

<sup>3</sup>  
 1 **Name of journal: World Journal of Hepatology**  
 2 **ESPS Manuscript NO: 16396**  
 3 **Columns: Editorial**  
 4  
 5 **Understanding the pathophysiological mechanisms in the pediatric <sup>3</sup>non-alcoholic fatty**  
 6 **liver disease: The role of genetics**  
 7  
<sup>11</sup>  
 8 Pierluigi Marzuillo, Anna Grandone, Laura Perrone, Emanuele Miraglia del Giudice  
 9  
 10 **Abstract**  
<sup>6</sup>  
 11 Classically, the non-alcoholic fatty liver disease (NAFLD) physiopathology and progression  
<sup>2</sup>  
 12 has been summarized in the two hits hypothesis. The first hit is represented by the action of  
<sup>2</sup>  
 13 hyperinsulinemia and insulin resistance, accompanying obesity, that leads to liver steatosis  
 14 increasing the absolute non esterified fatty acids (NEFAs) uptake in the liver and the  
 15 esterification to form triacylglycerol (TAG). The oxidative stress is involved in the second  
 16 hit leading to the progression to NASH because of its harmful action on steatotic  
 17 hepatocytes. However, at the present time, the two hits hypothesis needs to be updated

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