CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2013: 84: 300–301
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CLINICAL GENETICS
doi: 10.1111/cge.12068

Letter to the Editor

Mental retardation, short stature and synpolydactyly in a manifesting heterozygote of Bartsocas–Papas syndrome

To the Editor:

Bartsocas–Papas syndrome (BPS) is a severe and rare autosomal recessive (AR) disorder characterized by severe popliteal webbing, oligosyndactyly, and genital abnormalities (1). In a recent case report, we described a 16-year-old mentally retarded patient in an Egyptian family with BPS (2). This patient, the maternal uncle of two cases of BPS, showed some of the typical features of the syndrome, but lacked the major criteria as pterygi and orofacial clefts. He presented with microphthalmia, ptosis of left eyelid, and thin lips. The patient also had multiple café au lait spots, truncal obesity and hypoplastic external genitalia. A striking complete right thumb-index syndactyly and a short left thumb were detected. Radiographs of hands showed an abnormal hypoplastic middle phalanx with duplication of distal phalanx of the right second finger and a hypoplastic first metacarpal in both hands (Fig. 1).

Shortly after our report, the responsible gene was identified (3). Homozygous mutations in *RIPK4*; the gene encoding receptor-interacting serine/threonine kinase protein 4 (RIPK4), were shown to cause BPS in affected cases including the niece of our patient. The patient was subsequently tested; and surprisingly, he was found heterozygous for the mutation detected in his niece; a single base pair insertion in exon 5 (c.777-778insA). This insertion is predicted to cause a frameshift leading to a pre-mature stop codon (p.Arg260ThrfsX14) and a non-functional truncated protein.

As an AR disorder, BPS syndrome is not expected to be manifested in the heterozygous state, as it is the case with the healthy parents of the affected cases in this family. However, our finding suggests that this patient is possibly a manifesting heterozygote of BPS and that RIPK4 can show heterozygote expression.

In practice, there have been several observations of subtle and sometimes significant manifestations noted in heterozygous carriers of AR disorders (4–6). These cases have always formed an enormous clinical challenge to the geneticists. Manifesting heterozygotes have been described in a number of AR pedigrees of enzymopathies; such as phosphoglycerate mutase deficiency (6),

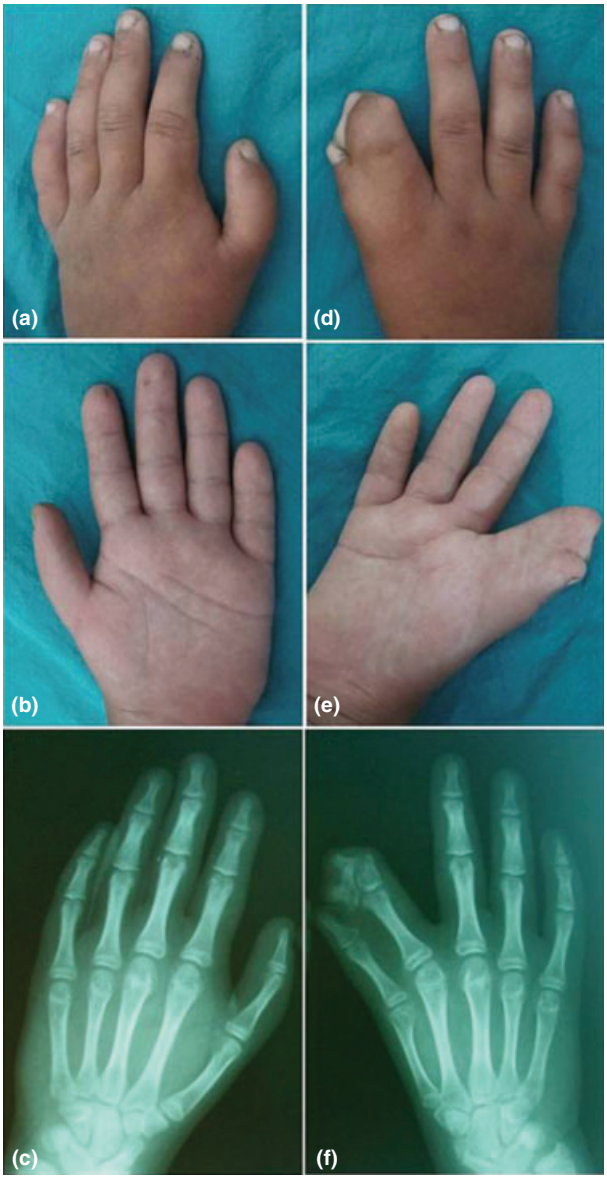

Fig. 1. Limb abnormalities in the Bartsocas–Papas syndrome heterozygous carrier. Hands photographs and radiographs showing (a–c) hypoplastic thumb in the left hand and (d–f) syndactyly between the first and second fingers, with an extra nail in the right hand [reprinted with permission from ref. (2)].

and 21-hydroxylase deficiency (7), which is mostly due to a decrease in enzyme activity below a critical threshold. Interestingly, some models of manifesting heterozygosity exist in disorders that are not related to enzymopathies, such as, ataxia telangiectasia (5) and few AR multiple malformation syndromes; the most explicit example being Meckel syndrome (4).

At present, we do not have a rational explanation for the clinical manifestations described in the presented case whereas the other two heterozygous family members, who carry the same molecular defect, are clinically normal. One potential explanation is the allelic expression imbalance with pre-dominance of the mutant allele in this patient; a phenomenon most likely explained by the presence of *cis*-regulatory polymorphisms (8). In this context, we are going to seek expression analysis for both the symptomatic and healthy carriers in the family. Moreover, modifier genes, other still unknown genetic or epigenetic factors and perhaps intrauterine environmental effects may be responsible for the occurrence of symptoms in some carriers of AR genes.

In summary, our finding points out to the possible occurrence of manifesting heterozygosity in BPS families. We, therefore, emphasize the importance of careful examination of family members. Finally, we recommend the use of expression analysis to examine the gene expression profiles of heterozygous carriers of BPS and other recessive diseases in order to improve our understanding of their phenotype.

Acknowledgements

We gratefully acknowledge the contribution of Ersan Kalay (Department of Medical Biology, Karadeniz Technical University Faculty of Medicine, Turkey) in the molecular testing.

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