***CDH1* germline mutations: different syndromes, same management?**

Patrick R. Benusiglio, MD, PhD

Just over 20 years ago, Gorlin *et al.* introduced a new medical entity, the blepharocheilodontic syndrome (BCD).¹ Its initial features were ectropion of the lower eyelids; euryblepharon with lagophthalmia (widening of the palpebral aperture with associated difficulty closing the eyes); distichiasis of the upper eyelids (disorderly, double row of eyelashes); sparse lower eyelashes, eyebrows and scalp hair; hypertelorism; cleft lip and/or palate (CLP); hypo/oligodontia; teeth with conical crowns; and syndactyly. Expressivity of these manifestations was variable. Subsequent descriptions of cases added imperforate anus and hypothyroidism/thyroid agenesis to the clinical spectrum.^{2,3} Even though BCD was clearly a genetic, autosomal dominant syndrome, the causative genes had yet to be identified.

In a remarkable paper published in this issue of *Genetics in Medicine*, Ghoumid *et al.* studied eleven individuals with BCD from eight families.⁴ They performed exome sequencing in five families and targeted sequencing in the remainder, and found in all of them pathogenic or likely pathogenic germline mutations in either *CDH1* or *CTNND1*. Overall, the association is convincing, even though in vitro experiments, in addition to the in silico simulations and expression studies already performed, would be needed to prove beyond reasonable doubt the pathogenicity of the three missense *CDH1* mutations (there is little doubt that the splice-site *CDH1* and truncating *CTNND1* mutations are pathogenic). With hindsight, the implication of these two genes is not surprising. Indeed, they code for E-cadherin and Catenin delta 1 (p120CTN) respectively, two interacting intercellular adhesion proteins that have, among others, a key role in craniofacial development.^{5,6} In addition, *CDH1* is an established susceptibility gene for nonsyndromic CLP, with, for example, 4/81 (5%) affected cases carrying a germline mutation in a Dutch study.⁷

The medical relevance of the findings reported by Ghoumid *et al.*⁴ would be limited to the possibility of preimplantation or prenatal testing for BCD patients planning to conceive, were it not for hereditary diffuse gastric cancer (HDGC), a complex and fascinating cancer susceptibility syndrome. Like BCD, HDGC is caused by germline *CDH1* mutations. In HDGC, carriers are at increased risk of diffuse gastric

cancer (DGC) and invasive lobular carcinoma of the breast (ILC), two cancers that invariably show somatic inactivation of E-cadherin or one of its partners. Multiple cases of DGC and/or ILC, often diagnosed at a young age, are therefore typically observed in HDGC families. DGC is a gastric cancer subtype composed of mucous cells that generally do not form glands but permeate the mucosa and wall as scattered individual signet-ring cells or small clusters in an infiltrative growth pattern.⁸ It is also called signet-ring cell carcinoma of the stomach. Cumulative incidence by age 80 is estimated at 70% for males and 56% for females.⁹ ILC, previously called lobular breast carcinoma, represents about 10% of breast carcinomas.¹⁰ Beyond E-cadherin inactivation, it has other similarities with DGC, mainly a diffusely invasive pattern. Cumulative incidence in females is estimated at 42% by age 80.⁹

Now let's move to the core of the problem: cancer risk management in *CDH1* mutation carriers who have not yet manifested cancer. The main consensual recommendation regarding DGC risk is a drastic and life-changing one: risk-reducing gastrectomy between the ages of 20 and 30.¹¹ Why are such radical measures endorsed by experts? Because in its early stages, DGC and its noncohesive pattern of signet-ring cells frequently evade detection by upper gastrointestinal endoscopy, as opposed to the exophytic or excavated appearance or the classic, intestinal-type gastric carcinoma.¹² Furthermore, in addition to the 56–70% cumulative incidence of clinically manifest DGC, malignant or premalignant changes are almost invariably seen in risk-reducing gastrectomy specimens, regardless of the upper endoscopy findings.^{11,12} In this context, one can ill afford leaving in place an organ likely to harbor, at least at some stage, a lethal disease. Annual upper gastrointestinal screening endoscopies with multiple stomach-wide biopsies are sometimes considered an acceptable alternative, but only a temporary one for patients wishing to delay gastrectomy, for personal or professional reasons. ILC risk management is more easily implemented. Women are offered annual screening breast magnetic resonance imaging starting at the age of 30, and risk-reducing bilateral mastectomy is performed should the patient request it.¹¹

CDH1 is therefore implicated in two very different syndromes, BCD and HDGC, and in nonsyndromic CLP. But is cancer prevention warranted in *CDH1*-associated BCD and CLP individuals? If yes, should the same measures as those recommended to HDGC families apply? When the *CDH1* mutation is clearly pathogenic, my answer is a cautious yes. In the absence of genotype–phenotype correlation, one should indeed consider that the risk of DGC or ILC is high enough to justify risk-reducing gastrectomy and ILC screening. Furthermore, there is obvious overlap between HDGC, BCD and nonsyndromic CLP. For example, in the paper by Ghoumid *et al.*⁴, the mother of a BCD case died at the age of 35 of gastric cancer, most likely of the diffuse type, while CLP has been reported in at least six HDGC families so far.^{6,13,14} Admittedly, four out of five *CDH1* families reported by Ghoumid *et al.*⁴ had no history of DGC, and this is why the authors do not envisage risk-reducing gastrectomies at this stage. I would like to emphasize, however, that one of the mutations had occurred de novo in the proband, explaining at least in part this lack of family history. In any case, it would be extremely informative and useful to follow prospectively all *CDH1* mutation carriers from BCD families, to perform annual upper endoscopies according to the Cambridge protocol, to at least discuss the possibility of risk-reducing gastrectomy, to offer women annual breast magnetic resonance imaging, and to report any cancer occurrence.

Preimplantation diagnosis is rarely discussed in HDGC because manifestations associated with *CDH1* mutations, i.e., DGC and ILC, were only known to affect adults and were to some extent preventable. Following this study, it is possible that the offspring of HDGC patients are at increased risk of malformations, and it would seem pertinent to address this issue with young HDGC patients planning to conceive.

Not all families with multiple cases of DGC and/or ILC carry *CDH1* germline mutations; the proportion is around 20%.¹⁵ There are therefore other susceptibility genes. Only one has been reliably identified so far: *CTNNA1*, a gene that, like *CDH1*, is involved in intercellular adhesion.⁹ The involvement of another catenin gene, *CTNND1*, in two families with BCD, raises the question of its implication in families with suspected HDGC who test negative for *CDH1*. Targeted *CTNND1* sequencing in a large number of such families is therefore warranted.

In conclusion, the findings published by Ghoumid *et al.*⁴ in this issue of *Genetics in Medicine* have implications that go well beyond the simple identification of the genes that cause

BCD syndrome. The involvement of *CDH1* means that BCD families are likely at high risk of both DGC and ILC, and that risk-reducing measures, however radical they might be, must be discussed. Reciprocally, it is possible that *CDH1* mutations overall increase the risk of congenital malformations. Finally, the involvement of *CTNND1* in BCD makes it an ideal candidate for future studies looking for new DGC/ILC susceptibility genes.

DISCLOSURE

The authors declare no conflict of interest.

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