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NEWS AND COMMENTARY

Chromosomal Microdeletions and Genes' Functions

A cluster of chromosomal microdeletions and the deleted genes' functions

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Cystinuria, one of the four inborn errors of metabolism, discussed by Garrod[1] as early as in 1908 (MIM 220100), is a relatively common authosomal recessive disorder, with an overall prevalence of approximately 1 in 7000.[2] It is owing to the defective transport of cystine and dibasic amino acids through the epithelial cells of the renal tubule and intestinal tract. Cystine has a low solubility and its precipitation results in the formation of calculi in the urinary tract. The clinical manifestations are predominantly renal, and the frequency of neurological deficits was found to be comparable to that in the general population.[3] However, lately, two novel clinical presentations associated with cystinuria were added; the first consisting of cystinuria, neonatal seizures, hypotonia, severe somatic and developmental delay, facial dysmorphism and lactic acidosis was described in seven patients of a small Bedouin clan,[4] and the second consisting of hypotonia and cystinuria was described in 11 patients from small regions of Belgium and France that appeared to have originated from a common ancestor.[5] In this issue, Martens *et al*[6] expand their original observation on hypotonia-cystinuria patients to four additional families from Netherlands, Italy, United States and Canada.

The additional clinical manifestations in these novel presentations are caused by homozygous gene contiguous deletions. The differences in phenotype between the two novel presentations can be explained by the size of the deletions, that is the number of genes involved. The Bedouin phenotype was caused by the deletion of 179 kb encompassing at least four genes: solute carrier 3A1 (SLC3A1), prolyl endopeptidase like (PREPL), protein phosphatase 2Cβ (PP2Cβ) and C2orf34, thus called the 2p21 deletion syndrome.[4,7] The hypotonia–cystinuria syndrome (HCS) is caused by the homozygous deletion of only two genes, SLC3A1 and PREPL; the transcription of the neighboring genes was not affected by the deletions that ranged in size from 24 to 75.5 kb.[5] The SLC3A1 gene encodes the heavy-chain subunit of the cystine and dibasic amino-acid transporter localized in the renal proximal tubule and small intestine. Inactivation of this gene product is known to cause isolated cystinuria type I.[8] The other clinical features of the HCS can therefore be attributed to the gene product of *PREPL*. Thus the absence of the PREPL gene causes neonatal and infantile hypotonia, and poor feeding during infancy, often necessitating nasogastric tube feeding or gastrostomy. Some dysmorphyism is present, particularly dolichocephaly and ptosis of the eyelids, as well as a striking nasal speech. Anorexia and hypotonia ameliorate with age, but gradually growth velocity decreases owing to IGF-1 insufficiency. Growth hormone deficiency was present in the majority of patients and they responded well to growth hormone treatment. Electromyography and brain MRI had been found to be normal. In addition, patients have classical cystinuria type I causing nephrolithiasis at variable ages. The 2p21 deletion syndrome patients are expected to have all the clinical presentation of the HCS patients and additional manifestations caused by the absence of two other genes: PP2Cβ and C2orf34. Indeed, in addition to the hypotonia resembling that described for the HCS patients, they present severe developmental retardation manifested as delay in speech that does not become comprehensive even later in life, neonatal seizures and distinct dysmorphic features that differ from those of the HCS patients, and most of the patients show elevated serum lactate levels during infancy. Two of the patients who were verified demonstrated reduced activity of the respiratory complexes, the subunits of which are encoded in the mitochondrial genome. However, the 2p21 deletion syndrome patients do not present all the manifestations of the HCS: thus, only one of the patients with the larger deletion had growth hormone deficiency and was treated by growth hormone administration. A possible explanation could be that the activity of modifier genes enhances the production and secretion of growth hormone in the Bedouin patients. One patient with HCS also showed reduced activities of the mitochondrial respiratory complexes, similar to patients with the large deletion; thus presently it cannot be deduced which of the three genes, PREPL, PP2Cβ or C2orf34, causes this defect. However, we would have expected more than one patient out of the 20 with HCS to demonstrate this defect if PREPL was the causal gene.

The phenotypes caused by the inactivity of any of these three genes cannot be predicted. PREPL is highly similar to the prolyl oligopeptidase family, especially prolyl endopeptidase, but no substrate has been identified so far.[5,9] The C2orf34 gene is predicted to have methyl transferase activity but the prediction is not supported by experimental data. No mutations in the PP2Cβ gene have yet been reported and its knock out in mice causes early pre-implantation lethality.[10]

Although copy number variation representing large-scale insertions and deletions is gaining recognition as a major contributor to human diversity, complete deletions causing genetic diseases are rare events. The finding of six different deletions in the same chromosomal region and

perhaps more, whose exact borders are presently undefined, would be unexpected unless this region is prone to these events. Verification of the Hap-Map database for copy number variations shows that none has been found within one million bases from either side. The mechanism causing the microdeletions is not known; for the 2p21 deletion, it was suggested that it could have been caused by an excision transposition event through alignment of Alu elements residing at the deletion borders. Of the five deletions observed for the HCS, two appeared multiple times and were globally distributed. The haplotypes of the microsatelite markers flanking the breakpoints were different; thus the deletions may have occurred long time ago and the ancestral haplotype decayed, or less plausibly, as the breakpoints are exactly the same, a genetic mechanism is promoting deletions in this region to happen on multiple chromosomes. One of the two recurring deletions found in 1872 chromosomes of the Belgian population is compatible with a founder effect and predicts that the disease will be rare in this population. Much additional work, either by identification of additional deletions in this region or targeted deletion of each gene in model system, will be needed to elucidate the function and the contribution of each of the three deleted genes, besides the SLC3A1 gene, to the patients' phenotype■

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