Combined association of Presenilin-1 and Apolipoprotein E polymorphisms with maternal meiosis II error in Down syndrome births

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Abstract

Alzheimer’s disease and Down syndrome often exhibit close association and predictively share common genetic risk-factors. Presenilin-1 (PSEN-1) and Apolipoprotein E (APOE) genes are associated with early and late onset of Alzheimer’s disease, respectively. Presenilin -1 is involved in faithful chromosomal segregation. A higher frequency of the APOE \( /c_101^4 \) allele has been reported among young mothers giving birth to Down syndrome children. In this study, 170 Down syndrome patients, grouped according to maternal meiotic stage of nondisjunction and maternal age at conception, and their parents were genotyped for PSEN-1 intron-8 and APOE polymorphisms. The control group consisted of 186 mothers of karyotypically normal children. The frequencies of the PSEN-1 T allele and TT genotype, in the presence of the APOE \( /c_101^4 \) allele, were significantly higher among young mothers (< 35 years) with meiosis II nondisjunction than in young control mothers (96.43% vs. 65.91% P = 0.0002 and 92.86% vs. 45.45% P < 0.0001 respectively) but not among mothers with meiosis I nondisjunction. We infer that the co-occurrence of the PSEN-1 T allele and the APOE \( /c_101^4 \) allele associatively increases the risk of meiotic segregation error II among young women.

Keywords: Chromosome, genetic polymorphism, karyotype, meiosis, microsatellite markers.

Received: May 19, 2016; Accepted: February 27, 2017.

Introduction

Alzheimer’s disease (AD), a progressive neurodegenerative disorder of old age, and Down syndrome (DS), an intellectual disability due to trisomy of chromosome 21, show co-occurrence. Brain imaging and autopsy studies revealed that Alzheimer’s-like neuropathological changes, such as beta amyloid plaques and neurofibrillary tangles were common in DS patients at their forties (Olson and Shaw, 1969; Glenner and Wang, 1984; Mann and Esiri, 1989; Cork, 1990; Yoshimura et al., 1990). The common molecular mechanisms bridging the two disorders include chromosomal missegregation (Potter, 1991; 2008), over-production of amyloid precursor protein (Rumble et al., 1989), oxidative stress and mitochondrial dysfunction (Pagano and Castello, 2012), nuclear factor of activated T cells (NFAT) and tau phosphorylation pathways (Jung et al., 2011; Perlui et al., 2014), endocytic pathway abnormality (Cataldo et al., 2000), mutation in amyloid precursor protein gene (APP) (van Leeuwen et al., 1998), presence of Apolipoprotein E epsilon 4 (APOE \( /c_101^4 \) allele (Del Bo et al., 1997). Familial association of AD and DS has been reported (Yatham et al., 1988; Schupf et al., 2001). Interactions among environmental agents, advancing age (Tanzi and Bertram, 2001; Grant et al., 2002) and a certain genetic polymorphisms (Bertram and Tanzi, 2005) account for 95% of sporadic late-onset AD, while only 5% AD are of early-onset type and due to mutations in APP (Goate et al., 1991), presenilin-1 (PSEN-1) (Sherrington et al., 1995) and presenilin-2 (PSEN-2) (Levy-Lahad et al., 1995; Rogae et al., 1995) genes on chromosome 21, 14 and 1, respectively. The PSEN-1 gene encodes a protein component of the
gamma-secretase complex involved in the processing of the amyloid precursor protein (APP) (Karran et al., 1998). Presenilin-1 protein is engaged in many cardinal mechanisms of several molecular pathways (Duff et al., 1996; Alberici et al., 1999; Woo et al., 2009; Ho and Shen, 2011; Trushina et al., 2012), which when impaired lead to the manifestation of AD. This protein also localizes to centromeres, the nuclear envelope of dividing cells, kinetochores at interphase, and is involved in faithful chromatosomal segregation (Li et al., 1997). Mutations in PSEN-1 lead to chromatosomal instability and trisomy 21 mosaicism in AD patients (Geller and Potter, 1999). Another well-documented molecular marker for both the early-onset (Corder et al., 1993) and sporadic (Brouwers et al., 2008) AD is a polymorphism in the Apolipoprotein E (APOE) gene on chromosome 19. Association of the APOE ε4 allele with AD has been demonstrated in ethnically different populations (Lehtimaki et al., 1995; Shimada et al., 1997; Tang et al., 1998; Panza et al., 1999; de-Andrade et al., 2000; Kim et al., 2001; Korovaitseva et al., 2001; Chen et al., 2003). On the other hand, DS is the most common aneuploidy in live born humans. The predominant cause of DS is the presence of a supernumerary chromosome 21, owing to nondisjunction in maternal gametogenesis in the overwhelming majority of cases (Sherman et al., 2007; Allen et al., 2009; Ghosh et al., 2010). Advanced maternal age (Hassold and Chiu, 1985; Allen et al., 2009) and an altered pattern of recombination (Warren et al., 1987; Sherman et al., 1991; Oliver et al., 2008) have been identified as two major risk factors for maternal meiotic errors. Avramopoulos et al. (1996) found a higher of the APOE ε4 allele in young mothers having DS children due to chromatosomal nondisjunction in the second meiotic division (meiosis II or MII) of oocytes. The association of PSEN-1 intron 8 polymorphism and late-onset AD in North American European descendants was first reported by Wragg et al. (1996) and later supported in many studies (Higuchi et al., 1996; Isoe et al., 1996; Kehoe et al., 1996; Brookes et al., 1997; Ezquerra et al., 1997; Nishiwaki et al., 1997; Tilley et al., 1999); arguments against this association were also produced (Pérez-Tur et al., 1996; Scott et al., 1996; Cai et al., 1997; Lendon et al., 1997; Singleton et al., 1997; Sorbi et al., 1997; Tysoe et al., 1997; Jiang et al., 1999; Bagli et al., 1999; Rodriguez et al., 2000; Chandak et al., 2002; Rassas et al., 2013). The study of a DS sample from Denmark revealed the association of the T allele of the PSEN-1 intronic polymorphism (rs165932) with maternal MII nondisjunction, and thus pointed to a putative role of this polymorphic allele in chromatosomal segregation (Petersen et al., 2000). The aim of the present study was to investigate the possibility of a collaborative effect of PSEN-1 and APOE polymorphisms on DS birth in the Indian subcontinent.

Subjects and Methods

Subjects

This study included 178 unrelated Bengali individuals with free trisomy 21 and their parents. We recruited 186 women that gave birth to karyotypically normal children as the control group. All subjects were randomly referred from different Medical Colleges and Hospitals of Kolkata and neighbouring areas. The study was approved by the ethical committee of the Maulana Abul Kalam Azad University of Technology. Peripheral blood was collected from the DS children and their parents, as well as from control mothers and their children after taking informed consent.

Cytogenetic analysis

Classical karyotyping was performed to select only free trisomy 21 DS cases. At least 30 metaphases were analysed from each DS sample to exclude mosaicism.

Determination of parental origin of extra chromosome 21

Genomic DNA was isolated from blood using a QIAamp DNA Blood Midi Kit (Qiagen). Ten highly polymorphic STR markers, mapped from the pericentromeric region to the telomeric region of the long arm of chromosome 21 were selected to determine the maternal or paternal origin of the extra chromosome 21: D21S1432 – D21S11 – D21S1437 – D21S1270 – D21S167 – D21S1412 – D21S2055 – D21S1260 – D21S1411 – D21S1446. For determining the stage of meiotic nondisjunction, i.e. MI or MII errors, four additional pericentromeric markers were genotyped: D21S369, D21S215, D21S258 and D21S120. The maternal MI error was inferred, when maternal heterozygosity for these markers was retained in the DS child. If maternal heterozygosity was reduced to homozygosity in the DS child, maternal MII error was considered.

Detection of APOE and PSEN-1 polymorphisms

Polymorphisms in APOE gene (rs429358 and rs7412) and PSEN-1 intron 8 (rs165932) were investigated by Restriction Fragment Length Polymorphism (RFLP), and direct DNA sequencing in an ABI PRISM 3700 DNA Analyzer platform (Applied Biosystems), after PCR amplification, using oligonucleotide primers previously described by Hixson and Vernier (1990) and Sherrington et al. (1995), respectively. Restriction fragment length polymorphism (RFLP) genotyping of APOE and PSEN-1 was done, as described by Hixson and Vernier (1990) and Wragg et al. (1996) respectively.

Statistical analysis

Maternal age was considered as predictor variable in all statistical analyses. For age analyses, both case and control mothers were stratified into young (< 35 years) and old
Weinberg equilibrium. and control mothers are presented in Supplementary Tables PSEN-1 section of Young, n = 71; (d) /c101 (times (Table 2). Both the allelic (/c101 /c101 children were also categorised as: (a) MI, - Young, n = 37; (f) n = 14; (d) /c101 /c101 positive, - MI, - Old, n = 13; (c) /c101 /c101 negative, - MI, - Young, n = 14; (d) /c101 /c101 positive, - MI, - Old, n = 8; (e) /c101 /c101 negative, - MI, - Young, n = 37; (f) /c101 /c101 negative, - MI, - Old, n = 40; (g) /c101 /c101 negative, - MI, - Young, n = 19; (h) /c101 /c101 negative, - MI, - Old, n = 23. The control mothers of karyotypically normal children were also categorised as: (a) /c101 /c101 positive, - Young, n = 22; (b) /c101 /c101 positive, - Old, n = 20; (c) /c101 /c101 negative, - Young, n = 71; (d) /c101 /c101 negative, - Old, n = 73. The distribution of PSEN-1 alleles and genotypes in each group of case and control mothers are presented in Supplementary Tables S1 and S2, respectively. All groups were in Hardy-Weinberg equilibrium.

**Results**

STR genotyping revealed that out of the 178 DS trisomies only eight had a paternal meiotic origin, and 170 were the result of maternal nondisjunction. MI nondisjunction was demonstrated in 106 cases (53 young mothers and 53 old mothers), and MII nondisjunction in 64 cases (33 young mothers and 31 old mothers). According to the presence of the APOE e4 allele, stage of nondisjunction and age at conception, the 170 case- mothers were stratified into eight groups: (a) e4 positive, - MI, - Young, n = 16; (b) e4 positive, - MI, - Old, n = 13; (c) e4 positive, - MII, - Young, n = 14; (d) e4 positive, - MII, - Old, n = 8; (e) e4 negative, - MI, - Young, n = 37; (f) e4 negative, - MI, - Old, n = 40; (g) e4 negative, - MII, - Young, n = 19; (h) e4 negative, - MII, - Old, n = 23. The control mothers of karyotypically normal children were also categorised as: (a) e4 positive, - Young, n = 22; (b) e4 positive, - Old, n = 20; (c) e4 negative, - Young, n = 71; (d) e4 negative, - Old, n = 73. The distribution of PSEN-1 alleles and genotypes in each group of case and control mothers are presented in Supplementary Tables S1 and S2, respectively. All groups were in Hardy-Weinberg equilibrium.

**PSEN-1 polymorphism and maternal age**

Stratified analyses for meiotic outcome groups revealed that the TT genotype was significantly more frequent in the group of young mothers with MII nondisjunction compared to young control mothers. (P = 0.0007; Table 1).

**APOE e4 allele and nondisjunction**

The detailed genotypes and alleles of APOE gene polymorphism in DS mothers and controls, according to age and meiotic nondisjunction stage are given in the Supplementary Table S3.

In young case mothers, the presence of e4/- genotypes (i.e. e4/e4, e3/e4 or e2/e4) increased the risk for DS 1.73 times (Table 2). Both the allelic (e4) and genotypic (e4/e4 + e3/e4 + e2/e4) frequencies were significantly increased in the MII nondisjunction young group when compared with young controls and with MI nondisjunction old group (P < 0.001, for genotypic and allelic frequencies). In the group of MII nondisjunction young mothers, the risk of nondisjunction was increased 2.48 times in the presence of the e4 allele when compared with the group of MI nondisjunction old mothers (OR = 2.48, 95% CI = 1.11 - 5.53; Table 2) and 2.23 times when compared with young control mothers (OR = 2.23, 95% CI = 1.12 - 4.47; Table 2).

**Combined effect of the PSEN-1 T allele and the APOE e4 allele and maternal aging on nondisjunction**

We found a significant increase in both TT genotypic and T allelic frequencies in APOE e4 positive, - MII nondisjunction,- young case mothers upon comparison with APOE e4 positive, - young control mothers (P < 0.00001 and 0.0002, respectively; Table 1).

These results suggest that the PSEN-1 T allele and the APOE e4 allele may collaboratively increase the risk of MII nondisjunction among young mothers.

**Discussion**

The aim of the present work was to explore the notion that the etiology of DS birth and AD is somehow related at the molecular level. The result of our analyses suggested that polymorphisms of PSEN-1 might explain the co-occurrence of DS and AD in one same family.

The result of our case control study showed that the ‘T allele’ of PSEN-1 intronic polymorphism (rs165932) was associated with MII nondisjunction, but not with MI nondisjunction. It is not clear at this point how this polymorphism impacts the chromosome segregation, but two hypotheses have been put forward to explain its molecular role. According to the first hypothesis, the PSEN-1 intron 8 T allele may be in linkage disequilibrium with a coding segment in the gene itself or in other gene(s) (Hutton and Hardy, 1997); and the second hypothesis postulates that this polymorphic site may affect the pre-mRNA splicing and give rise to a different isoform of the protein, which may affect chromosome segregation (Meshorer and Soreq, 2002). Abnormality in cell cycle regulation is apparent in both familial and sporadic AD cases (Potter, 1991, 2005, 2008; Arendt et al., 1996; Geller and Potter, 1999; Yang et al., 2001, 2006; Nagy, 2005; Yang and Herrup, 2007; Varvel et al., 2008).

The significant increase in T allelic and TT genotypic frequencies in e4 positive young mothers with MII nondisjunction would imply a collaborative effect of both alleles in increasing the risk of MI nondisjunction at young age. Avramopoulos et al. (1996) found higher APOE e4 allele frequencies in young mothers giving birth to DS child due to meiotic II nondisjunction error. This would be ex-
<table>
<thead>
<tr>
<th>Comparisons</th>
<th>TT genotypic frequency</th>
<th>(P) value of Chi-squared test</th>
<th>T allelic frequency</th>
<th>(P) value of Chi-squared test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case</td>
<td>Control</td>
<td></td>
<td>Case</td>
</tr>
<tr>
<td>Case mothers (N = 170) vs. Control mothers (N = 186)</td>
<td>55.29%</td>
<td>48.92%</td>
<td>0.36</td>
<td>72.35%</td>
</tr>
<tr>
<td>MI case mothers (N = 106) vs. Control mothers (N = 186)</td>
<td>49.06%</td>
<td>48.92%</td>
<td>0.98</td>
<td>68.39%</td>
</tr>
<tr>
<td>MII case mothers (N = 64) vs. Control mothers (N = 186)</td>
<td>65.63%</td>
<td>48.92%</td>
<td>0.02</td>
<td>78.91%</td>
</tr>
<tr>
<td>MII case mothers (N = 64) vs. MI case mothers (N = 106)</td>
<td>65.63%</td>
<td>49.06%</td>
<td>0.02</td>
<td>78.91%</td>
</tr>
<tr>
<td>Young case mothers (N = 86) vs. Young control mothers (N = 93)</td>
<td>55.81%</td>
<td>44.09%</td>
<td>0.08</td>
<td>73.26%</td>
</tr>
<tr>
<td>Old case mothers (N = 84) vs. Old control mothers (N = 93)</td>
<td>54.76%</td>
<td>53.76%</td>
<td>0.89</td>
<td>71.43%</td>
</tr>
<tr>
<td>MI - young case mothers (N = 53) vs. Young control mothers (N = 93)</td>
<td>49.06%</td>
<td>44.09%</td>
<td>0.45</td>
<td>68.87%</td>
</tr>
<tr>
<td>MI - old case mothers (N = 53) vs. Old control mothers (N = 93)</td>
<td>49.06%</td>
<td>53.76%</td>
<td>0.52</td>
<td>67.92%</td>
</tr>
<tr>
<td>MII - young case mothers (N = 33) vs. Young control mothers (N = 93)</td>
<td>66.67%</td>
<td>44.09%</td>
<td>0.0007</td>
<td>80.3%</td>
</tr>
<tr>
<td>MII - old case mothers (N = 31) vs. Old control mothers (N = 93)</td>
<td>64.52%</td>
<td>53.76%</td>
<td>0.14</td>
<td>77.42%</td>
</tr>
<tr>
<td>APOE e4 positive - young case mothers (N = 30) vs. APOE e4 positive - young control mothers (N = 22)</td>
<td>66.67%</td>
<td>45.45%</td>
<td>0.002</td>
<td>80%</td>
</tr>
<tr>
<td>APOE e4 positive - old case mothers (N = 21) vs. APOE e4 positive - old control mothers (N = 20)</td>
<td>52.38%</td>
<td>55%</td>
<td>0.72</td>
<td>69.05%</td>
</tr>
<tr>
<td>APOE e4 negative - young case mothers (N = 56) vs. APOE e4 negative - young control mothers (N = 71)</td>
<td>50%</td>
<td>43.66%</td>
<td>0.34</td>
<td>69.64%</td>
</tr>
<tr>
<td>APOE e4 negative - old case mothers (N = 63) vs. APOE e4 negative - old control mothers (N = 73)</td>
<td>55.56%</td>
<td>53.42%</td>
<td>0.77</td>
<td>72.22%</td>
</tr>
<tr>
<td>APOE e4 positive - MI - young case mothers (N = 16) vs. APOE e4 positive - young control mothers (N = 22)</td>
<td>43.75%</td>
<td>45.45%</td>
<td>0.80</td>
<td>65.62%</td>
</tr>
<tr>
<td>APOE e4 positive - MI - old case mothers (N = 13) vs. APOE e4 positive - old control mothers (N = 20)</td>
<td>46.15%</td>
<td>55%</td>
<td>0.23</td>
<td>65.38%</td>
</tr>
<tr>
<td>APOE e4 negative - MI - young case mothers (N = 37) vs. APOE e4 negative - young control mothers (N = 71)</td>
<td>51.35%</td>
<td>43.66%</td>
<td>0.24</td>
<td>70.27%</td>
</tr>
<tr>
<td>APOE e4 negative - MI - old case mothers (N = 40) vs. APOE e4 negative - old control mothers (N = 73)</td>
<td>50%</td>
<td>53.42%</td>
<td>0.64</td>
<td>68.75%</td>
</tr>
<tr>
<td>APOE e4 positive - MII - young case mothers (N = 14) vs. APOE e4 positive - young control mothers (N = 22)</td>
<td>92.86%</td>
<td>45.45%</td>
<td>&lt;0.0001</td>
<td>96.43%</td>
</tr>
<tr>
<td>APOE e4 positive - MII - old case mothers (N = 8) vs. APOE e4 positive - old control mothers (N = 20)</td>
<td>62.5%</td>
<td>55%</td>
<td>0.31</td>
<td>75%</td>
</tr>
<tr>
<td>APOE e4 negative - MII - young case mothers (N = 19) vs. APOE e4 negative - young control mothers (N = 71)</td>
<td>47.37%</td>
<td>43.66%</td>
<td>0.57</td>
<td>68.42%</td>
</tr>
<tr>
<td>APOE e4 negative - MII - old case mothers (N = 23) vs. APOE e4 negative - old control mothers (N = 73)</td>
<td>65.22%</td>
<td>53.42%</td>
<td>0.11</td>
<td>78.26%</td>
</tr>
<tr>
<td>APOE e4 positive - MII case mothers (N = 22) vs. APOE e4 positive - MI case mothers (N = 29)</td>
<td>81.82%</td>
<td>44.83%</td>
<td>&lt;0.0001</td>
<td>88.64%</td>
</tr>
</tbody>
</table>

Young mothers, < 35 yrs of age; Old mothers, < 35 yrs of age
MI, nondisjunction at meiotic division I; MII, nondisjunction at meiotic division II
Table 2 - Comparative analysis of APOE ε4- genotypic and ε4 allelic frequencies in mothers of DS children and control mothers of karyotypically normal children.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>APOE ε4 positive genotypic frequency (ε4/ ε4 + ε3 /ε4 + ε2 / ε4)</th>
<th>APOE ε4 allelic frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chi square</td>
<td>P value of Chi - squared test</td>
</tr>
<tr>
<td>Case mothers (N= 170) vs. control mothers(N= 186)</td>
<td>2.44</td>
<td>0.12</td>
</tr>
<tr>
<td>Young case mothers (N= 86) vs. Young control mothers (N= 93)</td>
<td>5.33</td>
<td>0.02</td>
</tr>
<tr>
<td>Old case mothers (N= 84) vs. Old control mothers (N= 93)</td>
<td>0.57</td>
<td>0.45</td>
</tr>
<tr>
<td>MI - young case mothers (N= 53) vs. Young control mothers (N= 93)</td>
<td>1.8</td>
<td>0.18</td>
</tr>
<tr>
<td>MI - old case mothers (N= 53) vs. Old control mothers (N= 93)</td>
<td>0.43</td>
<td>0.51</td>
</tr>
<tr>
<td>MII - young case mothers (N= 33) vs. Young control mothers (N= 93)</td>
<td>14.89</td>
<td>0.0001</td>
</tr>
<tr>
<td>MII - old case mothers (N= 31) vs. Old control mothers (N= 93)</td>
<td>0.86</td>
<td>0.35</td>
</tr>
<tr>
<td>MII - Young case mothers (N= 33) vs. MI - old case mothers (N= 53)</td>
<td>13.06</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Young mothers, < 35 yrs of age; Old mothers, > 35 yrs of age
MI, nondisjunction at meiotic division I; MII, nondisjunction at meiotic division II

explained by compromised microcirculation due to the high plasma cholesterol deposition in APOE ε4 allele carriers causing atherosclerosis in microvasculature surrounding ovarian follicles. This would imply reduced blood flow and oxygen supply, and increased anaerobic products such as lactic acid accumulation in the follicular cell and as a consequence the size of the spindle, could become reduced due to high pH inside the follicle, resulting in nondisjunction (Gaulden, 1992). Another explanation is that isoform-specific binding of ApoE to microtubule-associated protein would affect microtubule stability and function and, thus, hamper meiotic chromosomal segregation (Strittmatter et al., 1993, 1994; Hansen et al., 1998). Support to this prediction has been provided by Nagy et al. (2000), who showed that trisomy 13 and trisomy 21 conceptuses have a higher APOE ε4 allele frequency.

A recent study has shown that APOE regulates telomere dynamics, and the females who carry APOE ε4 allele experience a six-times higher rate of telomere shortening than non-carriers (Jacobs et al., 2013). Greater erosion of telomere length in Alzheimer’s patients with APOE ε4 allele is also evident (Takata et al., 2012). Interestingly, the study of Ghosh et al. (2010) revealed higher degree of telomere loss in mothers of DS patients resulting from MII nondisjunction than in MI nondisjunction cases and controls. But it is difficult at this point to explain how these data fit together.

Taking all the above into account, we may conclude that the T allele and TT genotype of PSEN-1 polymorphism is associated with MII nondisjunction in younger women giving birth to DS children. Petersen et al. (2000) reported similar findings in Denmark. This result is somewhat interesting as we (Ghosh et al., 2009) and others (Oliver et al., 2008) have found that MII nondisjunction is frequent among older mothers, and represents a maternal age dependent phenomenon. The present set of results suggests that MII nondisjunction can be a maternal age independent phenomenon, when mothers carry the APOE ε4 and PSEN-1 T alleles. The gradual increase in the association of the three factors - PSEN-1 T allele, APOE ε4 allele and young age with MII nondisjunction but not with MI nondisjunction, suggests that these two errors are mutually exclusive and involve different molecular mechanisms. Considering the findings of previous studies (Oliver et al., 2008; Ghosh et al., 2009) and the present data together, we could infer predictively that APOE ε4 allele and PSEN-1 rs165932 T allele create a microenvironment in the younger oocyte, which mimics the subcellular condition of chronologically older ovum and causes MI nondisjunction, a possibility warranting confirmation through elaborate molecular study. Nevertheless, our study provides the first independent confirmation of PSEN-1 as the prospective molecular candidate that relates AD with DS. The association of the T allele of PSEN-1 intronic polymorphism (rs165932) and the APOE ε4 allele would be the collaborative risk factor for both AD and DS, reciprocally exacerbating the risk of MII nondisjunction. Moreover, for the very first time we have clearly demonstrated that the distribution
of risk alleles is statistically similar among controls and MI nondisjunction groups. These results being in accordance with those of Peterson et al. (2000) suggest that the molecular risk factor underlying the association of AD and DS is independent of ethnicity. Our findings represent a step towards the understanding of the genetic basis of DS birth and AD occurrence within one same family.

Acknowledgments

We would like to thank the families participated in the study and professionals who helped us in collection of blood samples. We are thankful to the Director, Anthropological Survey of India, Kolkata, for providing laboratory facilities for some experimental work and Mr. Biswaroop Mookherjee, for his kind help regarding data analysis. The project was funded by Indian Council of Medical Research (ICMR) [grant sanction no. 54/10/2012-HUM-BMS, 31.03.2013].

References


Supplementary material

The following online material is available for this article:
Table S1 – PSEN-1 genotypic and allelic frequencies in mothers of DS children.
Table S2 - PSEN-1 genotypic and allelic frequencies in control mothers.
Table S3 - APOE genotypic and allelic frequencies in mothers of DS children and control mothers.

Associate Editor: Angela M. Vianna-Morgante

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PSEN-1 & APOE polymorphisms in DS births.