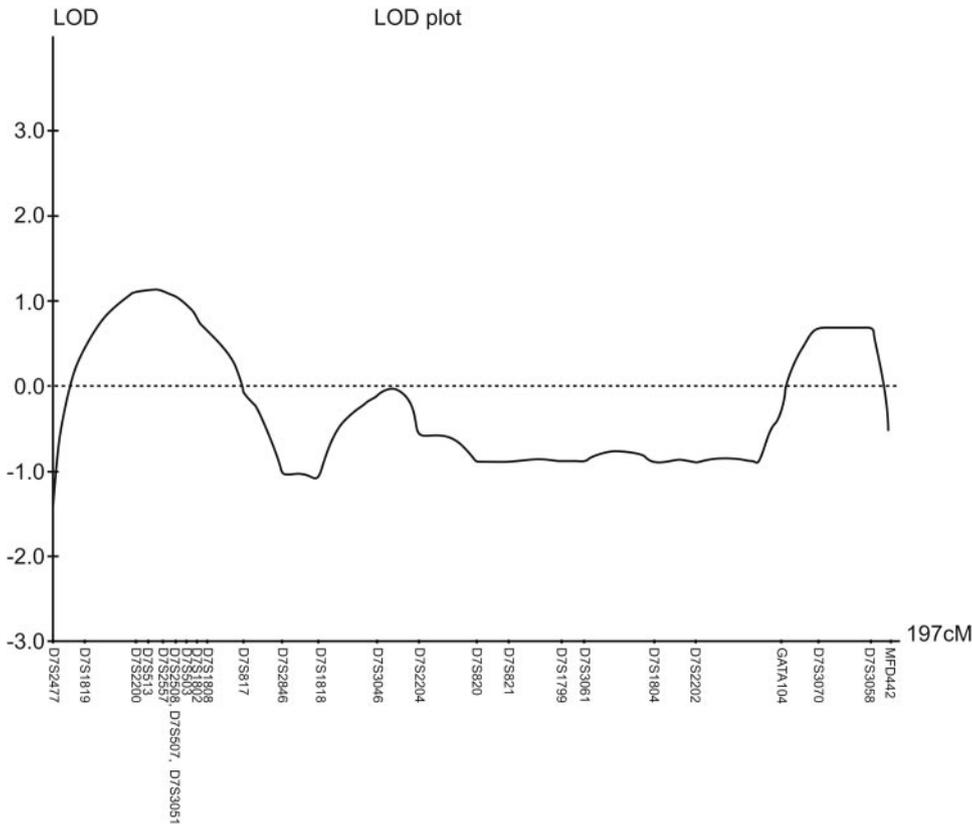


FIGURE 3. GENEHUNTER LOD plot under the recessive model for the PNCE family. Twenty-one microsatellite markers were spaced evenly along chromosome 7. Another six markers were clustered around the STBMS1 locus.

inheritance model (Fig. 4). The algorithm used in GENEHUNTER (Lander-Green algorithm) has limitations in the number of persons from the same pedigree who can be analyzed; large families are trimmed to reduce them to a smaller size. Thus, in this analysis, individuals 32, 30, 31, 33, 46, 37, 36, 908,

44, 45, 905, and 906 were dropped. Therefore, we undertook new multipoint analysis with another program, LINKMAP, based on the Elston Stewart algorithm, which easily handles large pedigrees without dropping any member but using a small number of markers. Four microsatellites (D7S507,

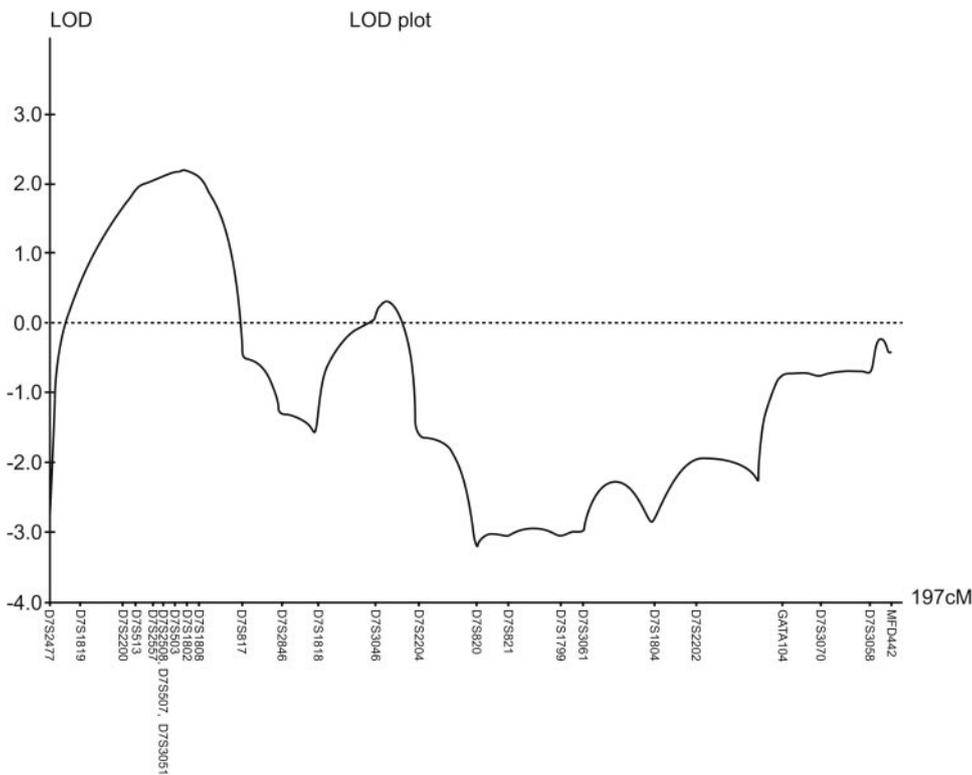


FIGURE 4. GENEHUNTER LOD plot under the dominant model for the PNCE family. Twenty-one microsatellite markers were spaced evenly along chromosome 7. Another six markers were clustered around the STBMS1 locus.

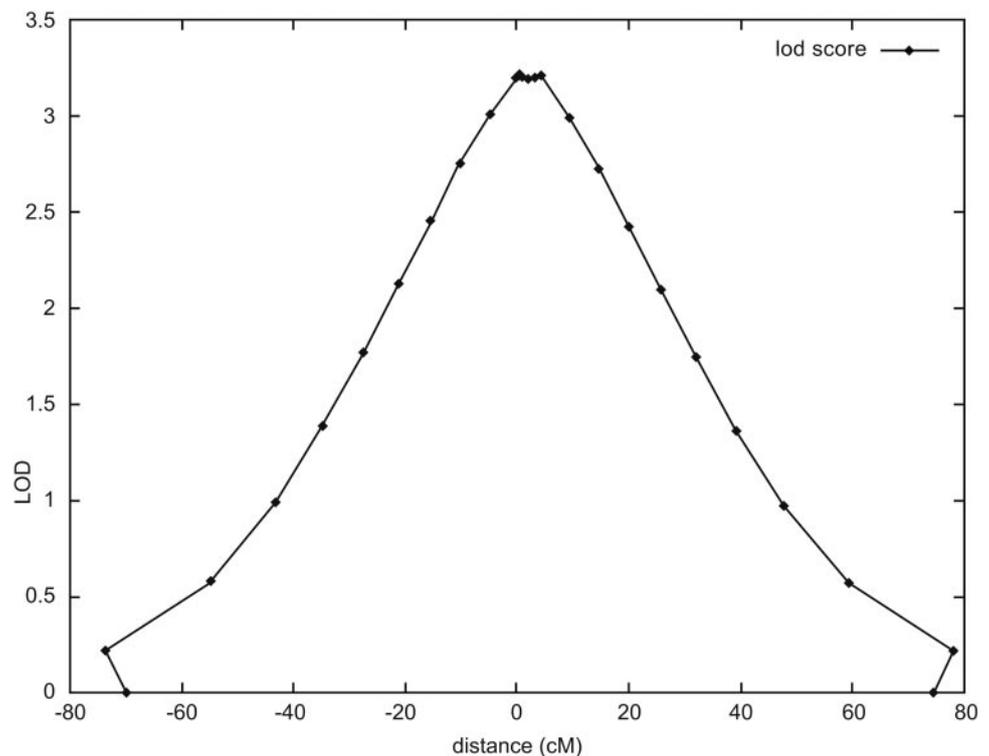


FIGURE 5. LINKMAP LOD plot under the dominant model for the Pnce family, using the microsatellite markers D7S507, D7S3051, D7S503, and D7S1802.

D7S3051, D7S503, D7S1802) lying in the region of maximum LOD score as given by GENEHUNTER were used. In this analysis of the full pedigree, a maximum LOD score of 3.21 was obtained in the same region as previously observed under the dominant model (Fig. 5). Similar analysis under a recessive model gave an LOD score of 1.2.

Given that we had hypothesized a penetrance of 90%, we undertook further analysis to examine the possibility that penetrance might have been overestimated in this and the previous study⁸ because of recruitment bias in the selection of large families. Analyses under a dominant model were rerun with penetrances of 0.8 and 0.7, giving maximum LOD scores of 3.08 and 2.93, respectively, still significantly higher than the level required for confirmation of a published locus.

Clinical Description

All members of the linked family except individual 32, whose phenotype was confirmed by a report from an optometrist, were assessed by one of the authors (AR or JH) (Table 1). Individuals 27, 49, 28, 41, and 904 had Pnce. Individual 27 has not undergone strabismus surgery, has worn spectacles since the age of 5, underwent occlusion therapy, has a current spherical equivalent of +7.50 DS (both eyes), and has primary esotropia with an accommodative component. Individual 49 has not undergone strabismus surgery, has worn spectacles from the age of 8, has a current spherical equivalent of +7.50 DS (both eyes), and has primary esotropia with an accommodative element. Individual 28 underwent strabismus surgery at age 10, stopped wearing spectacles at age 14, underwent occlusion therapy, and manifests residual esotropia. Individual 41 underwent strabismus surgery and occlusion therapy, has a current spherical equivalent of +0.25 DS right eye (RE) and +2.25 DS left eye (LE), and now has consecutive exotropia. Individuals 28 and 41 had primary esotropia before surgery, as confirmed by a review of family photographs; the original medical records have since been destroyed. Individual 904 underwent strabismus surgery (at 3 and again at 15 months of age) and occlusion therapy, has a current spherical equivalent

of +2.75 DS RE and +3.00 DS LE, and now has residual esotropia with an accommodative element. The primary deviation was infantile esotropia, as recorded in the original hospital record, before surgery. All other persons within the pedigree were found on examination to be unaffected. Of those persons defined as unaffected, only one had significant hyperopia, described as greater than +4.00 D.⁴¹ Individual 50 does not have Pnce and has a current mean spherical equivalent of +4.50 DS RE and +4.25 DS LE.

DISCUSSION

This study replicates linkage of Pnce to a region of chromosome 7p identified in a previous study as the STBMS1 locus. It also confirms that this locus accounts for only a proportion of cases and that other genetic loci remain to be identified. However, in contrast to the previous report,⁸ this study suggests dominant rather than recessive inheritance at the STBMS1 locus.

However, in both this study and the previous study, inheritance models were assumed rather than inferred because neither study had sufficient power to detect linkage and to prove the mode of inheritance. The best model in each case should therefore be considered an approximation of the true model. Nevertheless, findings in this study are consistent with dominant inheritance, suggesting that the recessive inheritance reported by Parikh et al.⁸ may not account for all STBMS1-linked Pnce families. Analysis of our data under a recessive model gives a positive but insignificant LOD score. This could imply that alleles at the STBMS1 locus can be dominant or recessive in their action, an observation that has been noted for other genes.⁴²⁻⁴⁵ Alternatively, it may imply complex inheritance, with the action of genes at other loci and environmental factors also contributing to the development of the condition. In these circumstances, STBMS1 alleles may be additive in their effect, contributing to a background of susceptibility to the trait. However, given that the trait in these families appears to

TABLE 1. Summary of the Clinical Findings for the Northern Irish Family Linked to the STBMS1 Locus

Individual	Right SE	Left SE	Strabismus	Strabismus Surgery
27	+7.50	+7.50	Primary esotropia with accommodative component	No
28	Plano	Plano	Primary esotropia	Yes
29	Plano	Plano	No	No
30	Plano	Plano	No	No
31	Plano	Plano	No	No
32	+2.25	Plano	No	No
33	+0.50	+1.50	No	No
34	Plano	Plano	No	No
35	Plano	Plano	No	No
36	Plano	Plano	No	No
37	+2.25	+2.00	No	No
38	+0.50	+4.00	No	No
39	+0.75	+0.25	No	No
40	+2.50	+2.75	No	No
41	+0.25	+2.25	Primary esotropia	Yes
42	-0.75	+1.00	No	No
43	Plano	Plano	No	No
44	Plano	Plano	No	No
45	Plano	Plano	No	No
46	-0.50	Plano	No	No
49	+7.50	+7.50	Primary esotropia with accommodative component	No
50	+4.50	+4.25	No	No
904	+2.75	+3.00	Infantile esotropia	Yes
905	Plano	Plano	No	No
906	Plano	Plano	No	No
908	Plano	Plano	No	No

Individual number refers to the pedigree (Fig. 2). Right SE, right eye spherical equivalent; left SE, left eye spherical equivalent.

fit a Mendelian model of inheritance, it is likely that STBMS1 alleles are major contributors to susceptibility in these families.

In contrast to previous genetic studies of strabismus,^{8,36} all family members who consented to this study either were examined by a study clinician or had a phenotype report completed by their own clinicians. Phenotype status was not dependent on verbal corroboration by the family member or a relative. Furthermore, every effort was made to refine the phenotype under investigation and to differentiate esotropia from exotropia; this meant that all family members who were scored as affected had PNCE.

All affected members of the STBMS1 family had primary esotropia. However, the five who were scored as affected did not all have the same subclassification of esotropia. Two siblings (27 and 49) had esotropia and an accommodative element associated with moderate hyperopia, whereas the remaining three (28, 41, 904) all had strabismus surgery and appeared to have had infantile/early-onset esotropia in association with mild hyperopia. The STBMS1 phenotype appears to vary in its expression in different persons, which may reflect environmental influences or the action of alleles at other susceptibility loci. This phenotype, with esotropia developed in infancy or childhood and some degree of hypermetropia, appears to be similar to that reported in the STBMS1 family described by Parikh et al.⁸

Eleven other families with PNCE were genotyped with the same marker set. Of these, three significantly excluded the STBMS1 locus (pedigrees A, B, G; Fig. 1). The remaining eight showed no significant evidence for linkage at the STBMS1 locus, confirming that PNCE does not result entirely from alleles at a single locus. Parikh et al.⁸ also reported six more families with strabismus unlinked to STBMS1. However, these families might have been unlinked to STBMS1 because they did not have primary esotropia given that no distinction was made between esotropia and exotropia. The Asian cohort reported by Fujiwara et al.³⁶ was too small to support any significant findings, and once again no distinction was made between

esotropia and exotropia. Nevertheless, based on this study and that of Parikh et al.,⁸ it appears that STBMS1 accounts for only a proportion of esotropia cases. It remains to be seen whether families with exotropia also map to this locus, suggesting that these two conditions are in fact allelic variants of the same phenotype, or whether esotropia and exotropia are genetically distinct.

A number of possible interpretations may be applied to the genotypes presented in Figure 2. However, a conservative evaluation of the haplotype data in our linked family suggests a 28-Mb interval defined by crossovers in individual 28 proximal to marker D7S2477 and in individual 49 distal to marker D7S1808. A similar analysis of the Parikh family suggests a 13-Mb interval between markers D7S1527 (located in the interval between markers D7S1819 and D7S2200) and 1931/1932 (approximately 100 kb proximal to D7S1802), as shown in Figure 2. Clearly, for a complex trait with incomplete penetrance and high phenocopy rate, such data must be interpreted with caution. Nevertheless, the fact that the smaller interval defined by the Parikh family lies fully within the larger interval defined in our linked family makes it highly likely that these families segregate PNCE because of alleles of the same gene. The 7p21.3-15.3 region is relatively gene poor, with only 33 annotated RefSeq genes in the 13-Mb region defined by a strict interpretation of haplotypes in the Parikh family. This observation, together with improvements in sequencing technology and confirmation of the locus in a second family, makes identification of the *STBMS1* gene a practical goal within the near future.

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