Diamine Oxidase Isoforms in Placenta: Structural Analysis and Implication in Pre-eclampsia

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Introduction

Diamine Oxidase (DAO) activity declines while histamine levels increase in pre-eclampsia (PE) (Brew and Sullivan, 2006). Two DAO isoforms (P19801-1 & P19801-2) have been identified in human placenta, where isoform P19801-2 was classified as non-functional (Zhang et al., 1995). This study used high throughput NGS technology and bioinformatics analysis to (1) determine if DAO isoform P19801-2 production in placenta could be associated with PE, and (2) whether differences in post-transcriptional conformation of DAO protein could contribute to the diminished activity in PE.

Methods

RNA-Seq raw data from a total of 84 pregnancies (NP = 55; PE = 29) that met inclusion criteria were obtained from NCBI SRA. Sample quality was assessed with Fastqc and all samples has phred scores >20. 0% failed MAPQ from Star aligner. AA sequence conservation in DAO was analysed with von Neumann entropy in PFAAT on MUSCLE. Sequence phylogeny was examined with MEGA-X, Protein hydrophobicity, 3D structure, protein bonds, torsional angles and Ramachandran plots were modelled with SWISS-MODEL.

Results

Three types of DAO proteins are found in placenta.

- All 3 subtypes were found in mothers with no clinical evidence of diminished DAO and PE.
- One subtype is structurally similar to DAO isoform 2, with a prevalence rate of 1.2%.
- Two other subtypes found have additional 152 AA insertion, preserved structural similar to DAO isoform 1; and occurs at a prevalence rate of 3.6%.
- Isoform 2 like protein found in placenta is functional.

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Table 1: Occurrence of Amino Variations in PE and NP DAO proteins

<table>
<thead>
<tr>
<th>Amino Acid Variants</th>
<th>NP DAO (%)</th>
<th>PE DAO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-conserved Beta-sheet</td>
<td>82 (64)</td>
<td>47 (36)</td>
</tr>
<tr>
<td>Non-conserved Loop</td>
<td>14 (58)</td>
<td>10 (42)</td>
</tr>
<tr>
<td>Conserved Beta-sheet</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Conserved Loop</td>
<td>2 (40)</td>
<td>3 (60)</td>
</tr>
</tbody>
</table>

Total of 162 amino acid variants were found in 84 protein sequences (NP = 55; PE = 29). About 2-fold less AA variations were found in PE than in NP samples. However, more Threonine and Serine residues were substituted for Methionine and Phenylalanine in PE than in NP proteins. Thus, rending PE proteins more hydrophobic than NP placental proteins.

Conclusion

- All 3 subtypes were found in mothers with no clinical evidence of diminished DAO and PE.
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References:
