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ORIGINAL INVESTIGATION

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Quasi-linkage: a confounding factor in linkage analysis of complex diseases?

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Abstract Human linkage analysis is based on the assumption that unlinked genomic loci, particularly loci located on non-homologous chromosomes, segregate independently during meiosis. An exception to this rule is the phenomenon of quasi-linkage (QL) that describes the non-random segregation of non-homologous chromosomes, which can undermine the basic concept of linkage. Molecular mechanisms of QL are not clear; however, observations in mice and plants suggest a possible affinity between non-homologous chromosomal regions containing repetitive or like sequences. QL has not been investigated in humans. As QL may generate false linkages in genome scans of complex diseases, we sought to determine whether genomic loci detected in such genome scans exhibit QL. A number of individual markers showing linkage to schizophrenia, asthma, multiple sclerosis, inflammatory bowel disease and type-1 diabetes were tested for QL in a pairwise linkage analysis against all other markers exhibiting evidence for linkage in each specific study. The Marshfield genotype dataset of eight CEPH families was used for this purpose. The best QL lod scores generated from the analysis were within the range of the "lukewarm" lod scores reported in the majority of linkage studies for complex disorders. In addition, we performed a genome-wide QL analysis on the Marshfield family database which detected eight QL lod scores >6. The replication of the best Marshfield QL scores was performed using the deCODE families and although none of the eight pairs demonstrated independent evidence for QL, three pairs generated maximal lod scores of 0.11, 0.3, and 1.51. In conclusion, although complex disease relevant markers did not produce high QL lod scores, the general phenomenon of QL in humans cannot be excluded and potentially can be a confounding factor in genetic studies of complex traits.

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Introduction

Genetic linkage is based on the analysis of co-segregation of a genetic marker with another marker or a putative locus that determines a genetic trait. If two such markers (or marker and a trait) tend to be inherited together ($\theta<0.5$), the most likely explanation is that they reside in close physical proximity on a chromosome. Conversely, random segregation of two markers ($\theta=0.5$) indicates that the markers are located far apart on the same chromosome or on non-homologous chromosomes. Hence the generally accepted rule, known as Mendel's second law, is that during gamete formation segregation of the alleles of one allelic pair is independent of the segregation of the alleles of another allelic pair given that two pairs are not syntenic.

Nevertheless, exceptions to this rule have been observed on numerous occasions over the last three quarters of a century. To our knowledge, the first observation of departure from random segregation of markers on non-homologous chromosomes was made by Gates in 1926 in backcrosses between two strains of mice. Subsequently, this original observation was confirmed in two independent studies of crosses between different strains of house mice (Michie 1953). Subsequently a series of similar studies demonstrated this phenomenon in other species, primarily plants such as lettuce, peas, tobacco, beans and wheat (reviewed in Korol et al. 1994). The departure from independent assortment of non-syntenic genetic loci was termed quasi-linkage (QL). A detailed analysis of several thousand meioses in tomatoes revealed half a dozen of Q-linked loci that were statistically significant (Korol et al. 1994). In the era of molecular genetic markers, evidence for QL

was observed for non-homologous chromosomes of the wild emmer wheat (Peng et al. 2000). QL has not been directly demonstrated in humans. However, non-homologous associations that potentially may result in evidence for QL have been observed between the human acrocentric chromosomes (13, 14, 15, 21, 22, and Y) and between the acrocentric chromosomes and the nucleolus during mitosis and meiosis (Ferguson-Smith 1964). Similar associations were observed using C-banding patterns during prophase of meiosis between paired heterochromatic bodies in mouse (Hsu et al. 1971). 'Heterochromatic attraction' was observed between the paracentric regions of human chromosomes 1, 9, and 16 and the acrocentrics during mitotic metaphase (Schmid et al. 1975). Non-homologous chromosomal pairings and connections between C-heterochromatic regions of a number of bivalents were demonstrated during male meiotic prophase (Driscoll et al. 1979). It is thought that these associations are mediated by the highly repetitive loci of the 18S and 28S ribosomal RNA genes (located on chromosomes 13, 14, 15, 21, and 22) or by the satellite DNAs, which are the main constituent of C-heterochromatic regions. The similarity in the DNA sequence could mediate the association between the heterochromatic regions. In addition, chromosomes 15 and 22 were found to be involved in rearrangements with chromosome 9 more frequently in comparison to rearrangements with other chromosomes. Interestingly these three chromosomes are "packed" with more satellite DNA than any of the other autosomes (Driscoll et al. 1979). It has also been proposed that homologous but non-repetitive sequences could generate heterologous associations. These in turn give rise to non-homologous chromosomal/allelic segregation data that is falsely suggestive of linkage (Mike 1977). Although direct evidence of QL in humans is not available, evidence for this phenomenon in many other organisms suggests that QL may also be present in humans.

Putative QL raises questions about the consequences of Q-linked loci in linkage analysis of complex human diseases, an approach that, as a rule, detects linkage of numerous loci to the disease. QL may give rise to false linkage relationships, and so could act as a significant confounding factor when performing genome-wide linkage analysis and eventually applying positional cloning techniques. A large number of genome scans for complex diseases have been performed to date; a recent review estimates 101 genome scans for 31 complex human diseases (Altmuller et al. 2001). A majority of the initial linkage findings failed to be replicated and identification of concrete disease genes has been a major challenge to human biologists, with not many successful findings in complex non-Mendelian diseases. In this context the potential confounding factor of QL is relevant. What if some of the putatively disease linked loci are not disease-associated but result from QL to the truly linked ones? We were interested in determining if QL represented a significant confounding factor; that is, if Q-linked loci exhibited co-segregation with disease in genome scans for complex diseases and produced false linkage results.

Materials and methods

Disease relevant QL analysis

Eleven reports of genome scans in Caucasian populations for the complex diseases, type-1 diabetes (IDDM), inflammatory bowel disease (IBD), asthma, multiple sclerosis, and schizophrenia, were investigated for QL. Four to five of the best 'disease-linked' markers or regions exhibiting lod scores greater than 1 (or $P<0.01$) reported in the publications were considered, and markers chosen from the Marshfield dataset were used for the QL analyses. In order to increase the number of informative meioses, two markers with heterozygosity ≥0.75 flanking each 'disease-linked' marker were selected from the Marshfield genetic map (http://research.marshfieldclinic.org/genetics/; Broman et al. 1998). The map was generated using >8,000 short tandem repeat polymorphisms in eight large three generation families from Centre d'Etude du Polymorphisme Humain (CEPH) collection containing 188 meiosis. The distance between most of the markers specified in the reports and the Marshfield selected flanking markers ranged between 0 and 3 cM (sex average). The distance between markers was greater (up to 20 cM) if a broader region, spanning several cM, was specified in the reports as exhibiting linkage. The sets of markers representing linked loci were tested for QL in a pairwise linkage analysis against all other sets of markers exhibiting evidence for linkage in each specific disease. Maximum two point linkage analysis was performed using the computer program CRIMAP (Green et al. 1990) with sex-specific recombination fractions and the Marshfield genotype data for the eight CEPH families, 1331, 1332, 1347, 1362, 1413, 1416, 884 and 102 (http://research.marshfieldclinic.org/genetics/indexmark.htm). In total, 193 markers representing 49 genomic loci were analyzed for QL. Only pairs of non-syntenic markers identified in the same genome scan were compared; thus, we performed a test for linkage for 1,545 marker pairs.

Genome-wide QL analysis

In addition to the disease relevant marker QL analysis, we performed pairwise linkage analyses on all pairs of non-syntenic Marshfield markers in the eight CEPH families. The data consist of 8,010 markers and over 30-million pairs of non-syntenic markers. For each lod score male and female recombination fractions were estimated.

In the attempt to replicate the best genome wide QL results in the CEPH families, the deCODE dataset was used. The top seven of the eight Marshfield marker pairs (pair AFM210xh8 and GATA171A04 was omitted as an appropriate pair was not available in the deCODE genetic map) were re-analysed in 146 Icelandic families using the deCODE genetic markers. The deCODE dataset consists of 5,136 short tandem repeat polymorphisms in 146 Icelandic families containing 151 sibships (Kong et al. 2002). Two-point linkage analyses were performed as described above with sex-specific recombination fractions.

Results and discussion

In the disease relevant search for QL, 43 pairs of markers (2.8% of all pairs) from non-homologous chromosomes of the Marshfield dataset exhibited lod scores ≥1 (Table 1). The highest lod score of 2.23 (θ_F=0.31 and θ_M=0.35) was obtained for two markers on chromosomes 11p15.2 and 19p13.3, the markers exhibiting weak evidence for linkage to asthma (The Collaborative Study on the Genetics of Asthma 1997). Although the detected lods did not reach the level of statistically significant linkage and correction for multiple testing would further reduce the evi-

Table 1 Results of QL analysis in human complex diseases. The well-established linkage of type-1 diabetes to the *HLA* region at chromosome 6p21.3 (IDDM1) and insulin at chromosome 11p15 (IDDM2) was not taken into account in our analysis. There is some overlap in the investigated families for separate studies of type 1 diabetes as well as asthma. In total, 43 marker pairs generated lod scores greater than or equal to 1. Markers and regions indicated in *bold* lie in pericentromeric or subtelomeric regions of the respective chromosome *MF* multiplex families, *F* families, *ASP* affected sib-pairs

Disease (reference)	Sample	Results from genome scans		Results of QL analysis		
		Markers/region	Lod score or *P* value	Locus 1	Locus 2	Q-lod
Type-1 diabetes (Cox et al. 2001)	831 ASP	D16S3098/16q22-24	3.93	2q31.3-32.3	**16q23.1-23.3**	1–1.7
		D10S565/10p11.21	2.80	2q32.2-32.3	**10p11.22**	1.38–1.91
		D2S1391/2q32.2	2.62			
		IDDM15/6q21	2.36			
		1q42	2.2			
Type-1 diabetes (Concannon et al. 1998)	679 ASP	D1S1644-D1S1656/1q32.1-q32.3	1.78–2.84			
		D6S409-D6S264/6q24-26.1-q26	1.14–1.7			
		D6S283/6q21	3.51			
Type-1 diabetes (Mein et al. 1998)	356 ASP	D6S281-DK6Q27/6q27-qter	1.9	**10p13-10q11.21**	19p13	1.02–1.31
		D10S191-D10S220/10p13-q11	4.7	**10q11.21**	19q13.12	1.32
		D14S70-D14S276/14q12-q21	2.0	14q13.1-23.3	**16q22.2-24.1**	1.1–1.88
		D16S515-D16S520/16q22-q24	3.4	**16q22.2-24.1**	19p13.13-13.2	1.14–2.08
		D19S247-D19S226/19p13	1.7			
		D19S225/19q13	1.6			
Inflammatory bowel disease (Cho et al. 1998)	174 F	D1S552/1p36.13	2.65	D3S3053-3q13.32	D4S1647–4q22.2	1.1
		D3S3053-D3S2427/3q13.32-26.33	2.29	**D3S2427-3q26.33**	5q14.3	1.0
		D4S1647/4q22.2	1.71	**3q26.33**	4q22.2	1.24
		D5S1462/5q14.3	1.19	**3q27.2**	D5S1462	1.07
Inflammatory bowel disease (Satsangi et al. 1996)	186 ASP	D2S142/2q24.1	P=0.0021	2q23.1-24.1	12q13.3-15	1.41–1.6
		D3S1573/3p21.31	P=0.00021	3p21.31-21.33	12q15-21.33	1.01–1.5
		D7S484-D7S527/7p14.1-q22.2	P=0.000082	3p21.31	**7p11.2**	1
		D12S368-D12S95/12q13.13-21.33	P=0.00000027			
Asthma (The CSGA 1997)	79 F	11p15	1.22	**11p15.2**	**19p13.3**	1.71–2.23
		19p13.3	1.8	**11p15.2**	19q13.13	1.14
		19q13	1.97	**11p15.2**	**13q33.3**	1.02
		6p21.3-23	1.08			
		12q14-24.2	1.5			
		13q21.3-qter	1.9			
		14q11.2-13	1.39			
Asthma (Xu et al. 2001)	129 F	D6S1281/6p21	1.91	**8p23.1**	**20p13**	1.51
		D8S1130/8p23	1.06			
		D19S198/19q13	1.02			
		D20S473/20p13	1.07			

Asthma (Wjst et al. 1999)	97 F	D2S2298/2pter	*P*=0.007			
		D6S291/6p21.3	*P*=0.008			
		D9S1784/9q13	*P*=0.007			
		D12S351/12q13	*P*=0.01			
Multiple sclerosis (Ebers et al. 1996)	100 ASP	D2S119/2p21	1.24			
		D3S1309/3q22.2	1.01			
		D5S406/5p15.32	4.24			
		D11S2000/11q22.2	1.38			
		DXS1068/Xp21.2	1.85			
Multiple sclerosis (Sawcer et al. 1996)	129 F	17q22-17q24.2	2.85			
		6p21.33-6p21.32	2.9			
Schizophrenia (Blouin et al. 1998)	54 MF	D13S174/13q32	4.18	**13q32.3**	D14S306/14q13.2	1.361.11
		D8S1771/8p21-22	3.64	D14S306/14q13.2	22q12.2	
		D14S306/14q13	2.57			
		D7S2212/7q11	2.50			
		D22S1265/22q12.3	2.42			

dence for QL, some of the lod scores may still be within the range of the majority of "lukewarm" reports of linkage in complex non-Mendelian diseases. For example, markers mapping to the IDDM regions 2q31.3-32.2 and 16q23.1, respectively, exhibited pairwise lod scores ranging between 1 and 1.7.

Since it has been shown that non-homologous chromosomes may form connections between C-heterochromatic regions and be a possible factor generating QL, we checked the band locations of the putatively Q-linked genomic regions that are listed in Table 1. None of the bands mapped to C-heterochromatic regions. Sequence similarities in non-homologous chromosomes are certainly not limited to C-heterochromatic regions and may originate through trans-chromosomal duplications that spread among non-homologous chromosomes with a particular bias towards the pericentromeric (e.g., 2p11, 10p11, 15q11, 16p11, and 22q11) and subtelomeric regions (Horvath et al. 2000; Ji et al. 2000). In our study, at least one marker from 34 marker pairs that generated QL lod scores ≥1 fall within the pericentromeric and subtelomeric regions and these are indicated in *bold* in Table 1. Of these, the following regions, 20p13, 7p11.2 and 10p11, are known to be sites of duplication (Horvath et al. 2000; Ji et al. 2000).

In the genome-wide QL investigation, approximately 3% of the pairs of markers exhibited lod scores above 3.0, and eight pairs demonstrated lod scores above 6.0 (Table 2). The largest lod score was 6.75, for the marker pair D9S1116 and D20S842. Results for all marker pairs giving lod scores >3.00 the genome wide QL study are available at http://www.biostat.jhsph.edu/~kbroman/data/. None of the markers with lod scores greater than 6 lie in the C-heterochromatic region; however, a number of them do fall within subtelomeric regions. The marker pairs mapping to chromosome 9 and chromosome 20 with the largest lod score of 6.75, 6.55 and 6.39 map to chromosome 20p13, a region known to have duplications, and chromosome 9, which has been observed in heterochromatic attraction (Schmid et al. 1975) and involved in chromosomal rearrangements (Driscoll et al. 1979). Due to the very large number of marker-marker tests, the QL results should be interpreted with caution. In an attempt to replicate our initial QL findings, we investigated seven of the eight Marshfield marker pairs in 146 Icelandic pedigrees using deCODE genetic markers (Table 2). Three sets of markers led to negative lod scores (lod=0, $\theta_{F;M}$=0.5), and therefore did not replicate the Marshfield QL data. The QL scores for the other three sets of markers, however, were more positive and varied from 0.3 (θ_M=0.0; θ_F=0.5) to 1.51 (θ_M=0.0; θ_F=0.5) for the markers D1S462 and D14S1432, D5S459 and DXS6793, respectively. Although the replication lod scores were not very high, QL cannot be excluded in the three out of six tested pairs of markers (Table 2).

In conclusion, in our study the disease relevant loci did not provide strong evidence for QL, however, the genome wide QL analysis suggests that QL may be operating between some chromosomal regions in humans. Identification of more than one region of linkage to a specific trait

Table 2 Results of genome-wide QL analysis

Marker pairs with lod scores greater than 6 – CEPH families and the Marshfield dataset			Icelandic families and the deCODE dataset		
Marker 1/region	Marker 2/region	QL lod score (θ-female; male)	Equivalent of marker 1	Equivalent of marker 2	QL lod score (θ-female; male)
GATA65D11/9q33.3	AFMa175vb1/20p13	6.75 (0.29; 0.19)	D9S1116	D20S842	0 (0.50:0.50)
AFM286yc5/9q33.2	AFMa131wf1/20p13	6.55 (0.31; 0.14)	D9S275	D20S199	0 (0.37:0.50)
AFM210xh8/8q21.12	GATA171A04/9q21.33	6.46 (0.19; 0.26)	No appropriate markers in the deCODE		
AFM286yc5/9q33.2	AFMa175vb1/20p13	6.39 (0.29; 0.14)	D9S275	D20S842	0 (not informative)
GATA113H03/1p21.1	GATA151F02/8p23.1	6.38 (0.15; 0.36)	GATA133A08[1]	GATA151F02	0 (0.49:0.50)
AFM063ya5/5q14.3	ATA14A02/Xq13.2	6.36 (0.22; 0.11)	D5S459	DXS6793	1.51 (0.50:0.001)
AFM331vb1/1p22.1-p21.3	GATA151F02/8p23.1	6.30 (0.17; 0.37)	D1S2819[2]	GATA151F02	0.11 (0.25:0.49)
AFM126xa1/1p31.2	GATA192E08/14q21.1-q21.2	6.01 (0.09; 0.3)	D1S462	D14S1432	0.3 (0.50:0.001)

[1]deCODE marker GATA133A08 used instead of Marshfield marker GATA113H03
[2]deCODE marker D1S2819 (AFMc026yf1) used instead of Marshfield marker AFM331vb1

may be an indication to test for QL between the markers that are putatively linked to a trait. Dedicated reference maps of quasi-linked loci of human and other genomes would be of significant help to the scientific community.

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