

## LETTERS TO THE EDITOR

### Kenny-Caffey syndrome without the CATCH 22 deletion

With regard to the recent report by Sabry *et al.*<sup>1</sup> we would like to present an additional case of Kenny-Caffey syndrome who, unlike their case, did not have a chromosomal deletion at 22q11.2 (the CATCH 22 region). We also report detailed test results for calcium metabolism and response to combination therapy with vitamin D, magnesium, and growth hormone.

The female patient was born after 40 weeks of an uneventful pregnancy to non-consanguineous, healthy, Japanese parents. She weighed 2750 g and measured 46 cm at birth. At 1 month, she had an episode of generalised convulsions because of hypocalcaemia. During this episode, her serum calcium, phosphorus, magnesium, calcitonin, and intact PTH were 5.0 mg/dl (reference range 8.6-9.7), 9.1 mg/dl (2.7-4.3), 1.2 mg/dl (1.8-2.2), 120 pg/ml (94-156), and <15 pg/ml (15-50), respectively. Oral 1 $\alpha$ -vitamin D (0.3  $\mu$ g/day) administration was started on the basis of a diagnosis of hypoparathyroidism. The patient's serum calcium levels were normalised although her intact PTH remained at low to low-normal levels. She had another episode of hypocalcaemic convulsions at 9 months of age. At the age of 5 years 1 month, she was referred to our hospital for further examination.

Physical examination showed her to be of proportionally short stature. Her height was 84.2 cm (mean -5.3 SD) and her weight was 12.2 kg. She had normal intelligence, a prominent forehead, and slender extremities. Her anterior fontanelle still showed an opening of 1  $\times$  1 cm. She had severe hyperopia with normal optic fundi. Radiological examination showed medullary stenosis of the long bones typical of Kenny-Caffey syndrome. CT scan of the brain showed fine calcification in the basal ganglia. Although her serum calcium remained normal with relatively low doses of vitamin D, the EDTA loading test (50 mg/kg) indicated a blunted response for i-PTH (basal 12.8 pg/ml, peak 17.5 pg/ml). The PTH loading test showed a normal response to exogenous PTH with increased urinary excretion of phosphorus and cAMP. Growth hormone provocative tests showed normal responses.

As in the case of Sabry *et al.*,<sup>1</sup> we also suspected the possibility of the patient having a deletion in the CATCH 22 region. However, FISH analysis on peripheral blood leucocytes using probe D22S75 (Oncor) showed a normal diploid state. The patient was then put on a combination therapy of vitamin D (1  $\mu$ g/day) and magnesium sulphate (0.4 g/day). Since her short stature did not improve with this therapy, growth hormone therapy (0.5 IU/kg/week) was initiated at the age of 7 years 5 months. After two years of this therapy, the height standard deviation for her chronological age improved from -5.4

SD to -4.4 SD without appreciable acceleration of bone maturation.

The reason for the discrepancy between the Bedouin family reported by Sabry *et al.*<sup>1</sup> and our case remains unclear. One possibility is the genetic heterogeneity of the syndrome. Of the 47 reported cases, more than half were familial and both autosomal dominant and recessive forms have been reported.<sup>2,3</sup> The cases reported by Sabry *et al.*<sup>1</sup> had interesting and unusual features for the syndrome, such as marked IUGR, microcephaly, and severe mental retardation, while our case had more typical features of the syndrome. Most of the Bedouin cases of the syndrome show mental retardation,<sup>1</sup> while this is rare in other populations. It is therefore possible that the syndrome in Bedouins is genetically different from that in other ethnic groups. Another possibility is that the gene is actually in the CATCH 22 region but the defect varies from large scale deletion to subtle mutations. It is also possible that the different phenotypes are caused by a contiguous gene effect. Without a large scale deletion, the phenotype would be more typical of the syndrome.

Finally, a combination therapy of vitamin D, magnesium, and growth hormone seems to be moderately effective in the treatment of short stature in these patients without increasing the risk of hypocalcaemic attacks. More efforts should therefore be made to improve the final height of these patients.

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- 1 Sabry MA, Zaki M, Hassan SJA, *et al.* Kenny-Caffey syndrome is part of the CATCH 22 haploinsufficiency cluster. *J Med Genet* 1998;35:31-6.
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- 3 Majewski F, Rosendahl W, Ranke M, Nolte K. The Kenny syndrome, a rare type of growth deficiency with tubular stenosis, transient hypoparathyroidism and anomalies of refraction. *Eur J Pediatr* 1981;136:21-30.
- 4 Franceschini P, Testa A, Bogetti G, *et al.* Kenny-Caffey syndrome in two sibs born to consanguineous parents: evidence for an autosomal recessive variant. *Am J Med Genet* 1992;42:112-16.
- 5 Khan KTS, Uma R, Usha R, Al Ghanem MM, Al Awadi SA, Farag TI. Kenny-Caffey syndrome in six Bedouin sibships: autosomal recessive inheritance is confirmed. *Am J Med Genet* 1997;69:126-32.

### Kenny-Caffey syndrome is part of the CATCH 22 haploinsufficiency cluster

Sabry *et al.*<sup>1</sup> reported an interesting Bedouin sibship with Kenny-Caffey syndrome. The two surviving children and their mother were found to have a microdeletion of the region commonly deleted in the CATCH 22 spectrum of phenotypes. On further investigation this was shown to be inherited from their phenotypically normal mother. The authors concluded that their observation widens the phenotypic spectrum of CATCH 22 to include the features of Kenny-Caffey syndrome, namely severe growth retardation and cortical thickening/medullary stenosis of the tubular long bones. However, Khan *et al.*<sup>2</sup> reported six Bedouin sibships all with paren-

tal consanguinity, with a total of 16 children with features of the disorder, suggesting that Kenny-Caffey syndrome is an autosomal recessive trait. There are at least two other possible explanations for the findings in the family described by Sabry *et al.*<sup>1</sup> The first is that the children have autosomal recessive Kenny-Caffey syndrome in keeping with this being a consanguineous family with the chromosome 22 deletion being a second, independent abnormality. The other possibility is that the deletion has unmasked a defect in the Kenny-Caffey locus on the normal chromosome in much the same way as Bernard-Soulier syndrome was mapped to this region of chromosome 22.<sup>3</sup> This hypothesis could easily be tested in the consanguineous Bedouin sibships reported.

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- 1 Sabry MA, Zaki M, Hassan SJA, *et al.* Kenny-Caffey syndrome is part of the CATCH 22 haploinsufficiency cluster. *J Med Genet* 1998;35:31-6.
- 2 Khan KTS, Uma R, Usha R, Al Ghanem MM, Al Awadi SA, Farag TI. Kenny-Caffey syndrome in six Bedouin sibships: autosomal recessive inheritance is confirmed. *Am J Med Genet* 1997;69:126-32.
- 3 Budarf ML, Konkle BA, Ludlow LB, *et al.* Identification of a patient with Bernard-Soulier syndrome and a deletion in the Di George/velo-cardio-facial chromosomal region in 22q11.2. *Hum Mol Genet* 1995;4:973-6.

### Kenny-Caffey syndrome is part of the CATCH 22 haploinsufficiency cluster

The paper by Sabry *et al.*<sup>1</sup> described four affected sibs with Kenny-Caffey syndrome, and on the basis of the cytogenetic findings the authors postulated that this disorder is part of the CATCH 22 haploinsufficiency cluster. They did, however, comment that the clinical features in these patients were atypical of those previously described in Kenny-Caffey syndrome.

Phenotypically these patients are much more like those described by Richardson and myself in 1990,<sup>2</sup> with a number of subsequent reports of similar children. These children have all been of Middle Eastern origin and do appear to represent a separate entity from Kenny-Caffey syndrome.

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- 1 Sabry MA, Zaki M, Hassan SJA, *et al.* Kenny-Caffey syndrome is part of the CATCH 22 haploinsufficiency cluster. *J Med Genet* 1998;35:31-6.
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### Genotypic/phenotypic heterogeneity of Kenny-Caffey syndrome

Several reports have accumulated delineating Kenny-Caffey syndrome (KCS) in presumed