

Genetic susceptibility to non-insulin dependent diabetes mellitus and glucose intolerance are located in HLA region

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Abstract

Objectives—To test the hypothesis that the genetic susceptibility to non-insulin dependent diabetes mellitus is the same as that to insulin dependent disease and to see whether glucose intolerance is associated with specific HLA haplotypes.

Design—Population based study of men in 1989 first tested for glucose tolerance in 1984. HLA haplotypes, including HLA-A, C, B, DR, and DQ, were defined serologically. HLA haplotype data from a population based Finnish study of childhood diabetes were used for predicting non-insulin dependent diabetes and impaired glucose tolerance.

Setting—Two communities in Finland.

Subjects—Representative cohort of Finnish men aged 70-89, comprising 98 men with non-insulin dependent diabetes mellitus and a randomly selected group of 74 men, who served as controls, who were tested for glucose tolerance twice within five years.

Main outcome measures—Non-insulin dependent diabetes, impaired glucose tolerance, blood glucose concentration.

Results—Diabetes associated HLA haplotypes were present in 94% (85/90) of diabetic subjects, 79% (27/34) of subjects with impaired glucose tolerance, and only 13% (3/23) of non-diabetic subjects. In this group of elderly men sensitivity of the diabetes associated HLA haplotypes for non-insulin dependent diabetes and impaired glucose tolerance was 90%, specificity 87%, and predictive power 97%. Mean fasting blood glucose concentration was only just significantly higher in men with diabetes associated haplotypes than in men with no such haplotypes, but there was a substantial difference in blood glucose values two hours after glucose loading (10.4 and 6.4 mmol/l in men with diabetes associated HLA haplotypes and men with no such haplotypes, respectively ($p < 0.0001$)).

Conclusions—These findings support the hypothesis that specific HLA haplotypes exhibit a common genetic determinant for insulin dependent and non-insulin dependent diabetes. Furthermore, HLA is a major genetic determinant of glucose intolerance in elderly Finnish men. The belief that the HLA predisposition to diabetes is specific for insulin dependent diabetes mellitus is largely incorrect.

Introduction

Both non-insulin dependent diabetes mellitus and insulin dependent diabetes are multifactorial diseases with a strong genetic basis.¹⁻⁴ Progress in identifying genes involved in non-insulin dependent diabetes mellitus has been disappointingly slow. This is in contrast with the rapid advances in insulin dependent diabetes mellitus, in which the major genetic susceptibility can be explained by associations with HLA

genes located on chromosome 6.⁵⁻⁷ Phenotype studies of non-insulin dependent diabetes mellitus in white people have failed to find an association with HLA. This has been used as an argument that non-insulin dependent and insulin dependent forms of diabetes mellitus are genetically separate entities.⁷⁻¹⁰ That there may be a common genetic basis between insulin dependent and non-insulin dependent diabetes mellitus has been suggested by several investigators. In 1950 Harris suggested that the difference between the two types of diabetes could be ascribed to a double dose of the gene in insulin dependent disease and a single dose of the gene in non-insulin dependent disease.¹¹ Furthermore, familial clustering of the two types of diabetes has been observed.^{12,13}

Finland has the highest incidence of insulin dependent diabetes mellitus in the world.¹³⁻¹⁵ We have recently characterised the genetic susceptibility to insulin dependent diabetes mellitus in this ethnic group in a nationwide population based prospective family study—"childhood diabetes in Finland."^{13,16} Non-insulin dependent diabetes mellitus in the adult population of Finland is also common, and a considerable proportion of elderly Finns have non-insulin dependent diabetes mellitus or impaired glucose tolerance.^{17,18} Taken together with the fact that the population of Finland is genetically homogeneous, it is an ideal country in which to test the hypothesis that genetic factors responsible for insulin dependent and non-insulin dependent diabetes mellitus are the same.

The rationale that insulin dependent diabetes mellitus associated HLA haplotypes might also confer susceptibility to non-insulin dependent diabetes mellitus came from two observations. Firstly, seven of the 11 non-insulin dependent diabetes mellitus parents (nine fathers, two mothers) in the childhood diabetes in Finland study had transmitted insulin dependent diabetes mellitus associated high risk haplotypes to their insulin dependent diabetic offspring (table I). Secondly, 80% of non-diabetic family members who carried the insulin dependent diabetes mellitus associated high risk HLA-A2,Cw1,B56,DR4,DQw8 haplotype had a family history of non-insulin dependent diabetes mellitus. This haplotype has been found only in Finnish insulin dependent diabetes mellitus patients, in whom it confers the highest haplotype specific absolute risk of insulin dependent diabetes.^{16,19}

Using HLA haplotype data from the childhood diabetes in Finland study, we tested the hypothesis that the genetic susceptibility to non-insulin dependent diabetes mellitus does not differ from that to insulin dependent diabetes mellitus.

Subjects and methods

Of a cohort of 1711 men born in two Finnish communities between 1900 and 1919 who were included in a multinational prospective cardiovascular

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disease study, 716 were tested for glucose intolerance.¹⁷ In 1989, when the oral glucose tolerance test was repeated, the men were 70-89 years old—that is, old enough for most of the potentially diabetic subjects to have developed the disease. The participation rates in these surveys were over 90%. The survey procedures have been described.^{17,20-22} In 1984 the blood glucose concentration was determined throughout the day for a capillary blood sample with a glucometer refractometer, and in 1989 it was determined in venous plasma with a Beckmann glucose analyser in the morning after an overnight fast.

METHODS OF HLA TYPING

Blood specimens were collected for HLA typing

TABLE 1—Diabetes associated high risk HLA haplotypes in Finnish elderly men. Results expressed as numbers of subjects

HLA haplotype						Diabetic status of elderly men			
						Non-insulin dependent diabetes (n=186)	Impaired glucose tolerance (n=68)	Unclear (n=44)	Non-diabetic (n=46)
A	C	B	Bw	DR	DQ				
<i>37 Haplotypes transmitted from parents with insulin dependent diabetes or shared among haploidentical affected siblings</i>									
2	1	56	6	4	8	3	1	0	0
3	1	56	6	4	8	1	0	0	0
2	3	60	6	4	8	3	1	0	0
24	3	60	6	4	8	2	0	0	0
28	3	60	6	4	8	1	0	0	0
2	3	62	6	4	8	7	1	1	1
3	3	62	6	4	8	2	0	1	0
24	3	62	6	4	8	0	0	0	0
2	4	62	6	4	8	2	0	0	1
2	7	18	6	4	8	1	1	0	0
3	7	18	6	4	8	1	0	0	0
30	5	18	6	4	8	1	0	0	0
1	7	8	6	3	2	5	4	0	2
2	7	8	6	3	2	1	3	1	0
3	7	8	6	3	2	2	0	0	0
28	7	8	6	3	2	4	2	2	0
24	3	8	6	3	2	0	0	0	0
33	8	14	6	3	2	1	0	0	0
24	3	71	6	4	8	0	0	0	0
24	7	39	6	4	8	0	0	0	0
32	7	39	6	4	8	1	1	0	0
2	4	35	6	4	8	1	0	0	0
3	4	35	6	4	8	5	1	0	0
24	x	51	4	4	8	0	1	0	0
2	7	44	4	4	8	3	2	0	0
3	7	44	4	4	8	0	0	0	0
28	7	44	4	4	8	3	0	0	0
32	x	44	4	4	8	1	0	0	0
2	6	13	4	4	8	0	0	0	0
3	6	13	4	4	8	0	0	0	0
2	7	7	6	4	8	0	0	0	0
3	3	7	6	1	5	0	0	0	0
24	3	62	6	1	5	1	0	0	0
2	3	60	6	2	6	2	0	0	0
3	3	18	6	5	7	0	0	0	0
2	6	13	4	7	2	1	2	0	0
2	4	62	6	8	4	1	0	0	0
<i>2 Haplotypes transmitted from parents with non-insulin dependent diabetes</i>									
3	7	7	6	6	6	4	3	1	0
24	7	39	6	8	4	1	0	0	0
<i>18 Other diabetes associated haplotypes*</i>									
2	1	56	6	6	6	1	0	0	0
3	1	56	6	8	4	1	1	0	0
2	3	60	6	1	5	2	0	0	0
2	3	60	6	8	4	2	1	0	0
3	3	60	6	4	8	2	0	0	0
3	3	62	6	6	6	1	1	0	0
24	3	62	6	1	5	1	0	0	0
2	4	62	6	6	6	1	0	0	0
28	3	62	6	1	5	2	0	0	0
2	1	62	6	4	8	1	0	0	0
2	3	62	6	8	4	4	1	1	0
24	7	8	6	3	2	1	0	0	0
24	1	39	6	4	8	1	0	0	0
2	x	51	4	4	8	3	0	1	0
2	1	44	4	4	8	1	0	0	0
24	x	44	4	4	8	2	0	0	0
3	7	7	6	4	8	2	0	0	0
2	7	7	6	6	6	2	1	0	0

*Originated from insulin dependent diabetes mellitus associated haplotypes by substitution of one allele only.

from the 98 living men who had been classified as diabetic in the 1984 survey and from 74 controls who had been classified as non-diabetic in 1984 (normal or impaired glucose tolerance). Controls were selected by using simple random sampling. In 1989 the mean body mass indices (weight (kg)/height (m²)) were 26.4 and 25.8 in diabetic men and controls, respectively, and the mean age was 77 years in both groups.

HLA-A,C,B,Bw,DR,DQ phenotypes were determined serologically in the 172 unrelated men by using 180 HLA antisera (120 class I, 60 class II) and the same test as in the childhood diabetes in Finland study.¹⁶ In three diabetic men DR and DQ results were not clear. DQ was defined either serologically or with sequence specific oligonucleotides or by nucleotide sequencing.^{19,23} All observed HLA phenotypes were transformed into the two most probable HLA haplotypes by two different algorithms—one taking known linkage disequilibrium into account and one assuming that all allelic combinations are equally possible. The assignments were based on 3528 Finnish haplotypes derived directly from 3314 HLA genotyped members of 882 different Finnish families¹⁶—namely, 757 families with a newly diagnosed insulin dependent diabetic child from the childhood diabetes in Finland study and 125 non-diabetic control families. Four locus (A, C, B, and DR) haplotype frequencies and three point delta values between the A, B, and DR loci were calculated.²⁴

DEFINITION OF DIABETES ASSOCIATED HAPLOTYPES

In the childhood diabetes in Finland study HLA haplotypes were determined in 757 newly diagnosed children with insulin dependent diabetes aged 14 or under and their families nationwide.^{13,16} Whole HLA haplotypes determined serologically by alleles of the class I loci A, C, and B and the class II loci DR and DQ were used as markers for susceptibility to insulin dependent diabetes mellitus. High risk insulin dependent diabetes associated HLA haplotypes were defined as those haplotypes which had been seen in families either as the haplotype transmitted from a parent with insulin dependent diabetes (66 families) to a child also with insulin dependent diabetes or as the haplotype shared among haploidentical siblings with insulin dependent diabetes (19 families) (table I). These high risk insulin dependent diabetes associated haplotypes carry the susceptibility gene (or genes) for insulin dependent diabetes except in the rare cases of recombination between the haplotype and the disease susceptibility locus (or loci). Thirty seven thus defined different high risk insulin dependent diabetes associated haplotypes were identified (table I). These 37 haplotypes explained the genetic susceptibility to insulin dependent diabetes in 83.8% (634/757) of the probands in the childhood diabetes in Finland study under the hypothesis that one high risk haplotype is sufficient to confer susceptibility to the disease.

Many of the haplotypes found in the 119 probands in the childhood diabetes in Finland study who did not carry the 37 high risk insulin dependent diabetes associated haplotypes differed from the high risk haplotypes by only one allele at either the A, C, or DR locus (table I). Eighteen of these haplotypes—all found to confer risk of insulin dependent diabetes in the childhood diabetes in Finland study or other studies—were also found in elderly Finnish men with non-insulin dependent diabetes and impaired glucose tolerance. As these 18 haplotypes undoubtedly originated from high risk insulin dependent diabetes associated haplotypes by substitution of one allele, they were also considered to be diabetes associated. Two additional haplotypes (HLA-A3,Cw7,B7,Bw6,DR6,DQ6 and A24,Cw7,B39,Bw6,DR8,DQ4) transmitted from a parent with non-insulin dependent diabetes to a child

with insulin dependent diabetes (table I) were also considered to be diabetes associated. Thus there were 57 diabetes associated haplotypes defined by the above criteria.

Glucose tolerance status in men was defined according to World Health Organisation criteria¹⁰ as: (a) diabetes (n=90) when the criteria for diabetes were met either in 1984 or in 1989 (in 1984, 15 of the diabetic men were treated with oral agents and one with insulin; in 1989, 19 were treated with oral agents, two with insulin, and two with both); (b) impaired glucose tolerance (n=34) when the WHO criteria for impaired glucose tolerance (but not diabetes) were met either in 1984 or in 1989 and the patients had not been given hypoglycaemic drugs; and (c) normal glucose tolerance (n=23) when both oral glucose tolerance tests (in 1984 and 1989) gave normal results. Men whose glucose tolerance status had not been determined either in 1984 or in 1989 (n=22) and the three men whose DR and DQ typing results were inconclusive were excluded from some analyses. Thus 147 men were classified by glucose tolerance status according to WHO criteria.

We predicted glucose tolerance status by using HLA haplotype data in the 147 men, who were classified into two groups—(a) men with diabetes associated haplotypes as defined in tables I and II (n=114); (b) men without any diabetes associated haplotypes (n=33).

STATISTICAL ANALYSES

HLA status (diabetes associated HLA haplotypes or no diabetes associated HLA haplotypes) in the 172 HLA phenotyped elderly men was assigned as diabetes associated when at least one of the 57 diabetes associated haplotypes was present, and as not diabetes associated when none of the diabetes associated haplotypes were present.

Differences in HLA antigen frequencies between diabetic men and men with normal glucose tolerance were tested by χ^2 test with Yates's correction or Fisher's exact test and appropriate correction for the number of comparisons. We used analysis of variance to compare fasting and two hour post-challenge blood glucose values in men with diabetes associated HLA haplotypes with those in men who had no diabetes associated HLA haplotypes. Because the blood glucose distributions were skewed to the right logarithmic transformation of the data was used.

Results

In 131 of the 147 elderly men (89%) for whom biochemical data were complete the diagnosis was correctly predicted by the HLA haplotype data (table II). Diabetes associated haplotypes were present in 94% (85/90) of diabetic men, 79% (27/34) of men with impaired glucose tolerance, and in only 13% (3/23) of non-diabetic men ($\chi^2=65.4$; $p<0.0001$). Sensitivity (probability of correctly identifying men with diabetes or impaired glucose tolerance associated with HLA haplotypes) was high for diabetic men (90%).

TABLE II—Prediction of abnormal glucose tolerance status by HLA. Results expressed as numbers of subjects

HLA haplotypes	Glucose tolerance status			Total
	Diabetes	Impaired glucose tolerance	Normal	
Diabetes associated	85	27	3	115
No diabetes associated	5	7	20	32
Total	90	34	23	147

Sensitivity was 90%, specificity 87%, and positive predictive power for diabetes associated HLA haplotypes 97%. In two non-diabetic men two alternative haplotypes (one diabetes associated, one non-diabetes associated) were equally probable. They were therefore allocated one per each HLA haplotype status category.

TABLE III—Mean and standard deviations of blood glucose concentration (geometric values) by year and HLA haplotype status

Year	HLA haplotypes				F value	p Value
	Diabetes associated		No diabetes associated			
	No	Mean (SD)	No	Mean (SD)		
<i>Fasting blood glucose (mmol/l)</i>						
1984	99	5.7 (2.0)	33	5.2 (1.1)	3.01	0.085
1989	95	6.4 (2.5)	32	5.8 (2.0)	4.17	0.043
Average	95	6.1 (2.0)	32	5.5 (1.4)	4.45	0.037
<i>Two hour post-challenge blood glucose (mmol/l)</i>						
1984	82	11.7 (2.8)	31	7.2 (2.8)	71.68	<0.0001
1989	79	9.3 (4.1)	24	6.1 (3.1)	22.31	<0.0001
Average	74	10.4 (2.7)	23	6.4 (2.0)	64.04	<0.0001

Specificity (probability of correctly identifying non-diabetic men by absence of diabetes associated HLA haplotypes) was also high (87%). The predictive power for diabetes associated HLA haplotypes to detect abnormal glucose tolerance was 97%.

Analysis of the elderly men restricted to the 37 different high risk insulin dependent diabetes associated haplotypes (rather than the full 57 diabetes associated haplotypes) still showed a highly significant difference among the three strata of men. Sixty three (70%) men with non-insulin dependent diabetes, 11 (32%) men with impaired glucose tolerance, and four (9%) non-diabetic men had an insulin dependent diabetes associated haplotype ($\chi^2=34.2$; $p<0.00001$).

HLA ANTIGEN FREQUENCIES

Neither HLA-A nor B antigen frequencies differed among the three strata of men (diabetic, impaired glucose tolerance, normal (data not shown)). The frequency of DR4 was significantly higher in diabetic men (57%) than in non-diabetic men (13%) ($p=0.003$, corrected for the number of comparisons made).

BLOOD GLUCOSE CONCENTRATION AND HLA HAPLOTYPES

Mean fasting blood glucose concentration was significantly higher ($p=0.037$) in men with diabetes associated HLA haplotypes than in men with no diabetes associated HLA haplotypes (table III). The two hour glucose challenge resulted in only a moderate rise in blood glucose concentration in men with no diabetes associated HLA haplotypes (mean value at two hours 6.4 mmol/l compared with 5.5 mmol/l fasting). In men with diabetes associated HLA haplotypes the shift in blood glucose distribution was pronounced (mean value at two hours 10.4 mmol/l compared with 6.1 mmol/l fasting). The difference in two hour post-challenge blood glucose concentration between the two strata according to HLA haplotype status was highly significant ($p<0.0001$).

Discussion

Our study shows common HLA susceptibility genes for insulin dependent diabetes mellitus, non-insulin dependent diabetes mellitus, and impaired glucose tolerance in the Finnish population. Most of the HLA haplotypes which carried a high risk of insulin dependent diabetes also carried risk of non-insulin dependent diabetes in this group of elderly men. As most people with genetic susceptibility to insulin dependent diabetes never develop the disease, a proportion of the general population carry the susceptibility genes for insulin dependent diabetes. From the non-diabetic control families in the childhood diabetes in Finland study we estimate this proportion to be about 20-25% of the Finnish population. These people are likely to develop abnormal glucose tolerance in old age.

We have also shown the value of defining haplotypes (by analysis of HLA-A, B, C, DR, and DQ as a whole) compared with the use of phenotypes (analysis of the same loci but each considered separately). Thus by using HLA diabetes associated haplotypes we identified almost all elderly men with diabetes (94% compared with 13% of controls), whereas only half of the diabetic men were identified at the DR locus (57% of diabetic men compared with 13% of controls possessed DR4) and no differences were found for HLA-A, B, C when considered separately. This may partly explain why in other studies which have been restricted to use of phenotypes only weak and inconsistent associations have been found between HLA phenotypes and non-insulin dependent diabetes.

Class I associations with non-insulin dependent diabetes have been reported in Xhosas (A2),²⁵ Pima Indians (A2),²⁶ Asian Indians (B61),²⁷⁻²⁹ West Indian blacks (B40),³⁰ Finns (Cw4),³¹ Chinese (B45),³² Nauruans (early onset; B56),³³ and Papuans (B62).³⁴ In most of these studies those HLA antigens which are the most commonly seen in non-insulin dependent diabetic patients were also frequent in the background population. Furthermore, in certain isolated ethnic groups the background population shows a restricted HLA polymorphism and a high degree of homozygosity. For instance, in the Pima Indians only four HLA-A locus antigens are found, of which A2 and A24 are the most common, with frequencies of around 49%.³⁵ Actually, A2 and A24 antigens were found in several diabetes associated HLA haplotypes in the Finnish population.

Our cohort of elderly men in Finland is renowned for its high incidence of and mortality from cardiovascular disease.^{20,22} Selection through cardiovascular disease mortality may indeed have removed some of the subjects with certain high risk insulin dependent diabetes associated HLA haplotypes. Four such haplotypes, all of which carried A24 and DR4,DQ8, were not seen in elderly men with non-insulin dependent diabetes. The importance of such selection is not known and warrants investigation.

A major problem in studies of genetics of non-insulin dependent diabetes has been that they have included people who may have been too young to develop diabetes. This weakens the probability of finding a true association. Secondly, many studies have used only known diabetic patients as index cases, leaving a considerable number of people with abnormal glucose tolerance among the "non-diabetic" groups. In our study the probability of such a misclassification was small. It is also unlikely that our patients had insulin dependent rather than non-insulin dependent diabetes, as most had been treated by diet alone over the five years. Furthermore, basal C peptide concentrations in those subjects tested were not compatible with the diagnosis of insulin dependent diabetes. Whether the factors determining glucose intolerance are the same in elderly men compared with middle aged men and women needs to be tested.

Our data suggest that the major histocompatibility complex contains a gene (or genes) which influences glucose homeostasis. We suggest that susceptibility to β cell damage is probably determined by several genes in the major histocompatibility complex and that genes in the HLA class I region modulate the risk determined by the HLA class II genes. With this hypothesis different polymorphic combinations of genes on the haplotype would determine the penetrance for diabetes. Thus the highest risk combinations would lead most frequently to insulin dependent diabetes mellitus, whereas lower risk combinations would lead to both non-insulin dependent and insulin dependent diabetes mellitus. The difference between the two types of diabetes is that in non-insulin dependent

Clinical implications

- More than one third of elderly people have either non-insulin dependent diabetes mellitus or glucose intolerance
- Non-insulin dependent diabetes mellitus has a strong genetic component, but identifying the relevant genes has been slow
- Almost all Finnish elderly men with non-insulin dependent diabetes mellitus (94% in this study) carry HLA haplotypes known to confer susceptibility to insulin dependent diabetes mellitus in Finnish children
- Part of the genetic background of insulin dependent and non-insulin dependent diabetes mellitus is similar and coded by genes in the HLA region on chromosome 6
- The belief that the HLA predisposition to diabetes is specific for insulin dependent diabetes is largely incorrect

diabetes, owing to the lower penetrance of the HLA haplotypes the β cell damage is not complete and is manifested only when associated with another cause of β cell failure or insulin resistance. The cause of worsening glucose tolerance with age is poorly understood. However, it is clear from our study in elderly men that abnormal glucose tolerance is not an inevitable consequence of aging and that the main predisposition to abnormal glucose tolerance is determined by genes within the major histocompatibility complex.

In conclusion, HLA in the Finnish population is a common genetic determinant of both insulin dependent and non-insulin dependent diabetes mellitus and also of impaired glucose tolerance in men. The importance of our observation should be tested in a further study, including not only middle aged Finnish men with non-insulin dependent diabetes mellitus but also other ethnic groups with varying risk of diabetes.

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Routine ultrasonography in utero and subsequent handedness and neurological development

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Abstract

Objective—To examine any associations between routine ultrasonography in utero and subsequent brain development as indicated by non-right handedness at primary school age and neurological development during childhood.

Design—Follow up of 8 and 9 year old children of women who took part in two randomised, controlled trials of routine ultrasonography during pregnancy.

Setting—Clinics of 60 general practitioners in Norway during 1979-81. Maternal and child health centres.

Subjects—2161 (89%) of 2428 eligible singletons were followed up, partly through a questionnaire to their parents and partly through information from health centres.

Main outcome measures—The dominant hand of the child was assessed by 10 questions. Deficits in attention, motor control, and perception were evaluated by five questions. Impaired neurological development during the first year of life was assessed by an abbreviated version of the Denver developmental screening test.

Results—The odds of non-right handedness were higher among children who had been screened in utero than among control children (odds ratio 1.32; 95% confidence interval 1.02 to 1.71). No clear differences were found between the groups with regard to deficits in attention, motor control, and perception or neurological development during the first year of life.

Conclusion—Our data suggest a possible association between routine ultrasonography in utero and subsequent non-right handedness, whereas no association with impaired neurological development

was found. As the question on non-right handedness was one of six initial hypotheses, the observed results may be due to chance. None the less, the results suggest that the hypothesis may have some merit and should be tested in future studies.

Introduction

The common indications for diagnostic ultrasound scanning in pregnancy and the routine screening offered in some countries result in most pregnant women in developed countries being exposed to the procedure. No adverse effects of diagnostic ultrasound screening in pregnancy have been reported. Possible long term effects among children exposed to ultrasound in utero, however, have been examined in only a few studies. The general consensus is that further research on this topic is warranted.¹

Abnormal development is typically related to disturbances during critical stages of gestation. Routine ultrasonography is usually done between the 16th and the 22nd week of pregnancy, which is an important phase of brain development.² At this point neurones migrate towards their destination in the fetal brain. Experimental studies in vitro have shown changes in the cell membrane³ and cell surface motility and architecture⁴ after exposure to ultrasound. Ultrasound might influence neuronal migration, and it has been suggested that altered cerebral dominance, dyslexia, or impaired neurological development may be the result of a disturbed migration of neurones.⁵ The dominant hand may serve as an indicator of cerebral dominance. The normal high prevalence of right handedness means that random damage to the hemispheres will increase left handedness.⁶

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