

A PROSPECTIVE GENETIC MARKER OF THE VISUAL-PERCEPTION DISORDER MEARES-IRLEN SYNDROME^{1, 2}

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Summary.—Prior investigations of scotopic sensitivity or Meares-Irlen syndrome have identified several features also found in attention deficit/hyperactivity disorder, chronic fatigue syndrome, and a subtype of dyslexia in which visual recognition is the primary deficit. In particular, anomalies in lipid metabolism, including low essential fatty acid status and decreased serum cholesterol, have been identified in all three disorders. Genetic expression of the transporter molecule apolipoprotein B-100 (APOB) has been correlated with abnormal lipid metabolism, particularly in relation to levels of cholesterol. Cholesterol esters are important carriers of essential fatty acids entering the retina. The APOB gene coding for apolipoprotein B-100 is located on the short arm of Chromosome 2, and closely neighbours a gene (DYX3) known to confer susceptibility to dyslexia. The APOB locus is also recognised as being one of the most highly polymorphic regions of the human genome, and thus provides a promising tool for genetic researchers. In this pilot study, certain allelic variants of the APOB gene were more common in participants diagnosed with Meares-Irlen syndrome than in individuals without the condition. This study appears to be a first in which a condition known to cause reading difficulties has been associated with the APOB gene.

In the past two decades, there has been an increase in reports of a visual-perception disorder known as the Meares-Irlen syndrome (MIS; also known as Irlen syndrome and scotopic sensitivity syndrome), a condition reported to affect reading in at least 5% of the general population (Kriss & Evans, 2005). To date, the most common method of diagnosis has been the Irlen Perceptual Reading Scale (IPRS), a widely purported means of identifying symptoms in individuals who have reading problems despite there being no optometric or ophthalmological abnormalities. Diagnostic criteria primarily include distortions of print (such as the text appearing to move or vibrate), declining oral reading speed and fluency, light and glare sensitivity, atypical difficulty in counting a series of identical symbols or parallel lines, and a clear and immediate improvement in such symptoms upon the positioning of a coloured transparency over the viewed page of text or symbols (Robinson, 1994; Stein, 2003). A further hallmark of MIS is that the span of word recognition (the number of words able to be seen

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clearly in one eye fixation) is significantly reduced (Robinson, Foreman, & Dear, 1996).

Although MIS symptoms affect reading, writing, spelling, and visual attention, the extent to which this occurs and the affect upon literacy and learning varies greatly amongst individuals with MIS. These differences may be due in part to the condition being equally prevalent across intellectual ability, including those who are gifted and talented. Researchers in this field have reported significant reductions in the symptoms of children and adolescents, as well as adults with MIS, through the use of coloured lenses or overlays (Irlen, 1994; Robinson, 1994; Bouldoukian, Wilkins, & Evans, 2002; Wilkins, 2002; Kriss & Evans, 2005).

Despite MIS often being referred to as a subtype of dyslexia (Sparkes, Robinson, Roberts, & Dunstan, 2006), this categorisation remains debatable if not hypothetical. Others describe MIS as a separate entity which can occur with or without dyslexia, albeit with significantly more prevalence in the dyslexic population, with reported incidences varying from 31 to 46% (Irlen & Lass, 1989; Kruk, Sumbler, & Willows, 2008). The dilemma in specifying whether MIS is related to dyslexia is perhaps made difficult in part by the absence of a clear and universally recognised definition of dyslexia. Accordingly, a lack of accord persists in explaining the increased prevalence of MIS in the dyslexic population (Northway, Manahilov, & Simpson, 2010).

Estimations of the prevalence of MIS in the population vary between 5% using strict criteria, such as an immediate improvement in reading speed $\geq 25\%$ when reading through coloured transparencies placed over text (Kriss & Evans, 2005), and 20 to 25% when reported symptoms of visual discomfort and print distortions form the basis of diagnosis (Robinson, Hopkins, & Davies, 1995; Allen & Hollis, 2008). However, there appears to be general consensus that estimations of MIS prevalence in the vicinity of 12% are reasonable (Jeanes, Busby, Martin, Lewis, Stevenson, Pointon, *et al.*, 1997; Northway, *et al.*, 2010). With respect to the prevalence of dyslexia, in a recent review commissioned by the British Government dyslexia was reported to affect 4 to 8% of the UK population (Rose, 2009).

Most estimations of MIS prevalence have either been based upon observable improvements in reading speed through the use of coloured overlays, or a self-reported reduction in visual stress associated with glare or print distortion by the participant when reading with a preferred overlay in place (Hollis & Allen, 2006). However, these traditional methodologies are likely to be vulnerable to subjectivity, both of the subject and, conceivably, the assessor (Hollis & Allen, 2006). Moreover, as individuals with MIS are known to be highly sensitive to certain forms of lighting, especially fluorescent lighting (Wilkins & Wilkinson, 1991; Whiting, Robinson,

& Parrott, 1994), unless the lighting conditions are controlled for when carrying out either of the above screening methods, the results and therefore diagnosis could potentially vary from one screening room to another. Thus, an adjunctive biological test for MIS morbidity (or predisposition to such) is needed. Also, recent legislation in many countries, mandating the use of compact fluorescent lighting in homes and elsewhere, increases the need to substantiate early diagnosis of MIS in children.

Symptoms of MIS and dyslexia have been associated with anomalies in lipid profiles, particularly essential fatty acid (EFA) status (MacDonnell, Skinner, Ward, Glen, Glen, MacDonald, *et al.*, 2000; Cyhlarova, Bell, Dick, Mackinlay, Stein, & Richardson, 2007). Although many trials involving EFA supplementation have shown equivocal results, some long-term trials have produced positive results (Lindmark, & Clough, 2007). Participants with MIS have also been reported as showing significantly decreased plasma total cholesterol, including low density lipoprotein (LDL) cholesterol (Sparkes, Robinson, Dunstan, & Roberts, 2003). Research by Brookes, Chen, Xu, Taylor, and Asherson (2006) indicated that alterations in omega-3 fatty acid metabolism may also be associated with ADHD, and this was corroborated in later studies (Chalon, 2009; Laasonen, Hokkanen, Leppämäki, Tani, & Erkkilä, 2009).

Atypical lipid profiles have also been identified in chronic fatigue syndrome patients (Robinson, McGregor, Roberts, Dunstan, & Butt, 2001; Maes, Mihaylova, & Leunis, 2006). Robinson, *et al.* (2001) further reported that several features of chronic fatigue syndrome overlap with MIS and, moreover, that the two disorders often occur comorbidly. Similarly, Loew, Marsh, and Watson (2009) found that seven of nine diagnostic symptoms of MIS, such as light sensitivities and visual fatigue, were equally prevalent in a group ($n = 12$) with attention deficit/hyperactivity disorder (ADHD) as compared to an MIS group ($n = 18$). In contrast, the same study identified highly significant variations in the prevalence of MIS symptoms between the ADHD group and a control group ($n = 46$).

Cholesterol is essential to maintaining functional levels of docosahexaenoic acid (DHA) in retinal-neuronal membranes, and it is also accepted that DHA almost exclusively crosses the blood-retinal barrier as a constituent of LDL cholesterol esters (Bretillon, Thuret, Grégoire, Acar, Joffre, Bron, *et al.*, 2008). That study reported a strong positive correlation of DHA concentrations in the neural retina to concentrations of LDL cholesterol esters in the retinal pigment epithelium. In a related study, retinal pigment was shown to reduce visual discomfort to short wavelengths of light (440–500 nm) within the scotopic band (Snodderly & Stringham, 2010). Interestingly, studies on animals with elevated plasma cholesterol levels have reported significantly lower photoreceptor electroretino-

graphic (ERG) responses to light (Brettillon, Acar, Seeliger, Santos, Maire, Juanéda, *et al.*, 2008).

Although MIS research has long been focused upon deficits in the magnocellular visual pathway that may affect the synchronisation of signals from the retina to the visual cortex, others have proposed that hypersensitivity of photoreceptors to specific wavelengths, or hyperexcitability of the visual cortex itself, are more prospective candidates. Indeed, the latter scenario has been well corroborated using functional magnetic resonance imaging (fMRI; Huang, Cooper, Santana, Kaufman, & Cao, 2003). However, the present authors question the practicability of readily excluding excessive neural firing in the retina (by hypersensitive photoreceptors for example) from being a potential cause of the hyperexcitability in the visual cortex detected in fMRI studies. Conversely, there is an abundance of evidence in the literature elucidating the vital role of cholesterol homeostasis in the retina for optimal functioning of the photo-transduction cascade by hindering or enhancing activation of rhodopsin (Albert & Boesze-Battaglia, 2005; Pitman, Grossfield, Suits, & Feller, 2005).

We therefore hypothesize that reduced cholesterol levels, as has been observed in individuals with MIS (Sparkes, *et al.*, 2003), may lead to increased rhodopsin-initiated photoreceptor responses to light and thus be a factor in symptoms of photo-hypersensitivity reported in MIS.

LDL cholesterol, which is vital to photoreceptor regulation, is circulated throughout the body as a bound component of apolipoprotein B-100 (APOB) transporter molecules. The APOB gene coding for these proteins was first shown to be highly polymorphic in early molecular-genetic studies (Knott, Wallis, Pease, Powell, & Scott, 1986; Boerwinkle, Xiong, Fourest, & Chan, 1989), and is known to be represented in the human population as an unusually wide variety of allelic variants. It is also well-recognized that a polymorphic area of this gene is located directly following the coding sequence as it is transcribed, commonly referred to as the downstream or 3' (3-prime) end of a gene. The 3' end of the APOB gene exhibits a variable number of tandemly repeated (VNTR) short A + T rich DNA sequences and the frequency of genetic polymorphisms in this region is exceedingly high in comparison to most human genes (Knott, *et al.*, 1986). Moreover, APOB VNTR allelic variants have been associated with abnormal cholesterol status in humans and other mammals (Das, Pawar, Saini, & Seshadri, 2009).

In humans, the APOB locus maps to the short arm (2p) of Chromosome 2. This locus is situated in a region of Chromosome 2 that includes both a gene (DYX3) believed to confer susceptibility to dyslexia (Fagerheim, Raeymaekers, Tønnessen, Pedersen, Tranebjærg, & Lubs, 1999; Petryshen, Kaplan, Hughes, Tzenova, & Field, 2002) and a further gene

(MDH1) associated with symptoms of chronic fatigue syndrome (Goldenberg, Simms, Geiger, & Komaroff, 1990; Abraham & Flechas, 1992). The proximity of APOB to DYX3 and MDH1 (Fig. 1) is such that genetic linkage of the inherited alleles of these genes is possible.

In view of the prior research associating atypical fatty acid metabolism with MIS and ADHD, and decreased LDL with MIS and CFS; the further evidence that LDL significantly participates in the supply of essential fatty acids to the retina; and the potential overlap of MIS visual symptoms with ADHD and CFS, this study explored the possibility of lipid-related transport mechanisms being associated with, and perhaps identifying, a biological marker of these conditions. Accordingly, the APOB gene which plays a crucial role in LDL transport was examined in order to test the hypothesis that inherited alleles of APOB might be dissimilar between a group of individuals with deficient reading attributable to MIS, and a control group comprised of normal readers without MIS.

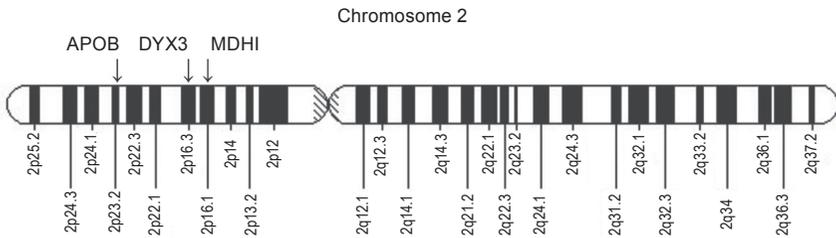


FIG. 1. Locations of APOB, DYX3, and MDH1 on Chromosome 2

METHOD

Participants

Ten participants (7 men, 3 women; all Caucasian; *M* age = 43.8 yr.) with MIS symptoms were recruited through academic and social networks at an open university in Australia. Only individuals who had a long-term history of deficient reading due to distortions of text, and who had reported a history of excessive sensitivity to fluorescent lighting and long-term (> 1 yr.) use of coloured lenses or paper, confirmed by means of a questionnaire and follow-up interview, were subsequently included in the study. Those with ophthalmological conditions, or optometric problems which had not recently been corrected, were excluded from the study. Eight of the 10 participants had previously been diagnosed with Meares-Irlen syndrome by certified Irlen Screeners [diagnosticians trained to screen for MIS morbidity using the Irlen Reading Perceptual Scale (IRPS)]. The two participants who presented without a formal diagnosis of MIS were screened by one of the authors (SJL), a certified IRPS screener. The two participants

were found to meet the IRPS criteria for a positive diagnosis of MIS; with one individual also reporting a prior diagnosis of ADHD, while the other individual reported a past diagnosis of CFS.

Eight control participants (5 men, 3 women; all Caucasian; *M* age = 45.9 yr.) were also recruited to the study through the above university networks. These individuals self-reported as not having any symptoms of MIS or suffering from any form of reading or visual deficit, and this was subsequently verified through the completion of a questionnaire designed to identify familiarity with any one of nine widely recognised symptoms of MIS, as described by Robinson (1994). All participants (*N* = 18) were drawn from similar socio-economic backgrounds, and all had signed a personal consent form verifying that their consent was given after being duly informed in writing of the aims and procedures of the study prior to commencement.

Ethics approval was obtained from the University of New England Human Research Ethics Committee (approval number: HEO9/018). All trial participants were recruited by means of notices posted on campus, in accordance with Human Research Ethics Committee guidelines.

Procedures

Buccal (cheek epithelial) cell samples from individuals were collected by scraping the inside of the cheek (3 to 4 times) with a plastic swab and were transferred to microfuge tubes by rinsing with 1 mL sodium chloride (0.9% w/v). Samples were centrifuged at $10,000 \times g$ for 1 min. and supernatants were removed and samples re-centrifuged for 1 min. The remaining supernatants were carefully removed and the residual pellet re-suspended by adding 1 ml of 0.1% v/v Triton X-100 and vortexing vigorously for 1 min. The DNA samples were labelled and stored at -20°C .

Amplification of the 3' VNTR region of the APOB gene was achieved in a polymerase chain reaction (PCR) mixture containing 5 μL buccal cell extract, 200 μM of each dNTPs, 1 μL *Taq* polymerase (1 U/ μL), 10 μL APOB buffer, 5 μL H_2O , and 1 μg of each of the primers (as per manufacturer's protocol). The sequence of the 5' oligonucleotide primer was 5'-ATGGAAACGGAGAAATTATG-3' and the 3' primer was 5'-CCTTCTCACTTGGCAAATAC-3' (Boerwinkle, *et al.*, 1989).

The amplification cycle was programmed as follows: initial denaturation at 94°C for 5 min., 55°C for 1 min., followed by 38 cycles at 94°C for 1 min., annealing and extension at 58°C for 6 min. A final chase cycle at 94°C for 1 min., 58°C for 15 min., and 25°C for 1 min. was applied. Electrophoresis of the amplified DNA was at 50V in 3% agarose gel for 6 hr.

Analysis

Following electrophoresis, the amplified DNA products were visual-

ized directly by staining with ethidium bromide and viewing under UV light. The lengths of APOB VNTR fragments were determined by comparison of their respective migration distances to a DNA fragment-sized marker [in 100 base pair (bp) increments] using high resolution gel-imaging software (Quantity One, Bio-Rad Laboratories, Hercules, CA). The lane containing the 100-bp DNA ladder (Lane 11) provided weak but discernable bands. The use of an internal marker also provided a clear delineation between the participants (Lanes 1–10) and the controls (Lanes 12–19).

The distances migrated by the DNA fragments (Fig. 2) identified 11 variants (out of a maximum of 36) of the APOB gene in the samples of the 18 participants and control subjects. The allelic variants were assigned appropriate nomenclature (AV1–AV11), with the shortest fragment labelled AV1 (Allele Variant 1). The data relating to the frequencies of these alleles, as detected in each of the two groups, were then assessed for distribution modality using Excel software to test the hypothesis that variances in allelic frequency distribution may exist.

RESULTS

Gel electrophoresis of the DNA samples identified 11 variant alleles of APOB amongst a total of 36 APOB alleles (one pair from each participant) (Fig. 2). The allelic variants were detected by comparing the measured migration distances of each allele to a marker of DNA fragments of known length to determine the fragment length of each allele. The 11 allelic variants were not uniformly distributed between the MIS and control groups. The two groups showed distinct patterns of APOB allele frequencies which were clearly distributed in a bimodal manner (Fig. 3). The mean distance travelled by the APOB VNTR fragments of the MIS group (Fig. 2) correlated to a mean fragment length of 704 bp, approximately

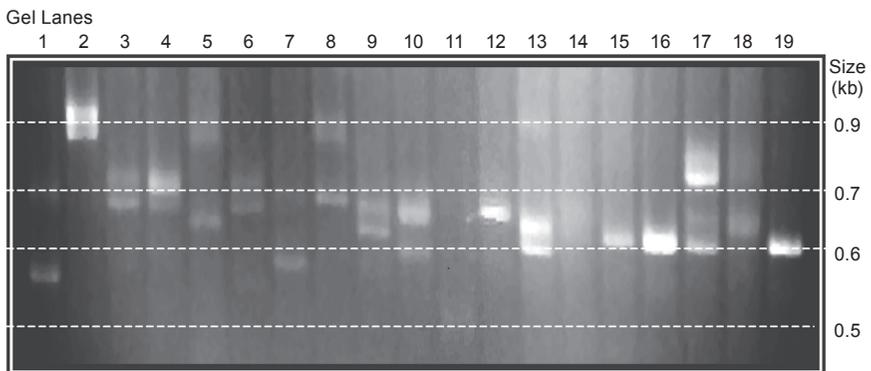


FIG. 2. Gel-electrophoretic analysis of DNA fragment-sizes. MIS group: Lanes 1–10; Controls: Lanes 12–19.

81bp (13.0%) longer than the 623 bp mean length of the DNA fragments from the control group.

All individuals inherit two alleles of each gene, one from each parent. In cases where the two alleles of a gene are identical, these homozygous alleles appear as a single DNA band on gel electrophoresis. Similarly, in cases where two alleles of a gene are not identical, these heterozygous alleles differ in length and will thus produce two DNA bands. Of the 18 participants, only four were homozygous for the APOB gene, and this presented an opportunity to independently assess between-groups variations in the mean fragment lengths of both the longest and shortest alleles of the 18 pairs of alleles. In respect to the four instances of homozygosity, identical lengths for both alleles were factored into the analysis.

In these comparisons, the mean length of the longer alleles of each pair differed between the two groups by 111 bp, a variance of 17.4% (MIS 749 bp, Controls 638 bp). The shorter alleles showed a similar trend in respect to group variation, with the mean DNA fragment length of the MIS group being 50 bp or 8.2% longer than that of the control group (MIS 658 bp, Controls 608 bp).

In each comparative analysis of APOB allele distribution, the mean length of the DNA fragments from the MIS group was markedly longer than that of the control group. Interestingly, if the two MIS subjects diagnosed with comorbid conditions (Lane 1: ADHD; Lane 7: CFS) were to be excluded from the above calculations, the variation in mean fragment lengths between the groups would be greater still (longer allele: MIS 765 bp, controls 638 bp; shorter allele: MIS 678 bp, controls 608 bp; mean of both alleles: MIS 722 bp, controls 623 bp).

A quantitative analysis of the distribution of individual APOB alleles (Fig. 3) showed further patterns of variation between the groups. There were three specific alleles (AV7, AV8, and AV10) relatively common to the MIS group, yet were not carried by the control group. In contrast, the alleles AV3 and AV4 were relatively common to the controls but not to the MIS group. None of the 10 MIS subjects were homozygotes ($p = .11$, one-sided, 95%CI = 0, 0.34, binomial distribution), whereas four of the eight control subjects (50%) were homozygous for alleles of APOB ($p = .05$, one-sided, 95%CI = 0.17, 0.83, binomial distribution) but neither result was significantly different from the expected proportion of 0.2 (Boerwinkle, *et al.*, 1989; Gene, Huguet, Sanchez-Garcia, Moreno, Corbella, & Mezquita, 1995; Frossard & Lestringant, 1999). However, the odds of the control group being homozygotes were significantly greater than the odds for the MIS group ($p \leq .03$, 95%CI = 1.04, ∞ , Fisher's exact test).

Of the 11 APOB variants detected in the total sample ($N = 18$), only three (AV3, AV5, and AV6) were carried by both the MIS and control

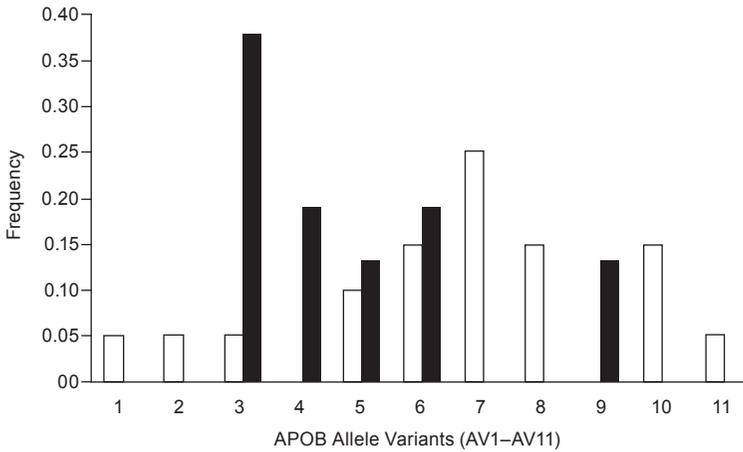


FIG. 3. Group-distributions of APOB alleles for MIS group (□) and control group (■).

groups. Thus, a bimodal distribution of the APOB alleles is evident in the quantitative analysis shown in Fig. 3. The most frequent allele in the control group was AV3, with a frequency of 0.38. The frequency of AV3 in the MIS group was 0.05. The most frequent allele in the MIS group was AV7, with a frequency of 0.25. In the control group the frequency of AV7 was zero. Thus, the frequencies of these two APOB alleles also depict a highly segregated pattern in the distribution of alleles carried by the two groups.

DISCUSSION

Examination of a highly polymorphic region of Chromosome 2, in proximity to a gene (DYX3) associated with dyslexia (Fagerheim, *et al.*, 1999; Petryshen, *et al.*, 2002), identified discernable variations between a group ($n=10$) with MIS and a control group ($n=8$). There were significant differences in allele frequencies pertaining to a neighbouring gene (APOB) known to affect lipid homeostasis. A large between-group variation in APOB 3' VNTR size was also detected, with the mean size of the VNTR fragments of APOB alleles carried by the MIS group being 81 bp (13%) longer than the corresponding fragments of the control group. The potential clinical significance of such variation is perhaps augmented by APOB 3' VNTR fragment sizes being reported as varying in length within a range confined to 570 bp to 900 bp, with 63% of these being either 659 bp or 691 bp in length (Boerwinkle, *et al.*, 1989). Thus, a mean size-variance of 81bp in the VNTR region of APOB alleles carried by MIS subjects is substantial enough to have potential use in detecting susceptibility to MIS.

Other results in this study were consistent with prior research on the APOB VNTR locus in which all 12 alleles identified exhibited fragment

sizes measuring between 570 bp and 900 bp (Boerwinkle, *et al.*, 1989). Subsequent DNA sequencing of these 12 alleles showed that the differing VNTR fragment sizes were brought about by insertions or deletions of short DNA segments comprised of two VNTR repeat units of 14 to 16 bp. Significantly, the VNTR fragments lengths of the 11 allelic variants identified in the present study differed in size by approximately 30 bp or multiples thereof, with the fragments lengths of all 11 variants also being between 570 bp and 900 bp. Furthermore, 78% of the study's 18 participants were found to be heterozygous for APOB alleles, a statistical result that is in agreement with previously observed heterozygosity indices of 75% (Boerwinkle, *et al.*, 1989), 80% (Gene, Huguët, Sanchez-Garcia, Moreno, Corbella, & Mezquita, 1995), and 81% (Frossard & Lestringant, 1999).

In contrast to the present study, many previous investigations of the APOB locus have restricted the recruitment of trial participants to populations from one principality and, in most cases, from one specific cultural background. For example, the 12 (or more) APOB alleles detected by Boerwinkle, *et al.* (1989) were identified in Caucasians who were all of French ancestry. Other studies of APOB polymorphisms have been confined to populations from specific locations as in a study of obese individuals in Tunis (Jemaa, El-Asmi, & Mebazaa, 2002). In a similar study of APOB polymorphisms, in which 14 alleles were identified in 121 individuals, 82 of the participants exhibited either obesity or hypertension and all were of Indian decent (Das, *et al.*, 2009).

The APOB 3' VNTR locus is a highly informative marker which has been widely used in genetic association studies. In this study, clear differences in the frequencies of APOB alleles identified in participants with MIS and reading deficiencies were readily distinguishable from those of a control group comprised of unimpaired readers without MIS. In addition, because anomalies in omega-3 metabolism have been associated with a number of well known reading, attention, and neurological disorders, potential benefits which might be gained through diagnostic access to a lipid associated genetic marker of any one of the above conditions could have far reaching implications.

In summary, the results of this pilot study indicate that the APOB 3' VNTR locus may offer a novel avenue of investigation for identifying a potential genetic marker for susceptibility to MIS and perhaps other related conditions. Furthermore, other biological variables known to be associated with the APOB gene such as serum levels of LDL, total cholesterol and apolipoprotein-B might also be prospective diagnostic indicators. To our knowledge, this study is the first to associate reading and attention disorders with the APOB gene.

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