LETTERS

Coexistent *MEFV* and *CIAS1* mutations manifesting as familial Mediterranean fever plus deafness

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We report two individuals with familial Mediterranean fever (FMF) confirmed on genetic testing who also had progressive deafness and mutations in the *CIAS1* gene. This is the first report of co-existent mutations in the *CIAS1* and *MEFV* genes in the literature.

Patient 1, a boy, was investigated for splenomegaly in infancy without an identified cause. He had speech delay at the age of 3 years with mild conductive hearing deficit and at 5 years sensorineural deafness of 60 dB bilaterally in the 2000–3000 Hz range. At 6 years of age he developed recurrent fever, abdominal pain, arthritis and raised inflammatory markers. FMF was diagnosed and he responded to colchicine treatment. He was diagnosed with Crohn's disease at the age of 14 years.

Patient 2, a girl, had anaemia and splenomegaly without any cause at 5 years of age and bilateral sensorineural deafness of 60 dB at frequencies of >1000 Hz with speech delay at 6 years despite previously normal audiometry. At the age of 8 years FMF was diagnosed after recurrent abdominal pain, fever, arthritis and raised inflammatory markers. Compliance with colchicine was poor and she died aged 13 of renal amyloidosis.

Neither family had any history of consanguinity or inter-relationship, and sequencing of *MEFV* exon 10 PCR products from probands showed that both were compound heterozygotes carrying the c.2177T>C (p.V726A) mutation and the complex c.2076_2078delATA-(p.I692del)/c.442G>C(p.E148Q) allele. Sequencing of exon 3 of the CIAS1 gene revealed that patient 1 carried the p.Q703K missense mutation, which is unlikely to be pathogenic based on its high allele frequency of 0.05, and patient 2 the p.V198M mutation, which is a reduced penetrance disease-associated mutation and is found in asymptomatic individuals with an allele frequency of 0.0074.[1]

Both patients had normal CT scans of the temporal bones and mutation analysis for the connexin 26 and *PDS* genes. The worldwide incidence of severe sensorineural deafness is approximately 1:2000 and at least 50% of cases are hereditary.[2] Of these, 70% are non-syndromic and autosomal recessive.[2] Mutations of the connexin 26 gene are thought to account for the majority of such deafness.[2] The aetiology of progressive deafness in Cryopyrin associated periodic syndromes (CAPS) is unknown, but recent work showing that *CIAS1* is highly expressed in chondrocytes[3] and cochlear enhancement on MRI scan in patients with CAPS suggests an inflammatory cause.[4]

We propose that synergistic heterozygosity between disease causing mutations in the *MEFV* gene and non-disease causing or low penetrance sequence variations of the *CIAS1* gene may have resulted in the clinical phenotype of FMF with progressive sensorineural deafness as seen in CAPS, possibly due to the role of both genes in the regulation of interleukin-1. Similar synergistic heterozygosity has been described in other conditions such as mitochondrial fatty acid oxidation disorders[5] and type 2 diabetes mellitus.[6] Furthermore, renal amyloidosis has been reported in a patient free of any symptoms of an inflammatory syndrome with heterozygous mutations in the *MEFV* gene and the *TNFRSF1A* gene, implicated in the tumour necrosis factor receptor associated periodic syndrome.[7]

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REFERENCES

1 **Aksentijevich I**, Putnam CD, Remmers EF, Mueller JL, Le J, Kolodner RD, *et al.* The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model. *Arthritis Rheum* 2007;**56**:1273–85.
2 **Sundstrom RA**, Laer LV, Camp GV, Smith RJ. Autosomal recessive nonsyndromic hearing loss. *Am J Med Genet* 1999;**89**:123–9.
3 **Feldman J**, Prieur A, Quartier P, Berquin P, Certain S, Cortis E, *et al.* Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in *CIAS1*, a gene highly expressed in polymorphonuclear cells and chondrocytes. *Am J Hum Genet* 2002;**71**:198–203.
4 **Goldbach-Mansky R**, Dailey NJ, Canna SW, Gelabert A, Jones J, Rubin BI, *et al.* Neonatal-onset mulitisystem inflammatory disease responsive to interleukin-1β inhibition. *N Engl J Med* 2006;**355**:581–92.
5 **Schuler MA**, Gower BA, Matern D, Rinaldo P, Vockley J, Wood PA. Synergistic heterozygosity in mice with inherited enzyme deficiencies of mitochondrial fatty acid β-oxidation. *Mol Genet Metabol* 2005;**85**:7–11.
6 **Kido Y**, Burks DJ, Withers D, Bruning JC, Kahn CR, White WF, *et al.* Tissue-specific insulin resistance in mice with mutations in the insulin receptor, IRS-1 and IRS-2. *J Clin Invest* 2000;**105**:199–205.
7 **Cigni A**, Ledda F, Satta AE. A complex case of renal amyloidosis with a rare co-occurrence of two mutations in separate hereditary periodic fever syndrome related genes. *J Nephrol* 2006;**19**:543–9.