ORIGINAL ARTICLE

Positive association of the *DIO2* (deiodinase type 2) gene with mental retardation in the iodine-deficient areas of China

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Background: Iodine deficiency is the commonest cause of preventable mental retardation (MR) worldwide. However, in iodine-deficient areas not everyone is affected and familial aggregation is common. This suggests that genetic factors may also contribute. Thyroid hormone (TH) plays an important role in fetal and early postnatal brain development. The pro-hormone T4 (3,3′,5,5′-triiodothyronine) is converted in the brain to its active form, T3, or its inactive metabolite, reverse T3, mainly by the action of deiodinase type 2 (DIO2).
Methods: To investigate the potential genetic contribution of the *DIO2* gene, we performed a case-control association study using three common SNPs in the gene (*rs225014*, *rs225012*, and *rs225010*) that were in strong linkage disequilibrium with each other.
Results: Single marker analysis showed a positive association of MR with *rs225012* and *rs225010*. Particularly with *rs225012*, TT genotype frequency was significantly higher in MR cases than in controls ($\chi^2 = 9.18$, $p = 0.00246$). When we compared the distributions of common haplotypes, we also found significant differences between mental retardation and controls in the haplotype combination of *rs225012* and *rs225010* ($\chi^2 = 15.04$, df 2, global $p = 0.000549$). This association remained significant after Bonferroni correction ($p = 0.0016470$).
Conclusion: We conclude that allelic variation in the *DIO2* gene may affect the amount of T3 available and in an iodine-deficient environment may partly determine overall risk of MR.

Fetal iodine deficiency is the commonest cause of preventable mental retardation.[1] Every year, 100 000 children are born with frank cretinism, and many times more are born with lesser mental and neurological deficits attributable to iodine deficiency,[2] as a result of inadequate amounts of thyroid hormone (TH) being available to the developing fetal brain. Thyroid hormones regulate the processes of terminal brain differentiation such as dendritic and axonal growth, synaptogenesis, neuronal migration and myelination. TH also modulates the establishment of neuronal networks through regulation of the number of microglial cells producing neurotrophic factors.[3]

The deiodinase play a key role in the maintenance of circulating and tissue levels of thyroid hormones. There are three types of deiodinase, type 1, 2, and 3 (DIO1, DIO2, and DIO3) iodothyronine. All are seleno-enzymes characterised by a selenocysteine in the catalytic domain of the enzyme encoded by a UGA codon in the presence of a characteristic 3′ untranslated region stem loop structure, the selenocysteine insertion sequence (SECIS). DIO2 is particularly important in the brain. The pro-hormone T4 (3,3′,5,5′-triiodothyronine) is converted in the brain to its active form, T3, or its inactive metabolite, reverse T3, mainly by the action of DIO2. DIO2 is involved in an activation step converting 3,5,3′5′-tetra-iodothyronine (T4) to 3,5,3′-tri-iodothyronine (T3), and a degradation step converting 3,3′5′-triiodothyronine (reverse T3) to 3,3′-diiodothyronine. Inactivation steps are mainly regulated by deiodinase type 3 (DIO3) when converting T4 to reverse T3 and converting T3 to 3,3′-diiodothyronine.[4] DIO2 appears to be a tissue-specific regulator of intracellular T3 concentrations in the brown fat, brain, and pituitary.[5] The *DIO2* gene maps to human chromosome 14q24.3, is about 15 kb in size, and the coding region is divided into two exons by a gap of approximately 7.4 kb.[6] In light of the important action of thyroid hormone in brain development and the regulation of the active form of thyroid hormone by DIO2 in the brain, and as, up to now, there have few genetic studies performed in this specific field, we decided to evaluate whether allelic variation in the *DIO2* gene might alter risk of susceptibility for MR in areas of iodine deficiency.

METHODS

Sample

The study included three groups, definite mental retardation (MR; n = 96), borderline mental retardation (border; n = 116), and controls (n = 331). The mean (SD) age of groups was 9.9 (2.9) years with a 49:51 female–male ratio (table 1). All subjects were identified and recruited from Zha Shui and An Kang counties in the Qin-Ba mountain region of Shaanxi province, Western China. There is widespread soil erosion in this region (average elevation 750–1500 m) and water iodine levels are low; we recorded an iodine (SD) level in water of 1.87 (0.46) μg/l.[7] There is no selenium deficiency. For several years the Shaanxi province health authorities have conducted iodination programs and popularised the use of iodine enriched common salt. This has resulted in a marked decline in the frequency of mental retardation in the Qin-Ba mountain region. However, the prevalence of mental retardation (2.78%) still remains higher than in most other areas of China (1.07%).[8] Moreover, we found familial clustering in the two counties with several families displaying

Abbreviations: LD, linkage disequilibrium; MR, mental retardation; PCR, polymerase chain reaction; TH, thyroid hormone

Table 1 Number of samples collected in each area, sex ratio and mean age

Area	MR	Sex ratio (F/M)	Mean age (SD)	Border	Sex ratio (F/M)	Mean age (SD)	Controls	Sex ratio (F/M)	Mean age (SD)	Total	Sex ratio (F/M)	Mean age (SD)
Zha Shui	52	26/26	10.9 (2.8)	74	40/30	10 (3.0)	245	118/124	9.6 (2.8)	371	184/184	9.9 (2.9)
An Kang	44	24/20	9.6 (2.8)	42	20/22	10.9 (3.1)	86	39/47	9.7 (3.0)	172	82/89	9.9 (3.0)
Total	96	50/46	10.3 (2.8)	116	60/56	10.4 (3.1)	331	156/171	9.6 (2.9)	543	266/273	9.9 (2.9)

multiple affected members in one or more generations. It is possible that genetic factors may interact with an iodine-deficient physical environment to determine overall risk of mental retardation.

Ethics
All subjects gave standard informed consent after explanation of the study. The protocol was reviewed and approved by the Ethical Committee of the National Human Genome Center. All subjects were Han Chinese in origin.

Screening for social adaptability or mental handicap
Participants were screened using the Adaptive Scale of Infant and Children revised by Zuo *et al*.[9] Using these scales each person was given a social adaptive score or mental handicap score. Those with no disability on these scales invariably have an IQ within normal range and, for purposes of the study, were therefore classified as normal controls.

IQ testing
Children 4–5 years old were tested with the Chinese-Wechsler Young Children Scale of Intelligence (C-WYCSI),[10] while those 6–16 years old were tested with the Chinese-Wechsler Intelligence Scale for Children (C-WISC).[11] We selected an IQ of less than 70 as the cut-off for mental retardation (MR). We defined IQs of less than 70 accompanied by social disability scores of 8 or less as mental retardation (MR), and IQs of 70–79 with social disability scores of 9 as borderline MR (border).

Neurological examination
It was usually not possible or appropriate to perform a formal IQ test in cases of frank cretinism, and we had to depend upon clinical diagnosis. A neurological examination, conducted by a physician, included tests of hearing, vision, voice and speech, reflexes, and posture and gait. We excluded from the study cases of MR if affected by trachoma, infection, trauma, toxicity, cerebral palsy, or birth complications. Controls came from the same iodine-deficient areas and were selected from families with no history of MR. If permission was granted, a blood sample was taken for routine haematology, serology, and DNA analysis. Blood samples were stored at -20℃. Genomic DNA was extracted from blood using a modified phenol/chloroform method.

Power analysis
We performed power calculations based on Cohen's method[12] using G*Power software and Epi info 2002. The present sample size showed over 90% power to detect significance ($\alpha<0.05$) in the association with allele, genotype, and haplotype under study conditions and an effect size index of 0.2 corresponding to ''weak to moderate'' gene effect was used. Furthermore, the present sample sizes had a power of >73% at $p = 0.05$ to detect allelic association of the allele, genotype, and haplotype at a presumed odds ratio (OR) of 2.

SNPs in the *DIO2* region
We selected SNPs located in the *DIO2* region from information sourced from the SNP Consortium (http://snp.cshl.org/) and dbSNP (http://www.ncbi.nlm.nih.gov/SNP/) and examined their allele frequencies in 24 controls (48 chromosomes) by the direct sequencing procedure described below. After evaluation of 22 SNPs by seven pairs of sequencing primer, we selected three SNPs with minor allele frequencies of over 0.05 in the *DIO2* gene. They were *rs225014* (A/G) in exon 2, and *rs225012* (T/C) and *rs225010* (A/G) in intron 1. *rs225014* and *rs225012* have an interval of 1.2 kbp and *rs225012* and *rs225010* have an interval of 1.5 kbp.

The SNP *rs225014* (A/G) in exon 2 was amplified by polymerase chain reaction (PCR) using the primers: forward: 5′-TACCTGCCATCATGCCTCTT-3′, and reverse: 5′-GGAAGT CAGCCACTGAGGAG -3′. PCRs were carried out in 96-well microtitre plates with a final reaction volume of 25 μl containing 50 mM KCl, 10 mM Tris-HCl (pH 8.0), 1.5 mM $MgCl_2$, 200 mM dNTPs, 5 μl Q solution (Qiagen, Valencia, CA, USA), 10 pM each primer, 20 ng DNA, and 2.5 U Taq polymerase (Life Technologies, Karlsuhe, Germany). Cycle conditions were one cycle with an initial 4 min denaturation at 95℃, followed by 35 cycles of 94℃ for 30 s, 57℃ for 40 s, 72℃ for 50 s, and a final extension period at 72℃ for 10 min, using the GeneAmp PCR System 9700 (Applied BioSystems, Foster City, CA). SNPs were typed by direct sequencing. The PCR products were processed by incubation with 0.1 U of shrimp alkaline phosphatase (Roche, Basel, Switzerland) and 0.5 U of exonuclease I (New England Biolabs, Beverly, MA) at 37℃ for 1 h, followed by heat inactivation at 80℃ for 20 min. The PCR products were sequenced with reverse PCR primer as the sequencing primer using an ABI Prism BigDye Terminator Cycle Sequencing Kit (Applied BioSystems, Foster City, CA) on an ABI Prism 377 or 3100 sequencer.

The genotyping of SNPs *rs225012* (T/C) and *rs225010* (A/G) combines kinetic (real-time quantitative) PCR with allele-specific amplification, which has been described elsewhere.[13] We used two separate real-time quantitative PCR reactions, each of which contains an allele-specific primer of SNP and the same common primer. Heterozygous samples have equal amounts of the two alleles, which should reach a detectable level of fluorescence at the same cycle number, but in heterogeneity the cycle number should be different for the two amplification reactions. For the *rs225012* (T/C) polymorphism a 55 bp PCR product was amplified using the common primer: 5′-GTGCAAAGGGAGCACATGAA-3′, a T allele-specific primer: 5′-TAAAATATTGGGGCAGAAGAA-3′, and a C allele-specific primer: 5′-TAAAATATTGGGG CAGAAGAG-3′. Amplification was performed in a 5 μl volume of 2.5 μl 2×TaqMan universal PCR master mix (Applied Biosystems), 10 ng genomic DNA, 0.2 μM allele-specific primer, 0.2 μM common primer, and 0.2×SYBR Green I (Molecular Probe). The PCR cycles began with an UNG digestion stage at 50℃ for 2 min, and an initial denaturation period at 95℃ lasting for 10 min, followed by 50 cycles at 95℃ for 15 s, an annealing phase conducted at 59℃ for 30 s, and a dissociation stage at 95℃ for 15 s. For the *rs225010* (A/G) polymorphism a 55 bp PCR product was amplified under the same cycling conditions except with the following primers: the common primer: 5′-AAATTTAT CTGCCTCAGTGAGCTT-3′, an allele-specific primer: 5′-GAACATAATCATATTTGGGTGAT-3′, and a G allele-specific

Table 2 Genotypes and allele frequencies for the three SNPs

Polymorphism	Genotype frequency			χ^2 (p value) MR versus control	χ^2 (p value) Border versus control	Total	Success rate of genotyping	Allele frequency (%)		χ^2 (p value) MR	χ^2 (p value) Border	Odds ratio (95% CI)	
rs225014	AA	GA	GG	AA versus GA and GG	AA versus GA and GG			A	G				
MR	12	43	39	0.72	0.86	94	97.9	0.6467	0.3533	0.45	0.09	1.123	1.049
Border	23	44	47	(0.39)	(0.35)	114	98.3	0.6053	0.3947	0.5	0.76046	(0.801 to 1.573)	(0.771 to 1.428)
Controls	54	145	131			330	99.7	0.6159	0.3841				
rs225012	TT	TC	CC	TT and TC versus CC	TT versus TC and CC			T	C				
MR	52	30	12	**9.18**	0.45	94	97.9	0.2935	0.7065	**4.59**	0.3	**1.491**	1.111
Border	75	35	5	**(0.00246)**	(0.5)	115	99.1	0.1957	0.8043	**(0.03)**	(0.58225)	**(1.033 to 2.152)**	(0.763 to 1.617)
Controls	203	112	14			329	99.4	0.2119	0.7881				
rs225010	AA	AG	GG	AA versus GG	AA versus GG			A	G				
MR	11	40	42	**4.05**	0.11	93	96.9	0.663	0.337	**4.01**	1.13	**1.43**	1.214
Border	7	37	70	**(0.044)**	(0.74)	114	98.3	0.7763	0.2237	**(0.045)**	(0.28712)	**(1.006 to 2.031)**	(0.849 to 1.734)
Controls	21	129	180			330	99.7	0.7242	0.2576				

Bold font indicates significantly associated statistic.

primer: 5′-GAACATAATCATATTTGGGTGAC-3′. To check for genotyping errors, eight DNA samples were randomly selected from each 96-well plate and re-genotyped. All genotypes were identical to those obtained from the first round of genotyping.

Statistical analysis

Allele frequencies were calculated using the SPSS 10.0 software for Windows (SPSS, Chicago, IL). Deviations from Hardy-Weinberg equilibrium, differences in allele and genotype distributions, and OR with 95% confidence intervals were calculated using the method of Finetti.[14] Linkage disequilibrium (LD) between two loci was measured using a two-locus LD calculator (2LD)[15] and EMLD software (http://request.mdacc.tmc.edu/~qhuang/Software/pub.htm). Haplotypes were inferred by Bayesian methods,[16] and implemented in the PHASE package version 1.0 (http://www.assertion.net/software/). Differences in genotype and haplotype distribution between patient and control groups were assessed by the Monte Carlo method using the CLUMP program version 1.9 with 10 000 simulations.[17] Statistical significance was set at $p<0.05$. Odds ratios with 95% confidence intervals were estimated for the effects of high-risk haplotype and calculated by Epi info 2002 software (http://www.cdc.gov/epiinfo/). Power analysis was performed using the G*Power program[18] and Epi info 2002 software.

RESULTS

SNPs

The *rs225014* SNP is an A/G polymorphism in exon 2 of the *DIO2* gene, predicting a change in amino acid 92 of the protein (Thr92Ala). The minor allele G frequency of *rs225014* was 0.3841 in the control population with a distribution meeting Hardy-Weinberg equilibrium ($p = 0.201$). The *rs225012* and *rs225010* SNPs are in intron 1 of the *DIO2* gene. *rs225012* is a T/C SNP with a minor allele T frequency of 0.2935 in our control population and an allele frequency of 0.272 in the Caucasian population. *rs225010* is an A/G SNP with a minor allele G frequency of 0.337 in our control population. The distributions of genotypes of *rs225012* and *rs225010* were both in Hardy-Weinberg equilibrium in controls. All samples were grouped together for statistical analysis because no significant difference was found in distribution of genotype frequencies between sample from Zha Shui and An Kang counties ($p>0.35$).

Singular-locus association analysis

Table 2 shows the group genotypes and allele frequencies of the three SNPs. No significant difference was observed in genotypes or allele frequencies for the three SNPs between borderline mental retardation and control groups. When MR and controls were compared, *rs225014* also revealed no significant difference in allele frequency ($p = 0.5$) or distribution of genotypes ($p = 0.39$). The G allele frequency of *rs225010* was higher in MR (0.337) than in controls (0.2576; $p = 0.045$; OR = 1.43, 95% confidence interval 1.006 to 2.031). The T allele frequency of *rs225012* was higher in MR (0.2935) than in controls (0.2119; $p = 0.03$; OR = 1.491, 95% confidence interval 1.033 to 2.152). The CC genotype frequency was significantly higher in MR (0.128) than in controls (0.043; $\chi^2 = 9.18$, $p = 0.00246$; OR = 3.29, 95% confidence interval 1.37 to 7.91).

Haplotype analysis

To calculate the extent of LD in pairwise combinations of the three SNPs, we calculated D′, r^2, and the p value, the

Table 3 Pairwise linkage disequilibrium

	rs225012				*rs225010*			
	D	D′	r^2	p	D	D′	r^2	p
rs225014	0.0712	0.8741 (SD 0.0465)	0.1282	<0.0001	−0.0731	0.7381 (SD 0.0575)	0.118	<0.0001
rs225012					−0.1359	0.8642 (SD 0.0335)	0.57864	<0.0001

Table 4 Haplotype frequencies between controls and MR

		Haplotype frequency								χ^2
		rs225014(A/G)-*rs225012*(T/C)-*rs225010*(A/G)								
Population	**n**	ATA	ATG	ACA	ACG	**GTA**	**GTG**	**GCA**	GCG	**Global p value**
MR	96	0.005	0.219	0.365	0.052	0.021	0.037	0.281	0.021	3.33
Control	331	0.017	0.19	0.358	0.051	0.003	0.003	0.364	0.014	0.343
p		0.404	0.44	0.93	0.88	**0.035**	**0.00033**	**0.04**	0.699	
OR (95% CI)		0.31 (0.01 to 2.33)	1.19 (0.79 to 1.80)	1.03 (0.73 to 1.46)	1.01 (0.46 to 2.19)	**7.02 (1.10 to 55.53)**	**12.49 (2.36 to 87.6)**	**0.68 (0.47 to 0.99)**	1.54 (0.40 to 5.55)	
		rs225014(A/G)-*rs225012*(T/C)								
		AT	AC	**GT**	GC					
MR	96	0.224	0.417	0.057	0.302					2.25
Control	331	0.207	0.409	0.006	0.378					0.325
p		0.507	0.92	**0.0000087**	0.06					
OR (95% CI)		1.16 (0.77 to 1.74)	1.03 (0.73 to 1.45)	**10 (2.90 to 37.68)**	0.71 (0.50 to 1.02)					
		rs225014(A/G)-*rs225010*(A/G)								
		AA	AGz	GA	**GG**					
MR	96	0.365	0.276	0.302	0.057					2.33
Control	331	0.375	0.242	0.367	0.017					0.312
p		0.973	0.382	0.1155	**0.00553**					
OR (95% CI)		1.02 (0.72 to 1.44)	1.20 (0.82 to 1.75)	0.75 (0.52 to 1.07)	**3.46 (1.37 to 8.73)**					
		rs225012(T/C)-*rs225010*(A/G)								
		TA	TG	**CA**	CG					
MR	96	0.078	0.333	0.469	0.12					**15.038**
Control	331	0.03	0.249	0.645	0.076					**0.000549**
p		**0.006**	0.067	**0.00001**	0.07					
OR (95% CI)		**2.72 (1.29 to 5.69)**	1.51 (1.05 to 2.16)	**0.49 (0.35 to 0.68)**	1.67 (0.96 to 2.89)					

All global p values with haplotype frequencies greater than 0.05 were calculated using CLUMP version 1.6. Individual haplotype p values and OR with 95% confidence intervals (95% CI) were calculated using Epi info 2002 software (Centers for Disease Control and Prevention, Atlanta, GA, USA). Bold font indicates significantly associated haplotypes and statistics.

normalised linkage disequilibrium statistic, in controls for all possible pairs of SNPs. The pairwise LD values are shown in table 3. Strong linkage disequilibrium among the three SNPs was observed (all $D'>0.7$, $p<0.00001$).

We constructed four sets of haplotypes. Three were derived from various combinations of two SNPs and one was derived from a combination of all three SNPs. All the haplotypes were estimated with the PHASE package (table 4).

We only found significant differences between controls and mental retardation in the haplotype of combination of *rs225012* and *rs225010* ($\chi^2 = 15.04$, df 2, global $p = 0.000549$). Furthermore, the data obtained from the study of haplotypes containing either *rs225012*C or *rs225010*A showed that the frequency of haplotype C-A was much lower in MR than in controls ($\chi^2 = 19.36$, df 1, $p = 0.00001$; OR = 0.49, 95% confidence interval 0.35 to 0.68). The three marker haplotypes GTA, GTG, GCA are all risk haplotypes for mental retardation, but haplotype GTG has the highest odds ratio (OR = 12.49, 95% confidence interval: 2.36 to 87.6).

DISCUSSION

In this study, we investigated the relationship between three polymorphisms in the *DIO2* gene and mental retardation in a Chinese Han population from the Qin-Ba mountain region, a traditionally iodine-deficient area in northwest China. This study has several strengths. First, we showed that our sample size had reasonable power to detect association even when these variants had small to medium effects (effect size = 0.2) on susceptibility. Furthermore, our child samples may be less influenced by non genetic social and culture factors than adult samples. Second, all subjects came from the Qin-Ba mountain region, a relatively isolated area in northwest China. Moreover, we did not find a significant difference in allele frequencies between the two counties, which reduced the risk of stratification bias. Third, according to the definition of mental retardation,[19] significantly subaverage intellectual functioning with an IQ score of 70–75 or below on a standardised individual intelligence test is classified as MR. In order to ensure the diagnosis of mental retardation, we set 70 as the IQ cut-off point of MR and classified the individuals identified with IQs of 70–79 as having borderline mental retardation. Finally we have obtained a significant result even after Bonferroni correction. *rs225014* (A/G) is a coding polymorphism (Thr92Ala) predicting a change in amino acid 92 of the protein. *rs225012* (C/T) and *rs225010* (A/G) are located in intron 1.

Single-locus analysis showed a positive association of MR with markers *rs225012* and *rs225010*. When we compared the distributions of common haplotypes between control and MR, we also found significant differences between controls and mental retardation in the haplotype with combined *rs225012* and *rs225010*. This association was still significant ($p<0.001647$) after Bonferroni correction.[20] The haplotypes of *rs225012*C and *rs225010*A showed that C-A was much more frequent in controls than in MR ($\chi^2 = 19.36$, df 1, $p = 0.00001$) and suggests a protective effect. We analysed whether or not two SNPs were located near an mRNA splicing site through in silico analysis by GENESPLICER (developed by

the Institute for Genomic Research (TIGR), http://www.tigr.org/tdb/GeneSplicer/gene_spl.html)[21] and found they were not.

Another possibility is that *rs225012* and *rs225010* and the haplotype combination with these two SNPs may simply be in linkage disequilibrium with a functional polymorphism elsewhere in the *DIO2* gene or in a gene nearby. The nearest functional polymorphism in the *DIO2* gene is *rs225014* (A/G), a common non conservative variant which predicts a Thr92Ala substitution. Although the crystal structure of type 2 deiodinase is not yet known, it is worth noting that this non conservative amino acid change (aliphatic for polar group), which is not located within the conserved deiodinase catalytic domain, could potentially affect its activity.[22] However, this region of the enzyme is not phylogenetically conserved. The homologous amino acid is represented by a proline in rodents and by a glycine in chick. In contrast, humans and amphibians share a threonine in this position. It is reported that this SNP is associated with obesity and insulin resistance.[23] However, we found no association between this polymorphism and mental retardation.

The nearest functional candidate genes are *PSEN1* (presenilin1) and *TSHR* (thyroid hormone receptor or thyrotropin receptor). *PSEN1* is reported to be associated with early-onset Alzheimer disease type 3.[24] *TSHR* is a important gene involved both in the metabolic pathway of thyroid hormones and in a wide range of sporadic and hereditary or genetically determined changes in thyroid function such as thyroid adenomas, thyroid cancer, non autoimmune hyperthyroidism, thyrotropin resistance, and congenital hypothyroidism.[25] Therefore, the effect of the combination of *DIO2*, *PSEN1*, and *TSHR* may play an important role in the pathogenesis of mental retardation.

It is also possible that the protective haplotype is in linkage disequilibrium with a regulatory element that affects expression of type 2 deiodinase. This in turn may influence T3 levels in the fetal brain and, if the brain is already compromised by iodine deficiency, influence the risk of mental retardation. Eighty per cent of brain T3 is formed through the enzymatic activity of type 2 deiodinase (DIO2). DIO2 is mainly found in astrocytes in vitro and vivo,[26] suggesting that circulating T4 is metabolised into T3 in the glial cells and then transferred to the neurons. To examine the physiological role of DIO2, Schneider *et al*[27] developed a *DIO2* knockout mouse strain lacking DIO2 activity. Mice homozygous for the targeted deletion had no gross phenotypic abnormalities, and development and reproductive function appeared normal, except for mild growth retardation in males. It is unclear whether a similar situation pertains for DIO2 deficiency in human fetal brain whose thyroid hormone function is already compromised by iodine deficiency. We suspect that normal deiodinase type 2 may be an important protection factor from late in the first trimester and early in the second trimester of gestation, because in this period DIO2 activity in the brain is evidently increased.[28] Further work is required to investigate the mechanisms by which DIO2 may affect fetal brain development in the context of iodine deficiency.

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ELECTRONIC-DATABASE INFORMATION

URL for data in this article are as follows: Locuslink: http://www.ncbi.nlm.nih.gov/LocusLink/ (for SNP selection); dbSNP: http://www.ncbi.nlm.nih.gov/SNP/ (for SNP selection); the SNP Consortium: http://snp.cshl.org/ (for SNP selection); GeneSplicer: http://www.tigr.org/tdb/GeneSplicer/gene_spl.html (for splicer site analysis of mRNA).

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