The prevalence of CHD7 missense versus truncating mutations is higher in patients with Kallmann syndrome than in typical CHARGE patients

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Résumé en anglais	CONTEXT: Mutations in CHD7, a gene previously implicated in CHARGE (coloboma, heart defect, choanal atresia, retardation of growth and/or development, genital hypoplasia, ear anomalies) syndrome, have been reported in patients presenting with Kallmann syndrome (KS) or congenital hypogonadotropic hypogonadism (CHH). Most mutations causing CHARGE syndrome result in premature stop codons and occur de novo, but the proportion of truncating vs nontruncating mutations in KS and CHH patients is still unknown. OBJECTIVE: The objective of the study was to determine the nature, prevalence, mode of transmission, and clinical spectrum of CHD7 mutations in a large series of patients. DESIGN: We studied 209 KS and 94 CHH patients. These patients had not been diagnosed with CHARGE syndrome according to the current criteria. We searched for mutations in 16 KS and CHH genes including CHD7. RESULTS: We found presumably pathogenic mutations in CHD7 in 24 KS patients but not in CHH patients. Nontruncating mutations (16 missense and a two-codon duplication) were more prevalent than truncating mutations (three nonsense, three frame shift, and a splice site), which contrasts with patients presenting with typical CHARGE syndrome. Thus, the clinical spectrum associated with CHD7 mutations may be partly explained by genotype/phenotype correlations. Eight patients also had congenital deafness and one had a cleft lip/palate, whereas six had both. For 10 patients, the presence of diverse features of the CHARGE spectrum in at least one relative argues against a de novo appearance of the missense mutation, and this was confirmed by genetic analysis in five families. CONCLUSION: Considering the large prevalence and clinical spectrum of CHD7 mutations, it will be particularly relevant to genetic counseling to search for mutations in this gene in KS patients seeking fertility treatment, especially if KS is associated with deafness and cleft lip/palate.
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