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Identification of an autosomal recessive stuttering locus on chromosome 3q13.2–3q13.33

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Abstract

Stuttering is a common speech disorder with substantial genetic contributions. To better understand the genetic factors involved in stuttering, we performed a genome-wide linkage study in a newly-ascertained consanguineous stuttering family from Pakistan. A linkage scan in this family using parametric linkage analysis revealed significant linkage only on chromosome 3q13.2–3q13.33, with a maximum two-point LOD score of 4.23 under an autosomal recessive model of inheritance.

Stuttering is a disorder of the flow of speech characterized by involuntary repetitions or prolongations of sounds or syllables, and by interruptions of speech known as blocks. While twin and family studies have suggested substantial heritability for this disorder, linkage studies have identified few highly significant linkage signals, and numerous suggestive linkage signals (Riaz et al. 2005; Shugart et al. 2004; Suresh et al. 2006; Wittke-Thompson et al. 2007). Because of marginally significant linkage scores and difficulties reproducing linkage observations across studies, we sought to increase the power to detect linkage using highly consanguineous families.

This study was approved by the Institutional Review Board (IRB) of the National Institutes of Health, USA (protocol number 97-DC-0057) and the IRB of the Center of Excellence in Molecular Biology, University of the Punjab, Lahore, Pakistan. Blood and speech samples were collected from all the available individuals of a consanguineous family (PKST77, Fig. 1), and written informed consent was obtained from each subject. Stuttering diagnosis was performed using the Stuttering Severity Instrument, 3rd edition (SSI-3) with individuals displaying severity scores above 16 (very mild) defined as affected. All individuals scored as affected were persistent stutterers, aged eight years or above who have stuttered for more than 6 months. A genome-wide linkage scan was performed using 6,090 SNPs assayed on

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the Illumina Human Linkage-12 Chip. Two-point parametric linkage analysis was performed using SuperLink v1.4 from the EasyLinkage v5.08 package (Hoffmann and Lindner 2005). The disease allele frequency was set at 0.01 and Caucasian allele frequencies provided by Illumina were used for the analysis. Due to the high degree of consanguinity in this family and in the Pakistani population, autosomal recessive inheritance was assumed. Significant evidence of linkage, with a LOD score of 3.23, was found at SNP rs7631540 on chromosome 3q13.31 (115.31 Mb) (Table 1). No marker showed significant linkage under either additive or dominant models of inheritance. The interval extending from markers D3S3044 (112.44 Mb) to D3S3636 (126.64 Mb) was genotyped with additional microsatellite and SNP markers. A two-point LOD score of 4.23 was obtained with the marker D3S1310 at 116.26 Mb (Table 1; Fig. 1). Multipoint analysis generated additional evidence for linkage, and an analysis including markers rs1317244, rs7631540, D3S1310, and D3S1303 under a recessive model generated a LOD score of 4.92.

One individual in PKST77 (#36) carries the stuttering-associated diplotype across part of this interval but he does not stutter. The genetics of stuttering are known to be complex (Suresh et al. 2006), and we hypothesize that this represents a case of non-penetrance, perhaps due to recovery from early childhood stuttering, both of which have previously been documented in this disorder (Kang et al. 2010).

A previous linkage study reported a nominal linkage on chromosome 3q, although somewhat more distally, at 192.02 Mb (Wittke-Thompson et al. 2007). A previous candidate gene association study of stuttering found a suggestive association with variants in the *DRD2* dopamine receptor gene (located on chromosome 11) (Lan et al. 2009). Another member of the dopamine receptor gene family (*DRD3*) is found in our linkage region. We sequenced all coding exons of this gene in all family members, however, no genetic variation was observed. In addition to the *DRD3* gene, there are 46 known and predicted genes in this region of chromosome 3q (3.24 Mb). Consanguineous families may provide a generally powerful resource for identifying linkage for this complex trait.

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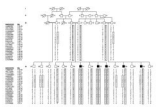

Fig. 1.
Pedigree of Pakistani stuttering family PKST77. Filled symbols represent affected individuals. Double horizontal lines represent the consanguineous marriage. The disease associated haplotype is shown in *vertical boxes*

Table 1

Two-point LOD score results for SNPs and microsatellite markers on chromosome 3q13.2–13.33

Markers	hg18 Physical	Two-point LOD score results at recombination fraction theta (θ)								
	Positions (Mb)	0	0.01	0.03	0.05	0.07	0.09	0.11	0.13	0.15
rs4682357	113.29	1.57	1.68	1.76	1.77	1.73	1.67	1.59	1.5	1.41
rs6773206	113.5	2.53	2.48	2.38	2.28	2.18	2.08	1.98	1.88	1.77
rs1317244	**113.53**	**3.13**	**2.75**	**2.65**	**2.54**	**2.43**	**2.32**	**2.2**	**2.09**	**1.98**
rs13062867[a]	113.6	0.73	0.94	1.14	1.22	1.24	1.23	1.19	1.14	1.08
rs950357	114.81	2.53	2.48	2.38	2.28	2.18	2.08	1.98	1.88	1.77
rs1025398	115.06	2.57	2.44	2.34	2.25	2.15	2.05	1.95	1.85	1.75
rs7631540	**115.31**	**3.23**	**3.16**	**3.02**	**2.88**	**2.73**	**2.59**	**2.45**	**2.3**	**2.16**
rs1039524	115.49	2.86	2.8	2.69	2.58	2.47	2.36	2.24	2.13	2.01
D3S1310	**116.26**	**4.23**	**4.15**	**3.97**	**3.79**	**3.61**	**3.43**	**3.25**	**3.07**	**2.88**
D3S1278	116.6	2.25	2.47	2.6	2.61	2.57	2.49	2.4	2.3	2.19
rs10511343	116.71	−0.68	−0.55	−0.37	−0.26	−0.18	−0.13	−0.08	−0.05	−0.02
rs714697[a]	116.84	1.53	1.74	1.87	1.87	1.83	1.76	1.67	1.57	1.46
D3S1579	117.42	1.43	1.66	1.83	1.88	1.88	1.85	1.8	1.74	1.66
rs4258973	118.11	1.11	1.32	1.48	1.52	1.51	1.48	1.42	1.35	1.28
rs2055426	118.7	0.87	1.1	1.28	1.34	1.35	1.33	1.29	1.25	1.19
D3S2460	118.88	2.71	2.7	2.65	2.56	2.46	2.35	2.23	2.1	1.97
rs1348969	119.54	2.45	2.4	2.31	2.21	2.12	2.02	1.92	1.82	1.73
D3S1303	**119.64**	**3.74**	**3.66**	**3.5**	**3.33**	**3.17**	**3.01**	**2.84**	**2.68**	**2.51**
rs1464311	119.68	0.09	0.09	0.08	0.07	0.07	0.06	0.05	0.05	0.04
D3S3515	120.01	−0.87	−0.74	−0.57	−0.45	−0.36	−0.3	−0.25	−0.21	−0.18
rs1147696	121.6	−0.46	−0.33	−0.17	−0.07	0	0.05	0.08	0.1	0.12

Markers in bold show significant two-point LOD scores

hg18 Human Genome Assembly 18

[a]Markers rs13062867 and rs714697 show the proximal and distal boundaries of the refined linkage region

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