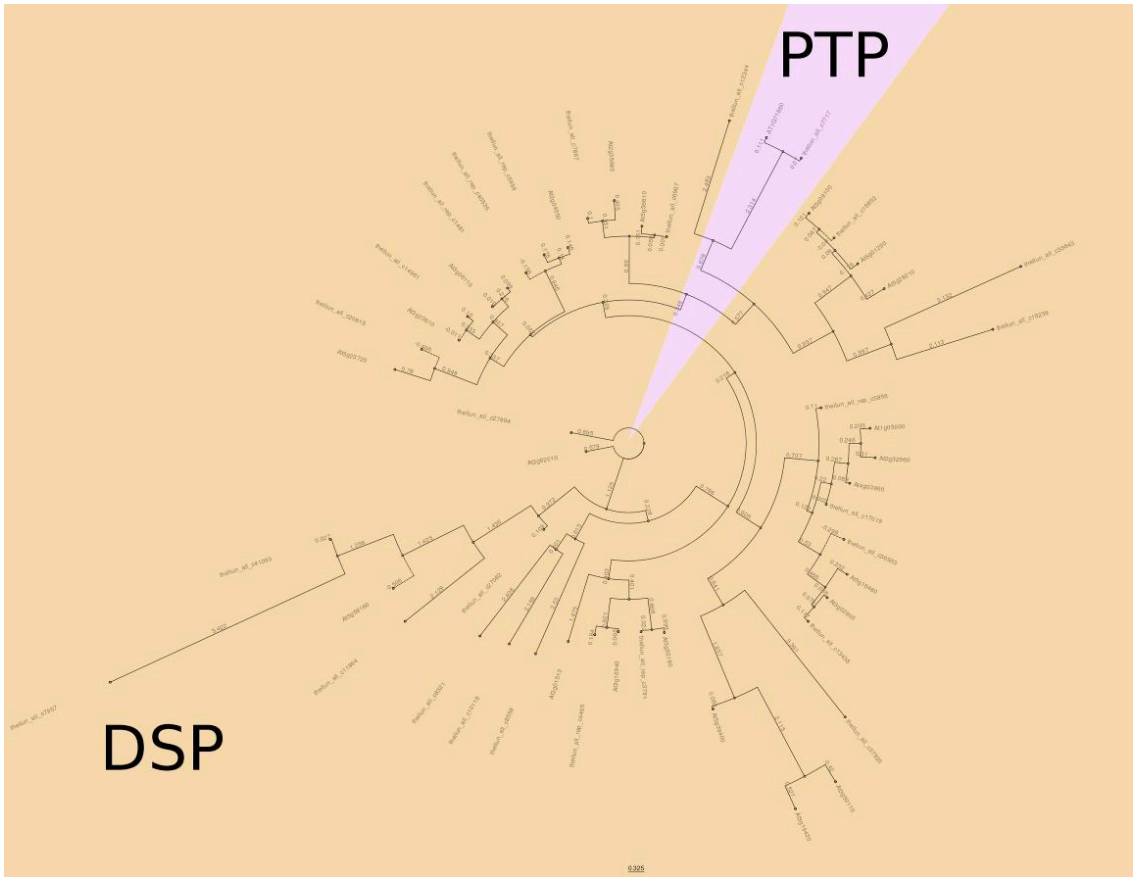**Additional file 6**