Rapid onset dystonia-parkinsonism (RDP) is a rare movement disorder with autosomal dominant inheritance, characterised by sudden onset of dystonic spasms and slowness of movement. To date, three families have been described that share linkage to the same location on chromosome 19q13, designated DYT12. Very recently, mutations in the ATP1A3 gene at the DYT12 locus have been demonstrated in seven unrelated patients, including the three previously linked families. A large RDP family is reported here, with eight definitively and one possibly affected members, that is not linked to the DYT12 region and has no mutation in the ATP1A3 gene. Predominant cranial-cervical involvement of dystonia occurred in this family, which has also been described in patients with idiopathic torsion dystonia linked to the DYT6 region on chromosome 8 and is a rare finding in DYT1 dystonia. Molecular genetic analysis also excluded linkage to the DYT6 locus and the GAG deletion in DYT1, suggesting at least one additional RDP gene.

METHODS

Patients

After obtaining informed consent, all available family members underwent a detailed neurological examination, and videotaping was carried out on the index patient (III.15) and her mother (II.9). Information on deceased individuals was obtained by reviewing medical records or by interview of family members. The diagnosis of RDP was established according to the current clinical criteria and rated using the RDP rating scale. Clinical investigations of the index patient included routine laboratory testing, copper and ceruloplasmin analysis, EEG, and brain magnetic resonance imaging (MRI).

DNA analysis

The index patient was screened for the GAG deletion in DYT1. Linkage analysis was carried out on all available family members at the DYT12 and DYT6 loci using the following microsatellite markers:

- **DYT12**: D19S224 (61.49cM) – D19S197 (63.10cM) – D19S223 (64.16cM) – D19S420 (66.30cM) – D19S900 (67.37cM) – D19S178 (68.08cM) – D19S574 (69.50cM) – D19S903 (69.90cM);
- **DYT6**: D8S1477 (60.34cM) – D8S1828 (71.00cM) – D8S1113 (77.89cM) – D8S1136 (82.26cM) – D8S2324 (94.08cM) – D8S1119 (101.01cM).

Primer sequences were taken from the genome database (www.gdb.org). In addition, following the identification of the RDP gene at the DYT12 locus, we sequenced the ATP1A3 gene in our index patient as described.

Statistical analysis

The computer program VITESSE was used for the LOD score analysis.

RESULTS

Patients

This German RDP family consists of 37 identified family members, 20 of whom could be examined, including all four living definitely affected members (fig 1). Information on the remaining 17 individuals was obtained by interview of relatives. Eight family members (four male, four female; mean (SD) age at onset, 7.1 (2.7) years, range 4 to 12) were definitely affected, five in generation II and three in generation III. In addition, individual I.2 (generation I) was affected by history and rated as possibly affected. Mode of inheritance appeared autosomal dominant.

No affected individual has been identified in generation IV as yet (current mean (SD) age, 17.3 (6.5) years; range 4 to 25). Of note, three individuals (II.5, II.6, and III.10) were definitely affected; note that II.6 and III.10 are possibly affected members.

Abbreviations: RDP, rapid onset dystonia-parkinsonism

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Intron boundaries in the index patient. Exclusion by direct sequencing of the coding region and exon–intron regions. In addition, mutations in the DYT6 gene were excluded in our family. Owing to the predominant orofacial involvement in DYT6 dystonia, that is somewhat reminiscent of the “bulbar dystonia” in RDP, we considered involvement of the DYT6 gene. This, however, also turned out to be negative. Owing to the early onset and broad spectrum of DYT1 dystonia, we tested for the GAG deletion in the DYT1 gene, and this was excluded as well.

Overall, our genetic results suggest the presence of at least one additional dominantly inherited gene causing RDP or a different disease mechanism in our family. The possibility of a mitochondrial (mtDNA) point mutation was investigated in a previous study but no disease causing mutation was found. As all affected individuals in our family inherited the disease from their mother, the mode of inheritance would be compatible with maternal transmission or with an autosomal dominant inheritance, possibly of a maternally expressed gene. This observation may thus warrant both analysis of the mtDNA and an investigation of the known paternally imprinted genes to identify a novel RDP gene in our family.

DISCUSSION
We describe the first family with RDP that is not caused by mutations in the ATP1A3 gene although it is clinically similar to the three previously described RDP pedigrees and to the Spanish sporadic case, and conforms to the RDP diagnostic criteria. In particular, our family also showed a combination of dystonic and parkinsonian signs with abrupt or subacute onset, predominant bulbar involvement, and no response to levodopa treatment. RDP onset was preceded by a febrile illness in three of the eight definitely affected individuals in our family. Similarly, a trigger (stress/trauma) was reported in four of eight members of the Irish RDP family. Our family also confirms the intrafamilial variability of symptoms and disease course.

It should be borne in mind that the current RDP diagnostic criteria are based on only two RDP families. In this context, several distinguishing features of our family are worthy of note. First, the mean age of onset of about seven years was lower than in the previously described families, in whom the disease mostly started in adolescence. Surprisingly, no member of generation IV has become affected as yet. This may in part be explained by the fact that at least some individuals may not yet have reached the age of onset. Second, three family members were born preterm and died in their first year of unknown cause, and three of the eight definitely affected individuals had fatal renal failure. In addition, the index patient and her mother also suffer from renal disorder; however, its potential relation to the RDP in this family remains elusive. Third, linkage to the RDP locus (DYT12 on chromosome 19q) and mutations in the ATP1A3 gene were excluded in our family.

Because of the predominant orofacial involvement in DYT6 dystonia that is somewhat reminiscent of the “bulbar dystonia” in RDP, we considered involvement of the DYT6 gene. This, however, also turned out to be negative. Owing to the early onset and broad spectrum of DYT1 dystonia, we tested for the GAG deletion in the DYT1 gene, and this was excluded as well.

Overall, our genetic results suggest the presence of at least one additional dominantly inherited gene causing RDP or a different disease mechanism in our family. The possibility of a mitochondrial (mtDNA) point mutation was investigated in a previous study but no disease causing mutation was found. As all affected individuals in our family inherited the disease from their mother, the mode of inheritance would be compatible with maternal transmission or with an autosomal dominant inheritance, possibly of a maternally expressed gene. This observation may thus warrant both analysis of the mtDNA and an investigation of the known paternally imprinted genes to identify a novel RDP gene in our family.
Clinical characteristics of definitely affected family members

<table>
<thead>
<tr>
<th>Pedigree No.</th>
<th>II.2</th>
<th>II.3</th>
<th>II.9 (L-1518)</th>
<th>II.11</th>
<th>II.13</th>
<th>III.9 (L-1799)</th>
<th>III.13 (L-1820)</th>
<th>III.15 (L-1519)</th>
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<tr>
<td>Sex</td>
<td>FM</td>
<td>F</td>
<td>M</td>
<td>FM</td>
<td>M</td>
<td>F</td>
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<td>F</td>
</tr>
<tr>
<td>Life span or current age (years)</td>
<td>72</td>
<td>1930 to 1991</td>
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<td>49</td>
<td>44</td>
<td>43</td>
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**Characteristics at disease onset**

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<tr>
<th>Age (years)</th>
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<th>561</th>
<th>2</th>
<th>4</th>
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<th>0</th>
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<td>Dysarthria, dystonia, dysphagia</td>
<td>Dysarthria, dystonia, dysphagia, seiarge dystonia of all four extremities, hypomimia, bradykinesia</td>
<td>Dysarthria, dysphagia, severe dystonia of all extremities, hypomimia, bradykinesia</td>
<td>Dysarthria, dysphagia</td>
<td>Dysarthria, dysphagia</td>
<td>Dysarthria, dysphagia, seiarge dystonia of all extremities, hypomimia, bradykinesia</td>
<td>Dysarthria, dysphagia, seiarge dystonia of all extremities, hypomimia, bradykinesia</td>
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<td>Trigger</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
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<tr>
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<td>Rapid</td>
<td>Rapid</td>
<td>Rapid</td>
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<td>Rapid</td>
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<tr>
<td>Hypomimia, bradykinesia</td>
<td>Hypomimia, bradykinesia</td>
<td>Hypomimia, bradykinesia</td>
<td>Hypomimia, bradykinesia</td>
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**Characteristics at most recent examination**

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<tr>
<th>Age (years)</th>
<th>Deceased</th>
<th>Deceased</th>
<th>71</th>
<th>Deceased</th>
<th>Deceased</th>
<th>48</th>
<th>43</th>
<th>39</th>
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<tbody>
<tr>
<td>Dysarthria, dystonia</td>
<td>Dysarthria, dystonia, dysphagia</td>
<td>Dysarthria, dystonia, dysphagia, seiarge dystonia of all extremities, hypomimia, bradykinesia</td>
<td>Dysarthria, dystonia, dysphagia, seiarge dystonia of all extremities, hypomimia, bradykinesia</td>
<td>Dysarthria, dystonia, dysphagia</td>
<td>Dysarthria, dystonia, dysphagia, seiarge dystonia of all extremities, hypomimia, bradykinesia</td>
<td>Dysarthria, dystonia, dysphagia, seiarge dystonia of all extremities, hypomimia, bradykinesia</td>
<td>Dysarthria, dystonia, dysphagia, seiarge dystonia of all extremities, hypomimia, bradykinesia</td>
<td></td>
</tr>
<tr>
<td>Disease duration (years)</td>
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<td>42</td>
<td>66</td>
<td>55</td>
<td>51</td>
<td>39</td>
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<td>34</td>
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<tr>
<td>Residual symptoms</td>
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<td>Dysarthria, hypomimia, bradykinesia</td>
<td>Dysarthria, hypomimia, bradykinesia</td>
<td>Dysarthria, hypomimia, bradykinesia</td>
<td>Dysarthria, hypomimia, bradykinesia</td>
<td>Dysarthria, hypomimia, bradykinesia</td>
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**Additional features**

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<tr>
<th>RDP severity scale</th>
<th>Cysts in the kidneys</th>
<th>None</th>
<th>None</th>
<th>None</th>
<th>Hypoplastic kidney</th>
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</thead>
</table>

**REFERENCES**

Genetic heterogeneity in rapid onset dystonia-parkinsonism: description of a new family

K Kabakci, K Isbruch, K Schilling, K Hedrich, P de Carvalho Aguiar, L J Ozelius, P L Kramer, M H R M Schwarz and C Klein

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