**The genetic perspective of familial glucocorticoid deficiency: in silico analysis of two novel variants**

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Supplementary Table1: Included articles with their description, clinical information, variants, protein change, zygosity of MC2R gene

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Number | Clinical phenotype | Other diagnosed phenotype | recruited patients | Nucleotide change | Protein change | mutated patients | Zygosity | Reference |
| 1 | FGD | adrenal hypo- and hyperplasia, Triple A, and autoimmune polyendocrinopathy syndrome type I | 17 | 1.c.424G>T  2.c.80C>G 3.433C>T | 1.Val142Leu 2.P27R 3.Arg145Cys | 1  1 | Homo  Hetero  Hetero | (1) |
| 2 | FGD | Febrile seizures shock, Hypoglycemia, Hyponatremia, mild Hyperpigmentation, coma,hypocortisolemia | 1 | 1.c.319G>A | 1.p.Asp107Asn 2.p.Pro281GlnfsX9 | 1 | Hetero | (2) |
| 3 | FGD1 | salt-losing forms of adrenal hypoplasia | 22 | 1.c.221G>T 2.437G>C,  3.560delT  4.579-.581delTGT | 1.Ser74Ile 2.Arg146His,  3.Val187Alafs\*29 4.Tyr193Ter | 1 | 1.Homo 2.compond Hetero 3.Homo | (3) |
| 4 | FGD | poor sucking, moderate axial hypotonia, hyporeactivity and vomiting. During clinical evaluation, a generalised seizure occurred and was followed by desaturation, laboured breathing, generalised hypotonia and lethargy. | 1 | c.761A>G | Tyr254Cy | 1 | Homo | (4) |
| 5 | PAI | hyperpigmentation, salt-wasting crisis/electrolyte imbalance hypoglycemia with/without convulsions , vomiting/abdominal pain , prolonged jaundice, fatigue , neonatal respiratory distress), frequent infections and failure to thrive or weight loss,DSD | 95/77 genetic diagnosis | c.307G>A c.347G>T c.409C>T c.427G>T NA c.674T>G NA c.697G>C NA c.560delT Deletion(Whole exon) | Asp103Asn Gly116Va Arg137T V142L T143S L225R G226R Ala233Pro Cys251Trp p.V187Afs\*29 | Total:25 mutations | Homo | (5) |
| 6 | Primary Cortisol Deficiency and Growth Hormone Deficiency | Hypoglycemia | 1 | c.634delA | p.R212Efs\*s4 | 1 | Homo | (6) |
| 7 | FGD |  | 1 |  | p.SER74Ile | 1 | Homo | (7) |
| 8 | adrenal unresponsiveness to ACTH | drenal crisis despite poor drug compliance, poor pubic hair development (Tanner stage 2), well-developed breasts (Tanner stage 5), and regular menstrual cycles. | 1 | c.307G>A  c.409C>T | Asp103Asn  Arg137Trp | 1 | Hetero | (8) |
| 9 | FGD1 | hyperbilirubinemia and hyperpigmentation/ low cortisol and high ACTH levels with normal serum electrolytes and renin-aldosterone axis | 1 | c.674T>G | p.Leu225Arg | 1 | Homo | (9) |
| 10 | FGD1 | hypoglycemia, seizure, skin hyperpigmentation, hyperbilirubinemia, cholestasis, and a tall stature | 1 | c.433C>T  c.712C>T | p.R145  p.H238Y | 1 | Hetero | (10) |
| 11 | FGD | hyperpigmentation, hypoglycemia, failure to thrive, and recurrent infections | 1 | 635insC | I154H | 1 | Homo | (11) |
| 12 | FGD | Severe hypoglycemia, unmeasurable cortisol, and grossly elevated ACTH but normal electrolyte | 1 | 866dupA | Met290Aspfs\*60 | 1 | Homo | (12) |
| 13 | FGD1 | FGD | 164 | 1.c.221G>T  2.c.459–460insC | 1.S74I 2.p.I154fsX248 | 42 of 34 families |  | (13) |
| 14 | ACTH resistance syndrome | chalasia and alacrima, besides the symptoms of adrenal insufficiency | 5 | c.347G>T | p.Gly116Val | 1 | Homo | (14) |
| 15 | FGD |  | 3 | c.427G>T  c.697G>C  c.360C>G | Val142Leu  Ala233Pro  Ser120Ar | 3 | Homo | (15) |
| 16 | Familial Glucocorticoid Deficiency | jaundice , hyperpigmentation | 1 | c.307G>A | D103N | 1 | Homo | (16) |
| 17 | familial glucocorticoid deficiency | skin hyperpigmentation muscle weakness, mild jaundice and constipation. Hormonal analyses revealed high ACTH and TSH serum concentrations, low serum cortisol concentration along with normal blood electrolytes | 1 | 137delT  c.145G>A | p.Leu46fs\*38 and p.Val49Met | 1 | Hetero | (17) |
| 18 | FGD | thyroid dysfunction and growth hormone deficiency (GHD) | 5 | c.459\_460insC | p.I154fsX248 | 5 | Homo | (18) |
| 19 | FGD | hypertonic seizures associated with hypoglycemia, skin hyperpigmentation, muscle weakness and mild jaundice. Hormonal analyses revealed high ACTH, low serum cortisol along with normal blood electrolytes | 1 | c.320A>G,c.433C>T | p.D107G,p.R145C | 1 | Hetero | (19) |
| 20 | FGD | isolated | 1 | 652-653insA | Gly217fs,  Promoter(-1017/44 bp) | 1 | Hetero | (20) |
| 21 | FGD | hypoglycemia after prolonged fasting during a respiratory tract infection | 1 | c.455C>A | T152K | 1 | Homo | (21) |
| 22 |  | FGD | 4 | c.221G>T  c.382C>T  c.132C>G  c.577-78delTA  c.437G>C | S74I  R128C  144M  L192fs  R146H | 4 | Homo | (22) |
| 23 | FGD | pneumonia and sepsis, collapse, bradycardia and hypotension at 8 months of age | 1 | c.833T>G  c.386A>G | F278C  Y129C | 1 | Homo | (23) |
| 24 | PAI/FGD |  | 63 | c.307G>A  c.676G>A | p.Asp103Asn  p.Gly226Arg | 1 FGD mutated | Hetero | (24) |
| 25 | FGD |  | 2 | c.476C>G | T159K  A233D  T159K | 2 |  | (25) |
| 26 | FGD | tall stature and skin pigmentation, | 1 | c.62G>A  c.437G>C | C21Y  R146H | 1 | Hetero | (26) |
|  |  |  |  |  |  |  |  |  |
| 27 | FGD |  | 1 | InsA1347  c.376G>T | G217fs  Ala126DSer | 1 | Hetero | (27) |
| 28 | HGD |  | 4 | c.221G>T  c.818C>A | Ser74Ile  Pro273His | 2 | Homo/Compound Hetero | (28) |
| 29 | FGD |  | 1 | c.761A>G | Tyr254cys | 1 | Homo | (29) |
| 30 | FGD |  | 2 | c.319G>A  c.752G>T  G217fs | Asp107ASn  Cys251Phe | 2 | Homo,CompondHetro | (30) |
| 31 |  | aphthous stomatitis and glossitis | 1 | c.61T>C  c.742A>G | C21R  S247G | 1 | Homo | (31) |
| 32 | HGD |  | 1 | c.601C>T  c.360C>G | Arg201Ter  Ser120Arg | 1 | ,CompondHetero | (32) |
| 33 | FGD | tall stature | 1 | c.437G>C | R146H | 1 | Homo | (33) |
| 34 | FGD |  | 11 |  | R146H  R146H  S74I/R128C  S74I  S74I  S74I | 1  1  1  1  1  1 | Homo  Homo  CH  Homo  Homo  Homo | (34) |
| 35 | FGD |  |  | c.476C>G  c.476C>G/ c.307G>A  c.221G>T/1052delC  c.221G>T/c.221G>T |  | 2  1  1  1 | Homo  CH  CH  Homo | (35) |
| 36 | FGD |  |  | c.221G>T/c.476C>G |  | 1 | CH | (36) |
| 37 | FGD |  |  | S74I/S74I  S74I/S74I  S74I/S74I  S74I/S74I S74I/R128C I44M/L192fs P27R/Normal |  | 1  1  1  1  1  1  1 | Homo  Homo  Homo  Homo  CH  CH  Hetero | (37) |

Continued supplementary Table 1- The genetic characteristics, number of patients, protein change, zygosity of MRAP gene variants in literature including

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Number | Clinical phenotype | Total recruited patients | Nucleotide change | Protein change | mutated MRAP patients | Zygosity | Reference |
| 1 | FGD | 1 | c.130delG | V44X | 1 | Homo | (38) |
| 2 | FGD | 1 | c.17\_23del | L31X | 1 | Homo | (39) |
| 3 | FGD | 106 | c.106+1G>A | NA | 1 | Homo | (40) |
| c.106+1G>T | NA | 1 | Homo |
| c.106+1G>C | NA | 2 | Homo |
| c.106+1delG | NA | 5 | Homo |
| c.106+3insT | NA | 3 | Homo |
| c.3G>A | M1I | 8 | Homo |
| c.128delG | V44X | 1 | Homo |
| 4 | FGD2 | 1 | c. 106+1delG | NA | 1 | Homo | (41) |
| 5 | FGD | 1 | c.106+1delG | NA | 1 | Homo | (42) |
| 6 | FGD | 95 | c.158T>C | Leu53Pro | 1 | Homo | (43) |
| c.106+3insT |  | 1 | Homo | (43) |
| c.106+1delG |  | 5 | Homo | (43) |
| c.88\_90delAAG | p.K30del | 2 | Homo | (43) |
| 7 | late-onset FGD | 2 | c.175T>G | pY59D | 1 | Homo | (44) |
| c.76T>C | p.V26A | 1 | Homo | (44) |
| 8 | FGD | 1 | c.106+2\_3dupTA | NA | 1 | Homo | (45). |
| 9 | FGD | 5 | c.3G>A | M1I | 1 | Homo | (46) |
| 10 | Abstract | NA | c.33C>A | Y11X | 39 |  | (47) |

**Supplementary Table 2: Genetic characterization of the reported MC2R and MRAP gene variants**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No. | Variant name | | Reported No. | Location | Mutation Taster | Polyphen-2 | Provean | CADD | Functional research reports | Ref |
| cDNA | Amino acid |
|  | MC2R |  |  |  |  |  |  |  |  |  |
|  | Indels |  |  |  |  |  |  |  |  |  |
| 1 | Whole gene deletion | NA | 6 |  | NA | NA | NA | NA |  | (43) |
| 2 | c.137delT | p.Leu46fsX38 | 1 | TM1 | DC | NA | NA | 27.6 |  | (48) |
| 3 | c.357delC | p.Phe119LeufsX5 | 1 | Cytoplasmic | DC | NA | NA | 25.2 |  | (35) |
| 4 | c.459\_460insC | p.I154HisfsX95 | 12 | TM4 | DC | NA | NA | 24.1 |  | (13), (18) |
| 5 | c.560delT | p.Val187AlafsX29 | 21 | TM5 | DC | NA | NA | 28.1 |  | (5), (3) |
| 6 | c.577-78delTA | p.Leu192fs | 2 | TM5 | DC | NA | NA | 34 |  | (22), (37) |
| 7 | c.579-581delTGT | p.Tyr193Ter | 2 | TM5 | DC | NA | NA | 20.3 |  | (3) |
| 8 | c.634delA | p.Arg212fsX215 | 4 | Cytoplasmic | DC | NA | NA | 18.88 |  | (6),(13) |
| 9 | c.635insC | p.Ile154His | 2 | TM6 | DC | NA | NA | 23.4 |  | (11) |
| 10 | c.652-653insA | p.Ala218Aspfs\*31 | 1 | Cytoplasmic | DC | NA | NA | 35 |  | (20) |
| 11 | c.702delC | p.Phe235LeufsX7 | 2 | TM6 | DC | NA | NA | 35 |  | (49) |
| 12 | c.842delC | p.Pro281GlnfsX9 | 1 | Cytoplasmic | DC | NA | NA | 34 |  | (35) |
| 13 | c.866insA | p.Met290AspfsX60 | 3 | Cytoplasmic | DC | NA | NA | 29.7 |  | (35),(12) |
|  | Regulatory |  |  |  |  |  |  |  |  |  |
| 14 | c.-1017del44 | NA | 1 | NA | NA | NA | NA | NA |  | (20) |
|  | Missense/nonsense |  |  |  |  |  |  |  |  |  |
| 15 | c.2T>A | p.Met1Lys | NA | Extracellular | DC | PD | N -0.227 | 23.0 |  | (50) |
| 16 | c.58G>A | p.Asp20Asn | NA | Extracellular | DC | B | N -1.079 | 19.35 |  | (51) |
| 17 | c.61T>C | p.Cys21Arg | 1 | Extracellular | DC | PD | D-6.958 | 41 |  | (31) |
| 18 | c.62G>A | p.Cys21Tyr | 1 | Extracellular | DC | PD | D-6.26 | 24.4 |  | (26) |
| 19 | c.80C>G | p.Pro27Tyr | 1 | Cytoplasmic | DC | PD | D-4.661 | 25.1 |  | (1) |
| 20 | c.128T>G | p.Leu43Arg | 2 | TM1 | DC | PD | D-4.663 | 24.7 |  | This study |
| 21 | c.132C>G | p.Ile44Met | 2 | TM1 | P | B | N-0.088 | 7.76 | (52) | (22), (37) |
| 22 | c.145G>A | p.Val49Met | 1 | TM1 | DC | PD | N-2.305 | 25.3 |  | (17) |
| 23 | c.164T>C | p.Leu55Pro | NA | Cytoplasmic | DC | PD | D-6.485 | 24.5 |  | (51) |
| 24 | c.221G>T | p.Ser74Ile | 56 | TM2 | DC | PD | D-5.536 | 26.6 | (52, 53) | (34), (35), (36), (37), (3), (7), (28) |
| 25 | c.251T>A | p.Ile84Asn | 2 | TM2 | DC | PD | D-5.554 | 24.9 |  | This study |
| 26 | c.307G>A | p.Asp103Asn | 7 | Extracellular | DC | PD | D-4.741 | 26.1 | (52) | (35), (5), (8), (16), (24) |
| 27 | c.319G>A | p.Asp107Asn | 3 | TM3 | DC | PD | D-4.835 | 25.6 | (52) | (30), (2) |
| 28 | c.320A>G | p.Asp107Gly | 1 | TM3 | DC | PD | D-6.77 | 25.8 | (52) | (51) |
| 29 | c.347G>T | p.Gly116Val | 4 | TM | DC | PD | D-3.283 | 24.4 | (52) | (5), (14) |
| 30 | c.360C>G | p.Ser120Arg | 3 | TM3 | DC | PD | D-3.467 | 22.6 | (52) | (15), (32) |
| 31 | c.376G>T | p.Ala126Ser | 1 | TM3 | DC | B | D-1.916 | 16.84 |  | (27) |
| 32 | c.382C>T | p.Arg128Cys | 3 | Cytoplasmic | DC | PD | D-7.805 | 29.4 | (52) | (34), (37), (22) |
| 33 | c.386A>G | p.Tyr129Cys | 1 | Cytoplasmic | DC | PD | D-8.884 | 28 | (52) | (23) |
| 34 | c.389T>A | p.Ile130Asn | NA | Cytoplasmic | DC | PD | D-6.356 | 28.6 |  | (54) |
| 35 | c.409C>T | p.Arg137Trp | 3 | Cytoplasmic | DC | PD | D-6.816 | 26 | (52, 53) | (5), (8) |
| 36 | c.410G>C | p.Arg137Pro | NA | Cytoplasmic | DC | PD | D-5.864 | 23.9 |  | (54) |
| 37 | c.415C>T | p.His139Tyr | NA | Cytoplasmic | DC | PD | D-5.799 | 24.4 |  | (54) |
| 38 | c.424G>T | p.Val142Leu | 6 | Cytoplasmic | P | B | N0.295 | 16.73 | (55) | (1), (5), (15) |
| 39 | c.427G>T | p.Thr143Ser | 2 | Cytoplasmic | DC | B | N0.295 | 25.6 | (55) | (5), (15) |
| 40 | c.433C>T | p.Arg145Cys | 2 | Cytoplasmic | DC | PD | D-6.194 | 27.7 |  | (10), (19) |
| 41 | c.437G>C | p.Arg146His | 12 | Cytoplasmic | DC | PD | D-4.559 | 27.6 | (52) | (34), (22), (26), (33) |
| 42 | c.455C>A | p.Thr152Lys | 2 | TM4 | P | B | N-1.219 | 9.268 | (52) | (21) |
| 43 | c.476C>G | p.Thr159Lys | 9 | TM4 | P | PD | D-2.906 | 7.277 | (52) | (35), (36), (25) |
| 44 | c.509A>T | p.His170Leu | NA | Extracellular | DC | PD | D-3.742 | 24.4 |  | (51) |
| 45 | c.539C>A | p.Ser180Ter | 2 | Extracellular | DC | NA | NA | 36 |  | (49) |
| 46 | c.573C>A | c.Cys191Ter | NA | TM5 | DC | NA | NA | 37 |  | (56) |
| 47 | c.593T>C | p.Leu198Pro | NA | TM5 | DC | PD | D-5.408 | 29.4 |  | (54) |
| 48 | c.601C>T | p.Arg201Ter | 1 | Cytoplasmic | DC | NA | NA | 41 |  | (32) |
| 49 | c.674T>G | p.Leu225Arg | 4 | TM6 | DC | PD | D5.227 | 27.8 | (52) | (5), (9) |
| 50 | c.676G>A | p.Gly226Arg | 3 | TM6 | DC | PD | D-7.553 | 31 | (52) | (24), (5) |
| 51 | c.697G>C | p.Ala233Pro | 7 | TM6 | DC | PD | D-3.929 | 26.5 |  | This study,(43), (15), (25) |
| 52 | c.712C>T | p.His238Tyr | 1 | TM6 | DC | PD | D-5.773 | 27.3 |  | (10) |
| 53 | c.742A>G | p.Ser247Gly | 1 | Extracellular | DC | B | N -1.947 | 22.7 | (57) | (31) |
| 54 | c.752G>T | p.Cys251Phe | 2 | Extracellular | DC | PD | D-10.587 | 27.5 | (52) | (30) |
| 55 | c.761A>G | p.Tyr254cys | 4 | Extracellular | DC | PD | D-7.581 | 27.4 | (52, 53) | (4), (29) |
| 56 | c.767C>T | p.Ser256Phe | NA | Extracellular | DC | PD | D-5.255 | 29.9 |  | (51) |
| 57 | c.818C>A | p.Pro273His | 1 | TM7 | DC | PD | D-8.321 | 28.7 | (52) | (28) |
| 58 | c.833T>G | p.Phen278Cys | 1 | TM7 | P | PD | D-6.107 | 32 |  | (23) |
| 59 | c.752G>A | p.Cys251Trp | 2 | Extracellular | DC | PD | D-10.587 | 27.0 |  | (43) |
|  | MRAP |  |  |  |  |  |  |  |  |  |
|  | Deletion |  |  |  |  |  |  |  |  |  |
| 1 | c.17\_23delACGCCTC | p.Gln6Metfs\*24 | 2 | TM | DC |  |  | 25.0 |  | (39) |
| 2 | c.88\_90delAAG | p.Lys29del | 4 |  | DC |  |  | 21.6 |  | (43) |
| 3 | c.128delG | p.Val44Ter | 4 | TM | DC |  |  | 29.0 |  | (38), (40) |
|  | splice |  |  |  |  |  |  |  |  |  |
| 4 | c.106+3insT |  | 8 |  | P |  |  | 10.75 |  | (40), (43) |
| 5 | c.106+2\_3dupTA |  | 2 |  | DC |  |  | 24.2 |  | (45) |
| 6 | c.106+1G>C |  | 6 |  | DC |  |  | 31 |  | (40) |
| 7 | c.106+1G>A |  | 2 |  | DC |  |  | 32 |  | (40) |
| 8 | c.106+1delG |  | 24 |  | DC |  |  | 23.9 |  | (40),(41),(42),(43) |
| 9 | c.106+1G>T |  | 2 |  | DC |  |  | 31 |  | (40) |
|  | Missense/nonsense |  |  |  |  |  |  |  |  |  |
| 10 | c.3G>A | p.Met1Ile | 18 | TM | DC | PD | N -2.188 | 24.0 |  | (46), (40) |
| 11 | c.33C>A | p.Tyr11Ter | NA | TM | DC | NA | NA | 35 |  |  |
| 12 | c.77T>C | p.Val26Ala | 2 | TM | DC | PD | D -3.834 | 25.7 |  | (44) |
| 13 | c.158T>C | p.Leu53Pro | 2 | TM | DC | PD | D -5.690 | 26.0 |  | (43) |
| 14 | c.175T>G | p.Tyr59Asp | 2 |  | P | PD | D -6.231 | 23.9 |  | (44) |

TM: Transmembrane; DC: Disease causing, PD: probably damaging, N: Neutral. P: Polymorphism, D: Deleterious, B: Benign

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