**REPORT**

**RAB23 Mutations in Carpenter Syndrome Imply an Unexpected Role for Hedgehog Signaling in Cranial-Suture Development and Obesity**


Carpenter syndrome is a pleiotropic disorder with autosomal recessive inheritance, the cardinal features of which include craniosynostosis, polydactyly, obesity, and cardiac defects. Using homozygosity mapping, we found linkage to chromosome 6p12.1-q12 and, in 15 independent families, identified five different mutations (four truncating and one missense) in *RAB23*, which encodes a member of the RAB guanosine triphosphatase (GTPase) family of vesicle transport proteins and acts as a negative regulator of hedgehog (HH) signaling. In 10 patients, the disease was caused by homozygosity for the same nonsense mutation, L145X, that resides on a common haplotype, indicative of a founder effect in patients of northern European descent. Surprisingly, nonsense mutations of *Rab23* in *open brain* mouse cause recessive embryonic lethality with neural-tube defects, suggesting a species difference in the requirement for RAB23 during early development. The discovery of *RAB23* mutations in patients with Carpenter syndrome implicates HH signaling in cranial-suture biogenesis—an unexpected finding, given that craniosynostosis is not usually associated with mutations of other HH-pathway components—and provides a new molecular target for studies of obesity.

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mutations were found. We next analyzed nonsense mutations in the orthologous murine Rab23 gene. We identified a single missense mutation, C85R, encoding a nonconservative substitution from an uncharged to a charged amino acid; this residue is in 1 of the 4 helixes contained in the extracellular domain of Rab23, at position 85 (fig. 4), suggesting that this substitution would disrupt normal folding of Rab23. This mutation was present in individual 3961, who was a compound heterozygote for the C85R and L145X alleles; all of the seven exons and surrounding intronic regions of Rab23 revealed an identical homozygous 434T→A transition encoding an L145X nonsense mutation (fig. 3A) in the four affected individuals from families 1 and 2, as well as in a further sporadic case (subject 3734). These five subjects were all identically homozygous for 30 fully genotyped consecutive SNPs on the Affymetrix 50K array (from rs10484709 to rs1577630) (fig. 2B), indicating that they were very likely to share a single ancestral mutation (see below).

To expand the mutation spectrum in Rab23, we ascertained 12 additional unpublished Carpenter syndrome cases unrelated by family history. Including the three families described above, the 15 independent families included 17 affected individuals from whom DNA was available; 6 cases arose from known consanguineous unions. The families originated from the United Kingdom (five), Brazil (five), The Netherlands (three), and Denmark and the United States (one each). The clinical features of these 17 cases, which represent the largest series of subjects with Carpenter syndrome to date, are presented in table 2. Craniosynostosis was present in all individuals, with the sutures affected with relative frequency sagittal-metopic-coronal-lambdoid. Abnormalities of the hands included postaxial polydactyly (9 of 17 cases), broad or bifid thumbs (6 of 17), cutaneous syndactyly (12 of 17), and absent middle phalanges (9 of 11). In the feet, preaxial or central polydactyly (16 of 17) and syndactyly (17 of 17) were nearly always present. High birth weight (9 of 9) and obesity (9 of 10) were prevalent. Other significant complications included umbilical hernia (8 of 17), congenital heart disease (3 of 17), deformities of the knees (4 of 14) or ankles (4 of 17), and cryptorchidism or hypoplastic testes in males (6 of 8). Brain imaging showed abnormalities in 7 of 10 subjects; 3 of 16 had hydrocephalus requiring insertion of a shunt. Significant learning disability was present in 6 of 13 individuals. The occurrence of an open neural-tube defect (family 2; subject 3624), although not previously described in Carpenter syndrome, is unlikely to be coincidental, because this is a cardinal feature of Rab23 mutation in the mouse; the mother of subject 3624 had taken periconceptional folic acid supplements.

Pathogenic sequence variants were found in all individuals with the classic phenotype (table 3 and fig. 3A), showing that mutations of Rab23 are the major cause of Carpenter syndrome. We identified five different mutations, all of which predict a loss of function. Four (E48fsX7, Y78fsX30, E137X, and L145X) of the five alleles are nonsense or frameshifting mutations that would generate truncated proteins. We identified a single missense mutation, C85R, encoding a nonconservative substitution from an uncharged to a charged amino acid; this residue is involved in β-sheet formation and is completely buried in the core of the protein (fig. 4), suggesting that this substitution would disrupt normal folding of Rab23. This mutation was present in individual 3961, who was a compound heterozygote for the C85R and L145X alleles; all

Figure 1. Clinical features of Carpenter syndrome. A, Affected sister of subject 4009, aged 6 years. Note metopic ridge and temporal bulging secondary to multisuture synostosis, arched eyebrows, epicanthic folds, antverted nares, and broad thumbs and halluces with syndactyly, brachydactyly, clinodactyly, and polydactyly (postaxial in hands, central in feet). B, Severe bilateral clubfoot in subject 4009. C, Three-dimensional CT skull reconstruction of subject 3541, aged 4 wk, showing complete synostosis of the coronal sutures. D, Preoperative radiographs of the hands and feet of subject 3734, aged 11 years. Note characteristic longitudinally split epiphyses at bases of several proximal phalanges, central polydactyly of the feet, and biphalangeal digits II of the hands and II and III of the feet.

2 combined, at chromosome 6p12.1-q12 (fig. 2A). The flanking heterozygous SNPs in family 1 were rs7766181 and rs10498828, and the affected individual in family 2 was homozygous throughout this region.

The interval of homozygosity shared by the two families contained 24 annotated genes (Ensembl Genome Browser). Initially, we considered Bmp5 a candidate, because mutation of murine Bmp5 causes a range of skeletal defects resulting in the short ear phenotype; however, no mutations were found. We next analyzed Rab23; recessive nonsense mutations in the orthologous murine Rab23 gene cause neural-tube defects, abnormal somites, polydactyly, and poorly developed eyes (opb [open brain] locus). With use of the primers listed in table 1, direct sequencing...
other affected individuals appeared homozygous for their particular mutation. When samples were unavailable from both parents but we had sufficient proband DNA, we excluded the possibility that one allele harbored a deletion (table 3) by multiplex ligation-dependent probe-amplification (MLPA) analysis using synthetic oligonucleotide probes to RAB23 exons 1, 3, and 7 (MRC-Holland). All mutations were absent in ≥292 control chromosomes, as assessed by diagnostic restriction digests (fig. 3A and table 4).

The L145X mutation was apparently homozygous in 10 probands (3 each from the Netherlands and the United Kingdom, 2 from Brazil, and 1 each from the United States and Denmark), 3 of whom had been shown by the Affymetrix SNP analysis to share a common haplotype around the mutation (fig. 2B). To check whether any of the other cases had arisen from an independent mutation, we genotyped them for a subset of 13 SNPs around RAB23 (table 5). All 10 patients shared a common haplotype comprising 7 SNPs and spanning 2.2 Mb. This haplotype—which, according to HapMart (International HapMap Project), is present in only 11 of 120 Utah-CEPH chromosomes from HapMap16—was delimited by ancestral recombinations, distally in the Danish family and proximally in two Dutch families, and contains only eight genes in addition to RAB23 (fig. 2C). These data indicate that a founder effect,
Table 1. Primers Used for PCR Amplification of RAB23

<table>
<thead>
<tr>
<th>Primer</th>
<th>Forward Primer Sequence (5′→3′)</th>
<th>Reverse Primer Sequence (5′→3′)</th>
<th>Product Size (bp)</th>
<th>Wave Temperature(s) (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAB23_1</td>
<td>CTCCACCTTGG6GATTTGAC</td>
<td>AACAGCCCTTTCTAGGCCTT</td>
<td>270</td>
<td>59</td>
</tr>
<tr>
<td>RAB23_2</td>
<td>CCACAGATGGCAGGGAAGA</td>
<td>AGATGCAACCTTGCAGAAC</td>
<td>333</td>
<td>56.4</td>
</tr>
<tr>
<td>RAB23_3</td>
<td>TTACCAAAATCTTTTTCAA</td>
<td>GCTTACAAAATATCATCCAA</td>
<td>188</td>
<td>54</td>
</tr>
<tr>
<td>RAB23_4</td>
<td>TGTGAATGTAATAGCTTAGTTG</td>
<td>TATAGGAAATCGGCCCCCTTCTC</td>
<td>250</td>
<td>56.5 and 58.5</td>
</tr>
<tr>
<td>RAB23_5</td>
<td>AAAAAAGCTATCAGAAGGCACC</td>
<td>CAACACAATTTTAAAAGCAG</td>
<td>207</td>
<td>54.5</td>
</tr>
<tr>
<td>RAB23_6</td>
<td>ATCACTAGGCTGGTTCATGGG</td>
<td>ATAGACAGCTGGATGCTCAGGTC</td>
<td>228</td>
<td>55</td>
</tr>
<tr>
<td>RAB23_7</td>
<td>TAACTAGGCGTGTACAGGGT</td>
<td>ATGCAGCAGATGCTGTTT</td>
<td>256</td>
<td>57</td>
</tr>
</tbody>
</table>

Note.—DNA was obtained from whole-blood samples by phenol-chloroform extraction and was amplified in a total volume of 25 µl containing 15 mM TrisHCl (pH 8.0), 50 mM KCl, 2.5 mM MgCl₂, 100 µM each deoxy-nucleoside triphosphate, 0.5 µM primers, and 0.75 units of Amplitaq Gold polymerase (Applied Biosystems). All PCRs were performed using an annealing temperature of 60°C. Cycling conditions consisted of an 8-min denaturation step at 94°C, followed by 35 cycles at 94°C for 30 s, at 60°C for 30 s, and at 72°C for 60 s, with a final extension at 72°C for 10 min.

Figure 3. RAB23 mutations in Carpenter syndrome. A, Sequence chromatograms and confirmatory restriction digests for the five pathogenic mutations identified. Note that patient 3961 is a compound heterozygote for the C85R and L145X mutations. B, top, The exon/intron organization of RAB23, with the coding part of the cDNA (GenBank [accession number NM_183227.1]; Ensembl Genome Browser [reference OTTHUMG00000014918]) in black and the UTRs in white (alternatively spliced 5′ noncoding exons omitted). Plain numbering refers to the first nucleotide of each exon, starting from the initiation codon, and italic numbering indicates the length of introns. Bottom, Functional domains in the 237-aa protein, GDP binding site, Mg binding residue, Prenylation signal, Switch domain.
rather than a recurrent mutation, underlies Carpenter syndrome in patients of northern European descent and does not support the possibility that the L145X mutation has particular functional consequences (see below). Two patients from eastern Brazil both appeared homozygous for the E137X mutation, which resides on a shared haplotype spanning at least 5.8 Mb (fig. 2C). The E48fsX7 and Y78fsX30 mutations were each found in one patient only.

To explore whether RAB23 mutations play a more general pathological role either in craniosynostosis or in limb malformations, we screened respective patient panels by a combination of Wave denaturing high-performance liquid chromatography (Transgenomic) and diagnostic restriction digestes for mutations identified in Carpenter syndrome. DNA from 256 patients with craniosynostosis (negative for the common mutations in the FGFR1, FGFR2, FGFR3, and TWIST1 genes),6 202 patients with limb malformations requiring plastic surgery, and 163 control individuals was analyzed using the assays detailed in tables 1, 4, and 6. None of the Carpenter syndrome mutations (table 3) were identified in any of these cohorts. Although six novel alleles—including an amino acid substitution, an amino acid deletion, and a nonsense mutation (all in six novel alleles—including an amino acid substitution, an amino acid deletion, and a nonsense mutation (all in 60 small guanosine triphosphatases (GTPases) that regulate intracellular trafficking of membrane-associated proteins13–15; other family members for which germline mutations cause human disorders are RAB7 (Charcot-Marie-Tooth disease type 2B, dominant inheritance [MIM #600882])18 and RAB27A (Griscelli syndrome type 2, recessive inheritance [MIM #607624]).19 Our finding of RAB23 mutations in Carpenter syndrome is unexpected, because similar nonsense mutations of the orthologous murine RAB23 gene (encoding K39X and R80X) in opb mice cause recessive embryonic lethality with exencephaly.10-12 It is unlikely that the human RAB23 mutations represent partial loss-of-function alleles of lesser severity than do the murine ones, for two reasons. First, prenylation at a consensus site in the C-terminus of RAB proteins by Rab geranylgeranyl transferase is essential for their correct membrane targeting,15 predicting that all truncating mutations should result in complete loss of function. Second, two of the human truncating mutations (E48fsX7 and Y78fsX30) occur upstream of the opb mutation R80X (fig. 3B),15 yet neural-tube defects were absent in the affected individuals. Consistent with this, we did not find any clear genotype-phenotype correlation for the human mutations, although the fetus 3965, with the most N-terminal truncation (E48fsX7), was the only subject terminated antenatally and might represent a more severe phenotype (table 2).

The original identification of Rab23 mutations in opb mice was driven by genetic studies to identify modifiers of hedgehog (HH) signaling in the neural tube. In mammals, there are three paralogous HH genes—Shh, Ihh, and Shh, Ihh, and Shh, Ihh.
Figure 4. Sequence conservation and structural context of C85R substitution. A, Amino acid sequence comparison of the Switch 2 region of human RAB23 (top) with 13 other species. The consensus sequence is shown at the bottom, and the position of the mutated C85 residue is indicated with an arrow. B, Structure of human RAB23 (Protein Data Bank [number 1Z22]), showing the C85 residue located in a β-strand (blue) and completely buried in the core of the protein. The bound Mg-GDP is shown in yellow. The structure was modeled using the Protein Workshop tool (Protein Data Bank).

Table 4. Primers and Restriction Enzymes Used for Confirmation of RAB23 Mutations

<table>
<thead>
<tr>
<th>Mutation and Primer</th>
<th>Primer Sequence (5′→3′) a</th>
<th>Product Size (bp)</th>
<th>Restriction Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>E48fsX7:</td>
<td></td>
<td>157</td>
<td>XcmI (−)</td>
</tr>
<tr>
<td>E48fsXdigF</td>
<td>AAAGACTACAAGAAAAACCATTGCCATG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAB23_2R</td>
<td>AGTTGCGACACCTCAGATC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y78fsX30:</td>
<td></td>
<td>188</td>
<td>StuI (−)</td>
</tr>
<tr>
<td>RAB23_3F</td>
<td>TTACCAAAATTTTTATTTTACA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAB23_3R</td>
<td>GCCAAAATAATATGCCCCAA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C85R:</td>
<td></td>
<td>156</td>
<td>BssSI (+)</td>
</tr>
<tr>
<td>C85RdigF</td>
<td>TTGTATGGGATAAAAGTGGCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C85RdigR</td>
<td>TTTGAATGGATAAAAGTTGCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E137X:</td>
<td></td>
<td>207</td>
<td>HindIII (+)</td>
</tr>
<tr>
<td>RAB23_5F</td>
<td>AAACAAGCTATCAGAAAGGCCACC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAB23_5R</td>
<td>CAACACAATTTTTAAAAGCGCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L145X:</td>
<td></td>
<td>120</td>
<td>HpaI (−)</td>
</tr>
<tr>
<td>RAB23_5F</td>
<td>AAACAAGCTATCAGAAAGGCCACC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAB23_L145XdigR</td>
<td>TCTTTCAGAATGGGCCAGAATGGT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note.—PCRs were performed using the same conditions as described in table 1.

a Nucleotides shown in bold represent mismatches incorporated into primers to engineer diagnostic restriction sites.
indicating that the Rab23 mutations bypass the requirement for Shh. In the neural tube, mutation of Shh has opposite consequences to mutation of Rab23, causing loss (Shh) and expansion (Rab23) of ventral markers; Patched1, a transcriptional target of Shh signaling, is activated in opb mice, showing that Rab23 is a negative regulator of HH signaling. Genetic analysis of epistatic relationships shows that Rab23 acts downstream of the key HH signaling intermediate Smoothened but upstream of both the effector transcription factors Gli2 and Gli3 and the intraglafellar transport proteins (such as those encoded by Ift88/polaris and Ift172/wim), required for their capacitation. As such, Rab23 is one of a number of genes (including iguana, talpid3, Fkbp8, and Ift family members) implicated in the regulation of Gli transcription–factor processing specifically in vertebrates and is the first of these implicated in a human disorder. Rab23 localizes to membranes and is expressed at multiple sites in the mouse, including embryonic neural tube, limb bud, brachial arches, tooth and palate, and adult brain; however, its precise membrane-transport activity has not been defined.

Given the evidence that Rab23 regulates the HH pathway, it is not surprising that some aspects of the phenotype of Carpenter syndrome resemble other human disorders associated with disturbed HH signaling. Most notably, the combination of postaxial polysyndactyly of the hands and preaxial polysyndactyly of the feet is very similar to the pattern that occurs in Greig syndrome (MIM #175700), which is due to haploinsufficiency of Gli3, and is consistent with the observed reduction in the proportion of Gli3 repressor in Rab23-mutant embryos. The brachydactyly present in Carpenter syndrome, characterized by hypoplasia or absence of the middle phalanges, resembles brachydactyly type A1, which is caused by heterozygous missense mutations in Shh—encoded sonic, Indian, and desert HH proteins, and implicates the regulation of Gli transcription–factor processing specifically in vertebrates and is the first of these implicated in a human disorder. Rab23 localizes to membranes and is expressed at multiple sites in the mouse, including embryonic neural tube, limb bud, brachial arches, tooth and palate, and adult brain; however, its precise membrane-transport activity has not been defined.

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tants,10–12,22 that are not well recognized features of perturbed HH signaling.20 Particularly interesting are the craniosynostosis and tendency to postnatal obesity, which may provide new clues for dissecting the pathophysiology of these phenotypes.

Relatively little is known about the role of HH signaling in the cranial sutures. In mice, Shh is expressed in the osteogenic fronts of the parietal bones and sagittal sutures only at a relatively late stage of suture development (embryonic day 17),23 and Shh−/− mice die too early to assess the developmental contribution to the cranial sutures. Although endochondral ossification is characteristically deficient in Ihh−/− mice, membranous ossification of the skull vault is maintained31; however, there are no published data on the expression pattern of Ihh in the sutures. Our work should stimulate efforts to identify the active HH ligand(s) and to explore the extent to which the well-documented developmental relationship among HH signaling, twist, and FGF receptors in the limbs34 is recapitulated.

The results have been conflicting as to whether this effect was inhibitory or stimulatory.37 The association of these phenotypes.

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Web Resources

Accession numbers and URLs for data presented herein are as follows:
dhsSNP http://www.ncbi.nlm.nih.gov/SNP/ (for SNPs, including rs1040461, rs1925179, rs2397214, rs2996842, rs1547625, rs6927258, rs6906792, rs3904827, rs6934928, rs1343391, rs1224703, rs1850417, rs2343013, and rs1689237)
Ensembl Genome Browser, http://www.ensembl.org/ (for RAB23 [reference OTTHUMG00000014918])
Protein Data Bank, http://www.rcsb.org/pdb/home/home.do (for RAB23 structure [number 1Z22] and Protein Workshop)

References

11. Eggenschwiler JT, Anderson KV (2000) Dorsal and lateral fates...


