lated NCAMs promote cell migration and, thus, they are thought to play a critical role in development. More specifically, it has been shown that, during diaphragmatic morphogenesis, the expression of polysialylated NCAMs is tightly modulated along each stage of myogenesis (Allan and Greer 1998).

Finally, although it is less likely, we cannot exclude the possibility that both the mentioned hypotheses are true. In this case, the critical region would be represented by the extent of the deletion in patient 8 (fig. 1).

Additional findings are needed to refine the search for a CDH gene in 15q chromosome. However, it seems likely that *NR2F2* and *ST8SIA2* are the best candidates.

Acknowledgments

This study was supported by the Italian Ministry of Health.

L. Castiglia,[1] M. Fichera,[1] C. Romano,[2] O. Galesi,[1] L. Grillo,[1] M. Sturnio,[1] and P. Failla[2]

[1]*Laboratorio di Diagnosi Genetica and* [2]*Unità Operativa Complessa di Pediatria e Genetica Medica, IRCCS Oasi Maria SS, Troina, Italy*

Web Resources

URLs for data presented herein are as follows:

NCBI Map Viewer, http://www.ncbi.nlm.nih.gov/mapview/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

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Address for correspondence and reprints: Dr. Marco Fichera, Laboratorio di Diagnosi Genetica, IRCCS Oasi M. SS. Via Conte Ruggero 73, 94018, Troina, Italy. E-mail: mfichera@oasi.en.it

0002-9297/2005/7705-0017$15.00

Am. J. Hum. Genet. 77:892–894, 2005

Reply to Castiglia et al.

To the Editor:

In response to our article in the May issue of the *Journal* (Klaassens et al. 2005), Castiglia et al. (2005 [in this issue]) address the strategy of including patients with a 15q deletion but without congenital diaphragmatic hernia (CDH). They defined a deletion on 15q26.1–26.2 in a girl with multiple congenital anomalies but without CDH. Combining data from this patient with previously published data from two patients with a 15q deletion but without CDH (Rogan et al. 1996; Tonnies et al. 2001), Castiliglia et al. (2005) found a discrepancy between our data and the CDH locus that they determined. Of the two hypotheses postulated to explain these contradictory results, we support the first one, which suggests that including patients without CDH in the analysis might be inappropriate because of the possibility that heterozygous deletion of a part of 15q (which results in haploinsufficiency for this locus) might not be completely penetrant. Incomplete penetrance could also explain, in part, the variability in phenotype of patients with CDH and a 15q deletion.

Since the publication of our article, we have been able to more precisely define the deletions in our patients with CDH. With CDH patients only, a 4-Mb common CDH region would be located between BAC clones RP11–

44A22 (overlapping with RP11–641M8 and RP11–261M12; see fig. 1 in Castiglia et al. [2005]) and RP11–616M17 (data not shown), with the telomeric boundary determined by the interstitial deletion of patient 1 (patient 8 in fig. 1 in Castiglia et al. [2005]). We, therefore, excluded some genes from the region, including the *SIAT8B* gene (MIM 602546) suggested by Castiglia et al. (2005) as one of the candidate genes for CDH. The remaining region still contains *NR2F2, IGF1R,* and three hypothetical genes. We are in the process of screening, with mutation analysis, all genes in this deleted region in a large group of CDH patients and screening with FISH for deletions. Of the genes located in this region, we still consider *NR2F2* to be the most likely candidate. The recent report by Tümer et al. (2004) supports this hypothesis. They analyzed three ring carriers, one of which had a different phenotype than the other two patients (Tümer et al. 2004). This third patient had CDH and other anomalies, and the deletion included the same genes as in the other two patients, except for the *NR2F2* gene, which was deleted only in the patient with CDH. In contrast to the opinion of Castiglia et al. (2005), we believe ring carriers can provide valuable clues in the search for chromosomal loci that could be involved in the etiology of congenital anomalies. Although ring chromosomes can be unstable, we have not observed gain or loss of other genetic material. In addition, the new chromosomal telomeric DNA of derivative chromosomes in unbalanced translocations could be of influence.

In conclusion, we hypothesize that 15q26.1–26.2, a gene-poor region, plays an important role in the etiology of CDH. Haploinsufficiency of this region might not be completely penetrant. We still propose *NR2F2* to be the most likely candidate, but disruption of a regulatory element or other gene in this region cannot be excluded as a cause of CDH.

M. Klaassens,[1,2] D. Tibboel,[1]
B. A. Oostra,[2] and A. de Klein[2]
Departments of [1]Pediatric Surgery and [2]Clinical Genetics, Erasmus MC, Rotterdam, the Netherlands

Web Resources

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Address for correspondence and reprints: Dr. Annelies de Klein, Department of Clinical Genetics, Erasmus MC, Postbus 1738, Rotterdam, 3000 DR. E-mail: a.deklein@erasmusmc.nl

0002-9297/2005/7705-0018$15.00