The MAP3K7 gene: further delineation of clinical characteristics and genotype/phenotype correlations.

Geeske M. van Woerden[1,2,3#*], Richelle Senden[2#], Charlotte de Konink[1,3], Rossella Avagliano Trezza[1,3], Anwar Baban[4], Jennifer Alisha Bassetti[5], Yolande van Bever[2,3], Lynne M. Bird[6], Bregje W. van Bon[7], Alice S. Brooks[2,3], Qiaoning Guan[8,9], Eric W. Klee[10,11], Carlo Marcelis[7], Joel Morales Rosado[10,11,12], Lisa A. Schimmenti[13], Amy R Shikany[14], Paulien A Terhal[15], K. Nicole Weaver[8,9], Marja W. Wessels[2], Hester van Wieringen[16], Anna C Hurst[17], Catherine F Gooch[17], Katharina Steindl[18], Pascal Joset[18], Marco Tartaglia[19], Marcello Niceta[19,20], Ype Elgersma[1,2,3] and Serwet Demirdas[2*]

Supplemental information

Male patient with FMD2.

Medical History

The patient was born with microcephaly, large fontanelle, receding chin, left hydronephrosis, a narrowing of the trachea, open ductis botalli and ventricle septum defect, congenital hip luxation on the right, congenital cholesteatoma on the right and severe hypospadia. A delay in motor development developed and some noticeable behavior disturbances. The patient is of above average cognitive development, attending high school at a pre-university level.

Complaints

The patient at age 16 years complained of not being able to move his elbows and shoulder well. His sight is mildly effected as he has +1 dioptre on one eye and -1 in the other. The patient has hearing loss due to severe conduction loss on both sides.

Physical Examination

Physical examination showed a high forehead, wide rimmed upper eye sockets, straight eye position, hearing aids on both sides, asymmetrical position of the shoulders (right heigher than left), wide elbows with luxation of the radius and contractures of the fifth digit on both hands.

Supplemental Table 1. Primers used to obtain the cDNA of *MAP3K7* and *TAB1*

Gene	Primers for mutagenesis PCR
MAP3K7	FW 5'- GTCTCACCCGGATTGTCC - 3' RV 5'- AATGTAACGGTCCCAGAG - 3'
MAP3K7 (AscI – PacI)	FW 5'- GAATTGCGGCGCGCCACCATGTCTACAGCCTCTGCC - 3' RV 5'- GAATCCTTAATTAATCATGAAGTGCCTTGTCG - 3'
TAB1	FW 5'- ATGGCGGCGCAGAGGAG - 3' RV 5'- CTACGGTGCTGTCACCAC - 3'
TAB1 (AscI – PacI)	FW 5'- GGCGCGCCACCATGGCGGCGCAGAGGAG - 3' RV 5'- TTAATTAACTACGGTGCTGTCACCAC - 3'

Supplemental Table 2. Primers used for site directed mutagenesis

Variant in nucleotides	Variant in amino acids	Primers for mutagenesis PCR
c.143G>A	p.(Gly48Glu)	FW 5'- GGAAGAGGAGCCTTTGAAGTTGTTTGCAAAGCT - 3' RV 5'-AGCTTTGCAAACAACTTCAAAGGCTCCTCTTCC - 3'
c. 208G>C	p.(Glu70Gln)	FW 5'- TAAACAAATAGAAAGTGAATCTCAGAGGAAAGCGTTTATTGTAGA - 3' RV 5'- TCTACAATAAACGCTTTCCTCTGAGATTCACTTTCTATTTGTTTA - 3'
c.248G>A	p.(Arg83His)	FW 5'- GCTTCGGCAGTTATCCCATGTGAACCATCCTAATA - 3' RV 5'- TATTAGGATGGTTCACATGGGATAACTGCCGAAGC - 3'
c. 299T>A	p.(Val100Glu)	FW 5'- GGAGCCTGCTTGAATCCAGAGTGTCTTGTGATGGAATAT - 3' RV 5'- ATATTCCATCACAAGACACTCTGGATTCAAGCAGGCTCC - 3'
c.329G>A	p.(Gly110Asp)	FW 5'- GATGGAATATGCTGAAGGGGACTCTTTATATAATGTGCTGC - 3' RV 5'-GCAGCACATTATATAAAGAGTCCCCTTCAGCATATTCCATC - 3'
c.337T>G	p.(Tyr113Asp)	FW 5'-TGAAGGGGGGCTCTTTAGATAATGTGCTGCATGG - 3' RV 5-CCATGCAGCACATTATCTAAAGAGCCCCCTTCA - 3'
c.502G>C	p.(Gly168Arg)	FW 5'- CTTACTGCTGGTTGCAGGGCGGACAGTTCTAAAAATTTG - 3' RV 5'- CAAATTTTTAGAACTGTCCGCCCTGCAACCAGCAGTAAG - 3'
c.586A>G	p.(Met196Val)	FW 5'- GGGAGTGCTGCTTGGGTGGCACCTGAAGTTT - 3' RV 5'-AAACTTCAGGTGCCACCCAAGCAGCACTCCC - 3'
c.616T>G	p.(Tyr206Asp)	FW 5'- GTTTTTGAAGGTAGTAATGACAGTGAAAAATGTGACG - 3' RV 5'- CGTCACATTTTTCACTGTCATTACTACCTTCAAAAAC - 3'
c.617A>G	p.(Tyr206Cys)	FW 5'- GAAGTTTTTGAAGGTAGTAATTGCAGTGAAAAATGTGACGTCTTC - 3' RV 5'- GAAGACGTCACATTTTTCACTGCAATTACTACCTTCAAAAACTTC - 3'
c.721T>G	p.(Trp241Gly)	FW 5'- CCCAGCTTTCCGAATCATGGGGGGCTGTTCATAATGGTAC - 3' RV 5'- GTACCATTATGAACAGCCCCCATGATTCGGAAAGCTGGG - 3'
c.1454C>T	p.(Pro485Leu)	FW 5'-ACTACAGCCTCTAGCACTGTGCCCAAACTCCAAAG - 3' RV 5'-CTTTGGAGTTTGGGCACAGTGCTAGAGGCTGTAGT - 3'