

Research Letter

Letter to the Editor: Novel *GJA1* Mutation in Oculodentodigital Dysplasia

Jari Honkaniemi,* Juha-Pekka Kalkkila, Pasi Koivisto, Veikko Kähärä, Terho Latvala, and Kalle Simola

Departments of Neurology, Clinical Genetics, Radiology and Ophthalmology, Tampere University Hospital and University of Tampere, Tampere, Finland

To the Editor:

Oculodentodigital or oculodentoosseous dysplasia (ODDD) is a well-known disorder that has been reported over 200 times [Loddenkemper et al., 2002]. It has been reviewed by Gorlin et al. [2000], who cited 47 references. The most common neurological symptoms are spastic paraparesis and bladder disturbances [Loddenkemper et al., 2002]. ODDD is caused by mutations in the gap junction alpha 1 (*GJA1*) gene encoding the connexin-43 protein [Paznekas et al., 2003]; 26 missense mutations and one codon duplication in the second exon have been described [Paznekas et al., 2003; Kjaer et al., 2004; Pizzuti et al., 2004; Richardson et al., 2004; Vitiello et al., 2005]. Here, we report a patient with a novel *GJA1* mutation.

A 47-year-old woman had slow progressive weakness of the lower extremities. She also had urinary incontinence. She had had a history of mild talipes equinovarus; syndactyly of



Fig. 2. Radiographs of the hands and feet. Note aplasia of the middle phalanges in the fifth fingers and in all toes.

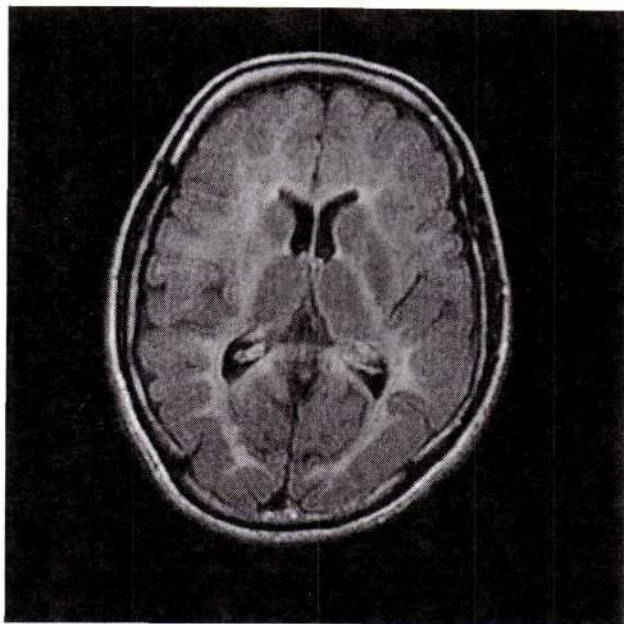


Fig. 1. Fluid attenuation inversion recovery imaging of the brain. Note mild hyperintensity of the white matter.

fourth and fifth fingers, which had been surgically corrected; and syndactyly of the right third and fourth toes. During the past year, she reported poor balance and episodes of falling. Motor examination showed moderate spasticity in both legs and scissor gait. Her tendon reflexes of upper and lower extremities were brisk, and Achilles tendon reflexes showed clonus. Babinski signs were negative and she had no sensory



Fig. 3. Appearance of the probanda. Note thin nose.

*Correspondence to: Dr. Jari Honkaniemi, University of Tampere, Department of Neurology, Biokatu 10, 33014 Tampere University, Tampere, Finland. E-mail: bljaho@uta.fi

Received 20 April 2005; Accepted 19 June 2005

DOI 10.1002/ajmg.a.30925

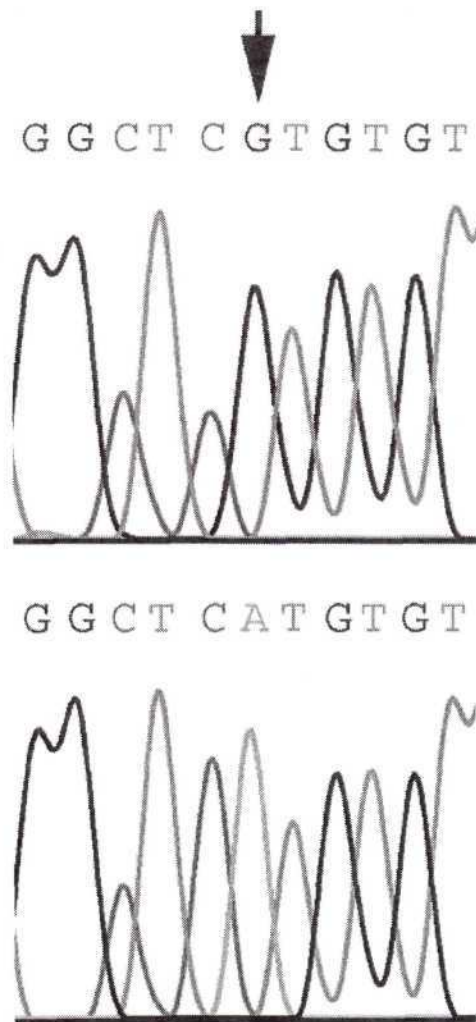


Fig. 4. Mutated (arrow) and intact allele of the patient's *GJA1* sequence.

deficits. Magnetic resonance imaging (MRI) showed no abnormalities in the spinal cord. Brain MRI demonstrated hyperintensity of the cerebral white matter in T2-weighted images, but no focal signs of demyelinating diseases (Fig. 1). Cerebrospinal fluid (CSF) examination showed normal cell, protein, and IgG-index levels. Isoelectric focusing of CSF proteins was normal. The patient's brother and parents did not have similar symptoms, but her daughter had syndactyly and severe clubfoot, both of which had been surgically corrected. Radiographs showed aplasia of the middle phalanges of the

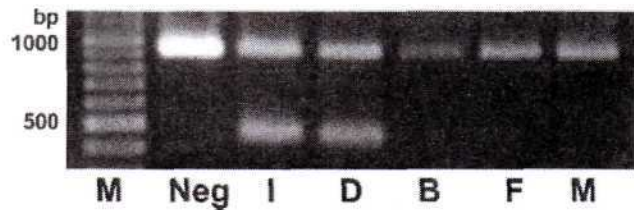


Fig. 5. RFLP analysis of the proposita (Ind) and her relatives. M, 100 bp molecular weight marker; Neg, negative control; I, Proposita (Ind) D, daughter; B, brother; F, father; M, Mother.

fifth finger and all toes (Fig. 2). The nose was thin and the teeth were hypoplastic (Fig. 3). Neuro-ophthalmological examination showed mild myopia and moderate atrophy of the optic disks, paracentral scotomas, and slightly delayed latencies in visual evoked potentials. Visual acuity, color vision, corneal diameters, and ocular motility examination were within normal limits.

A product was amplified from the second exon of *GJA1* containing the coding sequence for the first 238 amino acids of the *GJA1* protein using primers 5'-GATCTTTTCTTTCGTTGGC-3' and 5'-CTCTTTCCCTTAACCCG-3' [Paznekas et al., 2003]. We found a novel mutation in the second exon; 284A→G, resulting in His95Arg (Fig. 4). We then isolated DNA from the patient's daughter, brother, and parents and amplified the *GJA1* gene with the same primer. The daughter with talipes equinovarus and syndactyly had the same mutation. Her brother and parents showed intact alleles, suggesting a de novo mutation in the proposita (Fig. 5).

REFERENCES

- Gorlin RJ, Cohen MM Jr, Hennekam RCM. 2000. New York: Oxford University Press. pp 290–292.
- Kjaer KW, Hansen L, Eiberg H, Leicht P, Opitz JM, Tommerup N. 2004. Novel Connexin 43 (*GJA1*) mutation causes oculo-dento-digital dysplasia with curly hair. *Am J Med Genet* 127A:152–157.
- Loddenkemper T, Grote K, Evers S, Oelerich M, Stogbauer F. 2002. Neurological manifestations of the oculodentodigital dysplasia syndrome. *J Neurol* 249:584–595.
- Paznekas WA, Boyadjev SA, Shapiro RE, Daniels O, Wollnik B, Keegan CE, Innis JW, Dinulos MB, Christian C, Hannibal MC, Jabs EW. 2003. Connexin 43 (*GJA1*) mutations cause the pleiotropic phenotype of oculodentodigital dysplasia. *Am J Hum Genet* 72:408–418.
- Pizzuti A, Flex E, Mingarelli R, Salpietro C, Zelante L, Dallapiccola B. 2004. A homozygous *GJA1* gene mutation causes a Hallermann–Streiff/ODDD spectrum phenotype. *Hum Mutat* 23:286.
- Richardson R, Donnai D, Meire F, Dixon MJ. 2004. Expression of *Gja1* correlates with the phenotype observed in oculodentodigital syndrome/type III syndactyly. *J Med Genet* 41:60–67.
- Vitiello C, D'Adamo P, Gentile F, Vingolo EM, Gasparini P, Banfi S. 2005. A novel *GJA1* mutation causes oculodentodigital dysplasia without syndactyly. *Am J Med Genet A* 133:58–60.