A Whole-Genome Scan and Fine-Mapping Linkage Study of Auditory-Visual Synesthesia Reveals Evidence of Linkage to Chromosomes 2q24, 5q33, 6p12, and 12p12

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Synesthesia, a neurological condition affecting between 0.05%–1% of the population, is characterized by anomalous sensory perception and associated alterations in cognitive function due to interference from synesthetic percepts. A stimulus in one sensory modality triggers an automatic, consistent response in either another modality or a different aspect of the same modality. Familiality studies show evidence of a strong genetic predisposition; whereas initial pedigree analyses supported a single-gene X-linked dominant mode of inheritance with a skewed F:M ratio and a notable absence of male-to-male transmission, subsequent analyses in larger samples indicated that the mode of inheritance was likely to be more complex. Here, we report the results of a whole-genome linkage scan for auditory-visual synesthesia with 410 microsatellite markers at 9.05 cM density in 43 multiplex families (n = 196) with potential candidate regions fine-mapped at 5 cM density. Using NPL and HLOD analysis, we identified four candidate regions. Significant linkage at the genome-wide level was detected to chromosome 2q24 (HLOD = 3.025, empirical genome-wide p = 0.047). Suggestive linkage was found to chromosomes 5q33, 6p12, and 12p12. No support was found for linkage to the X chromosome; furthermore, we have identified two confirmed cases of male-to-male transmission of synesthesia. Our results demonstrate that auditory-visual synesthesia is likely to be an oligogenic disorder subject to multiple modes of inheritance and locus heterogeneity. This study comprises a significant step toward identifying the genetic substrates underlying synesthesia, with important implications for our understanding of the role of genes in human cognition and perception.

Results and Discussion

Synesthesia is a neurodevelopmental condition affecting between 0.05%–1% of the population[1–3] in which a stimulus in one sensory modality triggers an automatic, consistent response in another modality (e.g., sound triggers the perception of color)[4,5] or in a different aspect of the same modality (e.g., black text triggers the perception of color).[6,7] There is growing evidence that the simultaneous perception of normal and synesthetic percepts results in perceptual and cognitive dysfunction affecting linguistic[6] and numerical[8] processing, and in severe cases sensory overload can interfere with the ability of affected individuals to lead a normal life.[2,9] Conversely, synesthesia has been shown to result in "positive" cognitive alterations, including improved recall[10,11] and elevated performance on perceptual tests,[7] and has been anecdotally connected with absolute pitch (MIM 159300)[12] and eidetic memory.[9,13] Neuroimaging studies indicate that synesthesia results from altered neural connectivity, with confirmation of anomalous activation in brain regions involved in color processing when synesthetes are exposed to a synesthetic trigger[14] and observation of alterations in white matter that could indicate the existence of increased connectivity in the brains of synesthetes.[15]

The familiality of synesthesia was first noted by Sir Francis Galton in 1883.[16] Modern familiality studies show evidence for a strong genetic component, with >40% prevalence among the first-degree relatives of synesthetes.[1,2] Early pedigree analyses of families containing multiple synesthetes[2,17] supported the theory that synesthesia is a highly penetrant Mendelian disorder showing a major gene effect and a dominant (possibly X-linked) mode of inheritance. More females are affected than males, and there is a notable absence of confirmed cases of male-to-male transmission. However, further studies in larger samples indicate that the female predominance is not as great as previously believed and that the mode of inheritance is likely to be more complex.[1,18]

We conducted what is to our knowledge the first whole-genome scan for susceptibility genes linked to synesthesia in a sample of 43 multiplex families with auditory-visual synesthesia (n = 196, 121 affected, 68 unaffected, 7 phenotype unknown) recruited from the Cambridge Synaesthesia Research Group database. All auditory-visual synesthetes who had reported relatives with synesthesia on a preliminary screening questionnaire were contacted for a screening interview, and families with a history of neurological, ophthalmological, or psychiatric disorders or a positive drug history were excluded. Nineteen families (wave 1) were recruited during the initial recruitment period, and 24 families (wave 2) were recruited during the second recruitment period.

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Table 1. Loci with Multipoint NPL LOD Scores > 2 after Fine-Mapping of Potential Candidate Regions

Chr	Marker	Physical Position	Genetic Position (cM)	LOD	p value	Size of Linkage Peak (cM)
5	D5S436	5q32	150.91	1.08	0.013	
5	**D5S2090***	**5q33.1**	**153.6**	**2.3**	**0.0006**	**14.61**
5	D5S2049	5q33.3	165.52	1.82	0.002	
6	D6S282	6p21.1	69.99	1.83	0.002	
6	D6S1650	6p21.1	72.73	1.91	0.0015	
6	**D6S272***	**6p12.3**	**77.76**	**2.37**	**0.0005**	**13.03**
6	D6S257	6q12.1	83.02	1.63	0.003	
6	D6S460	6q14.1	94.44	1.17	0.01	
6	**D6S462**	**6q15**	**101.7**	**2.03**	**0.0011**	**11.01**
6	D6S300	6q16.1	105.45	1.24	0.008	
17	D17S798	17q11.2	58.69	1.79	0.002	
17	**D17S927**	**17q12**	**66.04**	**2.05**	**0.001**	**11.41**
17	D17S1814	17q12-21	70.1	1.27	0.008	

The data were generated in MERLIN 1.1a. Genetic position is the relative position from pter to qter in cM. The locus generating the highest LOD score for each peak is notated in bold. Asterisks indicate a locus meeting the Lander and Kruglyak criteria for suggestive linkage (LOD > 2.2). The size of a linkage peak is defined as the region encompassing a one-LOD drop on either side of the marker with the highest LOD score.

Clinical evaluation and phenotyping were performed with the Baron-Cohen et al. 1996 Test of Genuineness[2] (wave 1) and the Asher et al. Revised Test of Genuineness[19] (wave 2); an analysis of test results from nine individuals tested with both tests indicates that they are highly correlated ($r = 0.905$). Genomic DNA was extracted from blood (wave 1) or buccal swabs (wave 2) with Nucleon kits (Tepnel Life Sciences PLC) and from Oragene saliva kits (wave 2) (DNA Genotek). DNA samples underwent whole-genome amplification with GenomiPhi v2 (GE Healthcare). Written informed consent was given by all subjects, and where appropriate by parents or guardians. The study protocol followed the standards laid out in the Declaration of Helsinki and was reviewed and approved by the Local Research Ethics Committee of the Cambridge University Hospitals NHS Foundation Trust.

Prior to commencing the genome scan, we performed computer simulations in SLINK[20] using the best available data on prevalence and mode of inheritance to confirm the power of the sample to detect a major gene effect. The genome scan utilized 410 highly polymorphic microsatellite markers (mean intermarker distance = 9.05 cM (SEM = 0.21), with mean information content = 0.710 (SEM = 0.003). The Applied Biosystems (ABI) PRISM LMS v2.5 10 cM density microsatellite marker set supplied the core markers. Markers from the ABI LMS v2.5 5 cM marker set or custom markers designed with Primer3[21] were used when markers in the core set failed to produce usable genotypes after a minimum of three PCRs with at least two separate primer aliquots. Markers were also added to regions of the genome where information content was <60%. Genotyping was performed with ABI 377 and 3700 sequencing machines and GENESCAN/GENOTYPER software (Applied Biosystems). We used GAS v2.0[22] and PEDCHECK[23] to detect Mendelian inheritance errors and performed haplotype analysis with GENEHUNTER 2.0 and X-GENEHUNTER-PLUS v1.3.[24] We performed a final check for statistically unlikely genotypes with the error-checking algorithm in MERLIN/MERLIN-IN-X (MINX) 1.1a.[25]

An initial multipoint parametric linkage analysis was performed with MERLIN/MINX 1.1a under a dominant model constructed with pedigree analysis and the most conservative parameters from the available prevalence data. However, preliminary analysis indicated that the parametric model was a poor fit for the experimental data, suggesting genetic heterogeneity. Thus, a nonparametric approach was adopted for the full analysis of the genome scan.

Multipoint nonparametric linkage (NPL) analysis was performed with MERLIN/MINX 1.1a. Because of the relatively small number of families, the Whittemore and Halpern NPL_{all} statistic[26] was calculated with the Kong and Cox (1997) exponential function.[24] Fifteen potential candidate regions with LOD > 1 on 11 chromosomes (see Figure S1 and Table S1 available online) were detected. These regions were mapped further with additional microsatellites (mean intermarker distance 5.00 cM (SEM = 0.34), mean information content 0.78 (SEM 0.005) across fine-mapped regions). NPL analysis of the fine-mapped regions revealed four regions with LOD > 2, of which two had LOD > 2.2 on chromosomes 5q33 (D5S2090, LOD = 2.3, p = 0.0006) and 6p12.3 (D6S272, LOD = 2.37, p = 0.0005), the threshold for suggestive linkage put forth by Lander and Kruglyak[27] (see Table 1). All regions with LOD > 2 were supported by single-point LOD scores > 1 from at least three markers.

Additionally, a multipoint HLOD score analysis was performed with MERLIN under models derived from the best available estimates after pedigree analysis. Disease allele frequency was derived from published prevalence studies;[2,3] given that there is controversy regarding the prevalence of auditory-visual synesthesia (with estimates ranging from 0.05% to 1%), the conservative estimate was used (GF = 0.01). An examination of the pedigrees revealed a dominant inheritance pattern (see Figure S2). Given that skipping of generations has been observed in both our sample and those examined in the prevalence studies, the initial penetrance for the dominant model was set at 0.90, with further penetrances of 0.85, 0.75, and 0.65. Because a recessive mode of inheritance for a particular locus could not be ruled out entirely in the context of heterogeneity, a recessive model at penetrance = 0.75 was also tested. The following three models yielded the best fit: dominant with penetrance = 0.65, dominant with penetrance = 0.90, and recessive with penetrance = 0.75. The analysis was run with the fine-mapping data where available and data from the primary genome scan for the remainder of the genome.

Genome-wide empirical p values were calculated with the gene-drop function in MERLIN, with the null distribution estimated over all genetic models in each simulation to correct for multiple testing. One thousand replicates

Table 2. Loci with Multipoint HLOD Scores >2.03 Supported by Multiple Markers

Chr	Marker	Physical Position	Genetic Position (cM)	α	HLOD	Empirical p Value	Model, Penetrance	Single-Point HLOD	NPL (full sample)	NPL (contributing families)	Size of Linkage Peak (cM)
2	D2S151	2q22.3	165.9	0.487	2.577	0.153	dom, 0.90	2.622	0.73	2.13	
2	**D2S142**	**2q24.1**	**174.79**	**0.555**	**3.025**	**0.047**	**dom, 0.90**	**1.321**	**0.92**	**2.59**	**15.88**
2	D2S2330	2q24.3	181.78	0.448	2.442	0.202	dom, 0.90	1.751	1.01	3.03	
6	D6S1650	6p21.1	72.73	0.379	1.468	0.891	dom, 0.65	1.116	1.91	2.66	
6	**D6S272**	**6p12.3**	**77.76**	**0.407**	**2.272**	**0.275**	**dom, 0.65**	**2.002**	**2.37**	**3.10**	**10.29**
6	D6S257	6p12.1	83.02	0.341	1.181	0.988	dom, 0.65	0.680	1.63	2.80	
12	D12S310	12p12.3	39.13	0.438	2.675	0.118	rec, 0.75	1.038	0.95	1.55	
12	**D12S1617**	**12p12.1**	**48.09**	**0.484**	**2.849**	**0.073**	**rec, 0.75**	**2.226**	**0.23**	**0.94**	**14.92**
12	D12S345	12p11.2	57.58	0.346	1.562	0.835	rec, 0.75	1.593	0.10	1.20	

The data were generated in Merlin 1.1a. LOD = 2.03 is the threshold for suggestive linkage by gene-drop simulations. Data from the fine-mapping study were used for chromosomes 2, 5, 6, 8, 10, 11, 13, 15, and 17; data for all other chromosomes are from the primary genome scan. Alpha (α) refers to the proportion of families linked to that locus. Genetic position is the relative position from pter to qter in cM. The locus generating the highest multipoint HLOD score for each peak is notated in bold. Contributing families are those showing linkage to the HLOD peak. The size of a linkage peak is defined as the region encompassing a one-LOD drop on either side of the marker with the highest LOD score.

were generated under the null hypothesis of no linkage anywhere in the genome. The original pedigree structures and missing data patterns were retained to reflect the real data. Suggestive and significant linkage thresholds observed under the null hypothesis were calculated across the entire marker set. In accordance with the recommendations of Lander and Kruglyak, the cutoff for suggestive linkage was defined as the maximum LOD score expected to occur once per genome scan by chance alone (that is, 1000 LOD scores of equal or greater size were observed in 1000 simulations); the significant linkage threshold was defined as the maximum LOD score occurring with probability 0.05 in a genome scan (that is, 50 LOD scores of equal or greater size observed in 1000 simulations); and the highly significant linkage threshold was defined as the maximum LOD score occurring with probability 0.001 in a genome scan (that is, 1 LOD score of equal or greater size observed in 1000 simulations). The simulations yielded empirical genome-wide significance thresholds of 2.03 for suggestive linkage, 2.97 for significant linkage ($p < 0.05$), and 5.70 for highly significant linkage ($p < 0.001$). The empirical p value for a peak obtained with true data is determined by counting how often a simulated unlinked LOD score of greater or equal value to the observed result is seen in 1000 simulations.

The HLOD analysis revealed one region of significant linkage at D2S142 on chromosome 2q24.1 (HLOD = 3.025, empirical genome-wide p = 0.047) and three regions with evidence of suggestive linkage on chromosomes 6p12.3 (D6S272, HLOD = 2.272, empirical genome-wide p = 0.275), 12p12.1 (D12S1617, HLOD = 2.849, empirical p = 0.073), and 9q33.1 (D9S1776, HLOD = 2.473, empirical p = 0.188). A total of 23 regions obtained HLOD > 1 in this analysis; 12 of these, including the suggestive linkage peak on chromosome 6, were detected by the NPL analysis (see Tables S2 and S3). Single-point HLOD scores generated under the same parameters supported the results on chromosomes 2, 6, and 12 (see Table 2). However, the region on chromosome 9 was supported by only one marker in the single-point analysis, thereby raising the question of statistical artifact. For this reason, this locus was not considered a candidate region for the purposes of the discussion below. To further investigate the likelihood that the peaks detected by the HLOD represented real signals, we performed an additional set of NPL analyses focusing on the subsets of families contributing to each HLOD peak (see Table 2 and Figure S3). This analysis shows a significant increase in LOD score over the initial NPL analysis, indicating that the presence of significant heterogeneity at these loci was likely to have diminished the linkage signal in these regions and providing strong support for the HLOD result.

In sum, four candidate regions met criteria for suggestive or significant evidence for linkage with NPL or HLOD analysis. No support was found for linkage to the X chromosome in either analysis (maximum LOD = 0.62 in the NPL analysis). Furthermore, two families demonstrating what are to our knowledge the first confirmed cases of male-to-male transmission of synesthesia, with paternity verified through the genome scan, have been identified as part of this study (see Figure 1).

These findings have important implications for our overall understanding of the genetics of synesthesia, indicating that the genetic basis of synesthesia is rather more complex than originally believed. Rather than a single gene at a single locus, the results of the heterogeneity analysis support multiple modes of inheritance for different loci. The discovery of multiple peaks with relatively small genetic effects and the detection of significant linkage on chromosome 2q and suggestive linkage on chromosome 12p during the HLOD analysis when no significant linkage was found during the NPL analysis is consistent with a complex disorder with considerable genetic heterogeneity; the increase in the NPL LOD score observed when the heterogeneity in the sample was reduced provides further supporting evidence. This could potentially mean

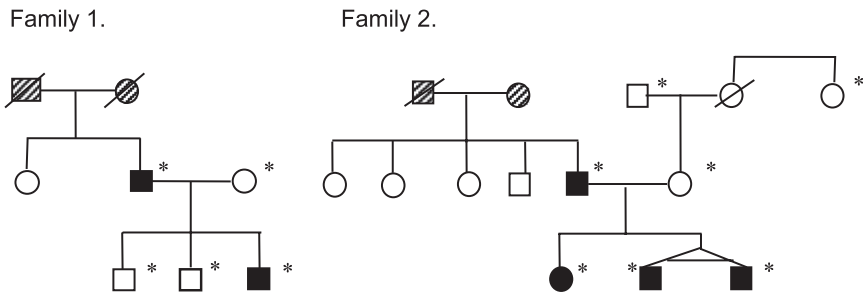

Figure 1. Pedigrees of Families with Male-to-Male Transmission of Auditory-Visual Synesthesia
Hatched = phenotype unknown. Asterisks indicate an individual from whom DNA was obtained.

a number of causative loci with different loci producing the clinical phenotype in particular families, consistent with findings in other neurodevelopmental disorders such as dyslexia (MIM 127700)[28] and specific language impairment (MIM 606711)[29] in which both epistatic (gene-gene) interactions and gene-environment interactions are believed to play an important role.

Distinguishing the true mode of inheritance will require significant further investigation that uses a much larger familial sample with precise phenotyping and subphenotyping and higher marker density. The use of additional phenotyping methods, notably neuroimaging, to further define subgroups within the synesthetic population would provide important additional information that could facilitate the search for susceptibility genes. However, even then it may not be possible to specify a single mode of inheritance for synesthesia; even if most cases are due to oligogenic inheritance, it is probable that there are individual families that show Mendelian inheritance, as in other neurodevelopmental disorders such as specific language impairment[30] and autism spectrum disorders (ASDs; MIM 209850).[31] The detailed analysis of such families with known chromosomal abnormalities or detectable copy-number variants may enable the identification of candidate genes and the delineation of pathways that play an important role in the etiological process.

Although the resolution of the scan makes identifying potential candidate genes within the candidate regions challenging, the uncertainty about the etiology of synesthesia makes the genetic location of the region of significant linkage of particular interest. The marker obtaining the highest LOD score (D2S142, with HLOD = 3.025) has been linked to autism.[32] Synesthesia is sometimes reported as a symptom in autism-spectrum disorders,[33] and sensory and perceptual abnormalities are a significant feature of ASDs.[34,35] Clinical reports indicate a potentially elevated prevalence of synesthesia among people with autism-spectrum disorders, as well as sensory overload similar to that reported by synesthetes (S.B.-C., unpublished data). Auditory stimuli trigger responses in both auditory and nearby visual brain regions in autistic individuals[36] as well as auditory-visual synesthetes.[14] Neuropathological studies have detected abnormally increased connectivity in the brains of individuals with autism,[37] and alterations in white matter that could indicate increased connectivity have been observed in the brains of synesthetes;[15] neuropathological studies of the brains of synesthetes would contribute significantly to the further elucidation of the underlying neural architecture. A recent case study indicates that savantism, long thought to be connected with autism, may in some cases result from the combination of autism and synesthesia.[38]

There are a number of interesting candidate genes in this region. *TBR1* (MIM 604616) induces the transcription of genes regulated by the T-box element,[39,40] including reelin (*RELN* [MIM 600514]), a gene that plays a vital role in the development of the cerebral cortex. Neuropathological examination of the brains of *tbr1* knockout mice shows abnormalities in the laminar organization of the cortex; these abnormalities could theoretically contribute to the altered neural connectivity observed in synaesthetes.[41,42] Defects in the sodium channel alpha-subunit genes *SCN1A* (MIM 182389) and *SCN2A* (MIM 182390), which encode voltage-gated sodium channels throughout the central nervous system,[43,44] have been identified as causes of generalized epilepsy with febrile seizures (MIM 604233) (*SCN1A*)[45,46] and benign familial neonatal-infantile seizures (MIM 607745) (*SCN2A*).[47,48] The pathogenesis of epilepsy as ectopic activity in the brain caused by underlying alterations in the connectivity and excitability of neuronal networks[49] has interesting implications for synesthesia, in which a lowered excitability threshold could result in increased crosstalk between neurons. Rare mutations of *TBR1*, *SCN2A*, and neighboring gene *SCN3A* have been observed in familial autism.[50,51] Other noteworthy candidate genes in this region include *GALNT13* (MIM 608369), a gene encoding a UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase that is expressed solely in neurons, in which it synthesizes GalNAc alpha-serine/threonine antigen,[52] and *ERMN* (MIM 610072), a homolog of the mouse gene *ermin* that is expressed exclusively on oligodendrocytes in mice and upregulated during the period of active myelination of CNS axons in rats.[53]

Interesting candidate genes for neurological and psychiatric disorders and CNS development are also located in the regions of suggestive linkage. The region on chromosome 6 detected by both NPL and HLOD analyses has been strongly linked to dyslexia and specifically to difficulties in phonological decoding and orthographic processing,[54,55] which is of particular interest given the importance of linguistic stimuli in synesthesia. Two genes

in this region, *KIAA0319* (MIM 609269)[56] and *DCDC2* (MIM 605755),[57] have been proposed as candidate genes for dyslexia; both have been shown to play roles in neuronal migration, which has important implications for synesthesia given the evidence for altered neural architecture in the disorder. This region has also been linked to juvenile myoclonic epilepsy (MIM 606904), and a causative gene (*EFHC1* [MIM 608815]) has been identified;[58] this gene plays a role in apoptosis, with the mutations seen in epileptic families lowering its apoptotic effect. A mutation with similar effect in synesthetes could play a role in the retention of neonatal synesthetic pathways.

The region on chromosome 12 detected in the HLOD analysis contains the N-methyl-D-aspartate (NMDA) receptor 2B subunit gene *GRIN2B* (MIM 138252). Of particular interest in the context of the eidetic aspects of synesthesia is the evidence that NMDA receptors play a vital role in long-term potentiation and the consolidation of learning and memory.[59] Mutations in this gene have been shown to affect both learning and memory stability, with overexpression resulting in enhanced learning and memory in mice,[60] which is particularly notable given new evidence for the role synesthesia may play in savantism.[38] It has been further linked to autism.[61]

The region on chromosome 5q identified in the NPL analysis includes *DPYSL3* (MIM 601168), a gene involved in neural plasticity, axonal growth and guidance, and neuronal differentiation.[62] In addition to being a good candidate given the known alternations in neural architecture in synesthetes, *DPYSL3* is highly expressed in the late-fetal and early-postnatal brain and spinal cord but not in the adult brain,[63] thereby making it an interesting candidate in the context of the evidence for a universal "neonatal synesthesia" that disappears over the course of normal development.

Formerly an obscure condition, synesthesia has attracted growing interest for its potential to advance our understanding of human cognition and perception. A greater understanding of the neural mechanisms underlying synesthesia will offer insight into typical as well as atypical cognitive development. Improved understanding of synesthesia has important implications for other neurodevelopmental disorders, many of which (e.g., autism spectrum disorders,[33] Williams-Beuren syndrome [MIM 194050][64]) involve abnormal sensory perception. Auditory-visual synesthetes link low musical pitches to dark colors and high pitches to light colors[5]—a pattern previously noted in nonsynesthetes—and similar trends have been detected in the grapheme-color pairings of synesthetes and nonsynesthetes,[65] implying that synesthesia stems from mechanisms common to all humans. Moreover, because synesthetic perception occurs in the absence of direct sensory stimulation, it may illuminate how the human brain integrates sensory data into conscious perception and may even shed light on the neural basis of consciousness.[66] The eventual identification and functional characterization of susceptibility genes linked to synesthesia will yield fundamental insights into the role of heredity in human cognition and perception.

Supplemental Data

Supplemental Data include three figures and three tables and can be found with this article online at http://www.ajhg.org/.

Acknowledgments

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Web Resources

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim

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