Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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TABLE S1

***RET* Germline Mutations**

Classical MEN2A

Families or single patients with germline *RET* mutations, MTC, and either pheochromocytomas, or hyperparathyroidism, or both. Includes families or patients with *RET* codon mutations, or chromosomal alterations activating *RET*, including: deletions, insertions, duplications, multiple mutations, and homozygous mutations.

Codon Mutations:
Exon 5: (*V292M*[1]*),* **Exon 8:** (*G533C*[2-7]), **Exon 10:** (C609*F*[8,9]/*G*[10-13]/*R*[9,14]/*S*[15-19]/*Y*[9,20-23], *C611R*[24]/*S*[25]/*W*[26]/*Y*[21,27,28], *C618F*[24,29,30]/*G*[24,31]/*R*[26,30,32-34]/*S*[30,35-39]/*Y*[24], and *C620F*[24]/*R*[24,32]/*S*[40-42] /*Y*[43]*),* **Exon 11:** (*C630R*[44,45]*Y*[46], *D631Y*[47-50], *C634F*[24,30,31,51,52]/*G*[24,31,52-55]/*R*[30,43,52,54-59]/*S*[57]/*W*[51,52,55,59,60]/*Y*[51,52,54,55,57,59,61], *S649L*[62-64], and *K666E*[65,66]*),* **Exon 13:** (*L790F*[67] and *Y791F*[68-70]), **Exon 14:** (*V804L*[71-73] and *V804M*[74-82]*),* and **Exon 15:** (*S891A*[83,84]*)*

Deletions/insertions:
Exon 11: (*D631del*) of a 3 base pair (bp) segment, GAC; aspartic acid[85]), **Exon 11/Exons 4-16:** *(C634R/*and a large intragenic deletion of the normal allele; a somatic mutation which occurred only in a metastasis.[86]*)*

Duplications:
Exon 11: (in frame duplication of 9 bp, The codons 634,635, and 636 were repeated before the normal sequence was continued, resulting in an extra cysteine residue.[87]), **Exon 11:** (heterozygous mutation in exon 11 of the RET proto-oncogene representing a duplication of 12 bp. After the first base of codon 635 the previous 12 bp are repeated, resulting in the insertion of four amino acids between codon 634 (Cys) and 635 (Arg). This results in a new histidine codon (CAC) at the 5' breakpoint and creates an additional cysteine at the 3' end of the insertion. The codons for glutamine and leucine in the middle of the duplicated part are conserved.[88])

Double mutations:
Exon 10/Exon 13: (*C620F*)/*Y791F*[89]), **Exon 11/Exon 11:** (*C634S/A641S*[90]), **Exon 11/Exon 11:** (*C634R*/*V648I*[91]), **Exon11/Exon11:** (*C634W/R635G*[61]*)*, **Exon 11/Exon 11:** (*C634R/A640G*[92]*),* **Exon 11/Exon 13:** (*C634Y/Y791F*[93]*),* **Exon 11/Exon 11:** (*C634W/S649L*[62])

Combined germline and somatic RET mutations:
Exon 11/Exon 16: (*C634S/M918T*[94]), **Exon 11/Exon 16:** (*C634R/M918T*[94]*)*

Triple mutations:
Exon 11 /Exon 14/Exon 14: (*D631Y/S819I/E843D*[95]*),* and **Exon 11/Exon 11/Exon 11:**

(*C634R/A640G/M700L*[96]*)*

Quadruple mutation:
Exon 2/Exon 5/Exon11/Exon18:(*R67H/V292M/C634Y/R982C*[97]*)*

Homozygous mutation: Exon 14: *(V804L*[73]*)*

MEN2A with Hirschsprung's Disease

Exon 10: (C609*F*[8,9]*/G*[10-13]*/R*[9,14]*/S*[15-19]*/Y*[9,20-23]*, C611R*[24]*/S*[25]*/W*[26]*/Y*[21,27,28], *C618F*[24,29,30]*/G*[24,31]*/R*[26,30,32-34]*/S*[30,35-39]*/Y*[24], and *C620F*[24]*/R*[24,32]*/S*[40-42] */Y*[43]*)*

MEN2A with Cutaneous Lichen Amyloidosis

Exon 11: *C634F*[24,30,31,51,52]*/G*[24,31,52-55]*/R*[30,43,52,54-59]*/S*[57]*/W*[51,52,55,59,60]*/Y*[51,52,54,55,57,59,61]

FMTC
FMTC-1: Includes families who meet the original strict criteria defining this syndrome.[98]

Codon Mutations:
Exon 10: (*C611F*[11,55,99]*),* **Exon 13:** (*E768D*[100-104]), and **Exon 16** (*R912P*[105])

FMTC-2: Small families (of at least 2 generations, with at least 2 but less than 10 *RET* gene carriers) who have MTC but not pheochromocytoma or hyperparathyroidism. Includes families or patients with *RET* codon mutations, or chromosomal alterations activating RET, including: deletions, insertions, duplications, multiple mutations, and homozygous mutations.

Codon Mutations:
Exon 5: *(G321R*[106]**),* **Exon 8:** (*C515S*[107]*)*, **Exon 10:** *(K603Q*[108]**, Y606C*[65,109], and *C611G*[110]*),* **Exon 11:** (*K666M*[111], **Exon 13:** (*R770Q*[112]**, Q781R*[113]**, Y791N*[112]**, N777S*[114]*),* and **Exon 15:** *L881V*[112], and *R886W*[28]***.

Duplications, insertions, and deletions:
Exon 8: (after codon 531 the previous 9-bp sequence [AGGAGTGTG] is repeated, and then the normal sequence is continued, resulting in addition of a new cysteine codon.[115], **Exon 11***:* (R635-T636 insertion of E, L, C, and R amino acids and missense T636P[65]*), **Exon 11/Exons 4-16:** *(C634R/and a large intragenic deletion of the normal allele, leading to LOH, the latter a somatic mutation which occurred only in metastases*[86]***, and *K666/N*[116]*, also* (delGinsTTCT) leading to an Asn to Lys change [K666N] and to a serine insertion at codon 667[117])

Double mutations:
Exon 14/Exon14: *(V804M/R844L*[118]**)*, **Exon13/Exon14:** *(V778I/V804M*[119]**),* **Exon**

14/Exon16: *(V804L/M918T[120]*)* **Exon 11/Exon 14:** (*S649L/V804L[62]**)

Combined germline and *M918T* somatic mutations:
Exon 10/Exon 16: (*C618R/M918T[94]*), **Exon 10/Exon 16:** *(R620R/M918T[94]*), Exon 14/Exon 16: (V804L/M918T)[120]

Triple mutations:
Exon 2/Exon 5/Exon16: (*R67H/V292M/R982C[97]*)*

Homozygous mutations: Exon 14: (*V804M[121]*) and **Exon 14:** (*A833T[122]*)

FMTC-3: Single individuals or small families with 2 or less members with MTC in a single generation with no evidence of pheochromocytoma or hyperparathyroidism.

Codon Mutations: Exon 8:
(*A510V[116], E511K[116], C531R[116]*)**, Exon 10:** (*R600Q[123]* and *C620W[124]**)**, Exon 11:** (*C630F/R/S/Y[40,125,126]*, *E632K[127]*), **Exon 13:** (*V778I[128]**), and **Exon 14:** (*E819K[9]*, R833C[129], R844Q[9]*, M848T[130]*,* and *S904F[130]*).*

MEN2B

Includes families with the typical phenotype who have either *RET* germline mutations or double mutations:

Codon Mutations:
Exon 15: (*A883F[131,132]*), and **Exon 16:** (*M918T[133-135]*),

Double mutations:
Exon 14/Exon14: (*V804M/Y806C[136,137])*, **Exon 14/Exon 14:** (*V804M/E805K[138])*, **Exon 14/Exon 15:** (*V804M/ S904C[139]),* **Exon 13/Exon 14:** *(V804M/Q781R[140]),* **Exon 13/Exon 16:** (*Y791F/M918T[57,89]),* and **Exon 16/Exon16:** *(M918T/S922Y[141])*

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