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RESEARCH LETTER

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Cornelia de Lange syndrome and cancer: An open question

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To the Editor,

Cohesin is an evolutionarily conserved protein complex implicated in all biological processes involving chromatin and chromosomes, such as replication, recombination, repair, transcription, and chromatin remodeling. Somatic variants in cohesin genes are associated with several types of cancer (Di Nardo et al., 2022), whereas germline variants are responsible for a class of human rare diseases currently called disorders of transcriptional regulation (DTRs) (Izumi, 2016), previously known as "cohesinopathies." Cornelia de Lange syndrome (CdLS, OMIM #122470, #300590, #610759, #614701, #300882), with an estimated incidence of between 1:10,000 and 1:30,000 live births, is the most frequent among DTRs (Ramos et al., 2015). CdLS is a dominant condition characterized by multiple structural and physiological anomalies including microcephaly, facial dysmorphism, growth retardation, upper limb malformations, and neurodevelopmental delay (Kline et al., 2018). CdLS is caused by pathogenic variants in cohesin structural and regulatory genes, namely *NIPBL*, *SMC1A*, *SMC3*, *HDAC8*, *RAD21*, *BRD4*, and *ANKRD11* (Sarogni et al., 2020). CdLS cell lines show genome instability (Cukrov et al., 2018; Pallotta et al., 2021) and CdLS-causative variants confer sensitivity to genotoxic treatments, suggesting that cohesin pathogenic variants impair DNA repair (Revenkova et al., 2009; Vrouwe et al., 2007). Variants in genes responsible for maintaining genome integrity are causative for human diseases such as Fanconi Anemia, Bloom syndrome, Werner syndrome, Ataxia Telangiectasia, and others, which are all characterized by cancer predisposition (Keijzers et al., 2017; Terabayashi & Hanada, 2018). Until now, no systematic study had been performed to investigate whether CdLS patients are predisposed to cancer. To gain new insight into the relationship between CdLS and cancer, we performed a systematic review of published literature listed in PubMed (https://pubmed.ncbi.nlm.nih.gov/). We manually checked 1267 manuscripts published from 1980 to 2022, as of August 2022. Moreover, the search was refined by using the strings "Cornelia de Lange syndrome and cancer," "Cornelia de Lange syndrome and Barrett's esophagus," Cornelia de Lange syndrome and Wilms tumor" as keywords search. In addition, we sent a questionnaire to the 10 main clinical groups and laboratories working on CdLS and five of them participated in this study. By these approaches, 17 manuscripts dealing with CdLS and cancer were found and 29 patients with clinical and/or molecular diagnosis

Maria M. Pallotta and Maddalena Di Nardo contributed equally to this work.

TABLE 1 CdLS patients with concomitant cancer development

Cancer type	Number of patients	CdLS-causative gene	Variant	Effect	Age of cancer diagnosis	References
Acute lymphoblastic leukemia	1	*NIPBL*	c.7977dupT	Premature truncation	8 years	Fazio et al. (2019)
Acute megakaryoblastic leukemia	1	*NIPBL*	c.6344–2A>G	Premature truncation	3 years	Vial et al. (2018)
Esophagus (premalignant Barrett's esophagus, adenocarcinoma)	15	Unknown				DuVall & Walden (1996); Kline et al. (2007); Luzzani et al. (2003); Macchini et al. (2010); Pei et al. (2000); Schrier et al. (2011)
Choroid plexus papilloma	1	Unknown				Chico-Ponce de León et al. (2015)
Endometrial carcinoma	1	Unknown				Tate et al. (2019)
Gastric cancer	1	Unknown				Schrier et al. (2011)
Intracranial germinoma	1	Unknown				Sato et al. (1986)
Lymphoma	1	Unknown				Schrier et al. (2011)
Liver haemangioendothelioma	1	Unknown				Maruiwa et al. (1988)
Pancreatic neuroendocrine/endometrial cancer	1	*NIPBL*	c.620 C>G	Premature truncation	27 years	Wright et al. (2022)
Sacrococcygeal teratoma	1	*NIPBL*	Exons 42–47 deletion	Amino acids deletion	20 weeks of gestation	Banait et al. (2015)
Suprasellar germinoma	1	Unknown				Sugita et al. (1986)
Wilms tumor	3	*NIPBL* Unknown	c.4920 G>A	Splice alteration	4 years	Charles et al. (1997); Maruiwa et al. (1988); Santoro et al. (2016)

Abbreviation: CdLS, Cornelia de Lange syndrome.

of CdLS were identified with concomitant cancer development (Table 1). Most cancers (15 of 29, 51.7%) were related to the esophagus. Most of them were Barrett's esophagus (13 of 15, BE). BE is a premalignant condition that occurs when stratified squamous-type mucosa of the lower esophagus is replaced by intestinal-type columnar mucosa. It is thought that most esophageal adenocarcinomas (EA), a lethal malignancy with poor survival, arise from underlying BE tissue. This notion is supported by the observation that two cases of EA were described (DuVall & Walden, 1996; Macchini et al., 2010). Furthermore, three patients developed Wilms tumor, two developed leukemia, and two patients developed endometrial carcinoma, one of which had associated pancreatic neuroendocrine cancer (Table 1). A molecular diagnosis was available for a few of the patients with cancer development. For these patients, all identified causative variants affect *NIPBL*. Their phenotype ranges from mild to severe, suggesting that no correlation exists between CdLS phenotype and cancer development. NIPBL, a 316 kDa protein, is essential to load cohesin onto chromatin in collaboration with its molecular partner, MAU2. In addition, it is necessary to stimulate cohesin's ATPase activity, for chromatin looping, and it is crucial for cohesin's ability to extrude DNA into loops (Davidson & Peters, 2021; Davidson et al., 2019; Kim et al., 2019). The five detected *NIPBL* pathogenic variants are unique to each condition (Table 1, Figure 1). The variant associated with acute megakaryoblastic leukemia maps in the acceptor splice site of intron 36, whereas a deletion of *NIPBL* gene was identified in a sacrococcygeal teratoma. The last three *NIPBL* pathogenic variants are two missense substitutions and an out-of-frame duplication, which were identified in Wilms tumor and pancreatic neuroendocrine cancer and in acute lymphoblastic leukemia, respectively. Most variants cause a predicted truncated protein that likely leads to a partial reduction in NIPBL production, resulting in haploinsufficiency.

The risk of developing BE and EA increases in presence of gastroesophageal reflux disease (GERD). GERD may be seen in a variety of congenital developmental syndromes, and it is the most frequent and severe gastrointestinal complication in CdLS (Kline et al., 2018). In particular, GERD is almost always present in patients with classic phenotype, that is, carrying *NIPBL* pathogenic variants (Huisman et al., 2017; Luzzani et al., 2003; Nizon et al., 2016). It has been suggested that untreated GERD or chronically unrecognized reflux, with the absence of obvious symptoms, may lead to BE over time (Kline et al., 2007). Though BE is reported in the general population overall with an age at onset over 60 years of age, its incidence in the CdLS cohort is higher than expected and it usually appears at an early age (Bonino & Sharma, 2006; DuVall & Walden, 1996; Kline et al., 2007; Luzzani et al., 2003).

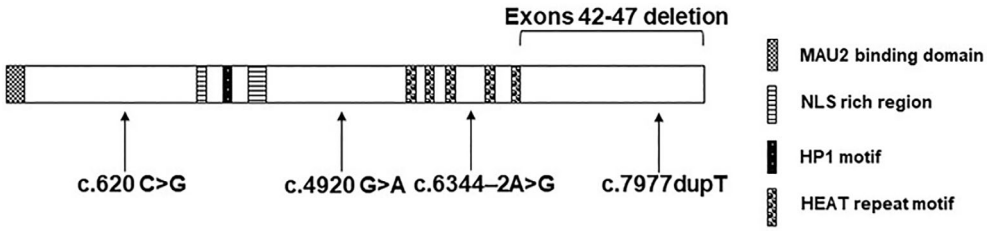

FIGURE 1 Overview of *NIPBL* variants identified in Cornelia de Lange syndrome patients with concomitant cancer development. *NIPBL* consists of 47 exons and the different domains of *NIPBL* are indicated: MAU2 interaction domain, HP1 interaction domain, nuclear localization signal domain (NLS) and HEAT domain consisting of five repeats. The pathogenic variants, c.620 C>G, c.4920 G>A, c.6344–2A>G, c.7977dupT, and exons 42–47 deletion, are distributed along the entire protein. The protein length is not in scale.

In some syndromes virtually all affected subjects develop a tumor, or associated tumors occur more frequently than in the general population (Postema et al., 2021). The present study indicates that there is no increased risk of cancer in patients with CdLS, although *NIPBL* variants may genetically predispose to early BE development in CdLS. This notion is intriguing since CdLS is caused by pathogenic variants in cohesin structural and regulatory genes, which are also associated with cancer development (Adane et al., 2021; Sarogni et al., 2019). It is still unclear why associated tumors occur with such highly variable frequency in malformation syndromes. Tumorigenesis occurs over the course of many years as a consequence of the accumulation of specific mutations. It is likely that further genetic changes are necessary for a fully malignant transformation, beyond cohesin mutations. The mutational combination of germinal variants of cohesin genes with somatic variants in cancer-prone genes could be related to specific tumors. In this regard, the identification of mutations and/or the gene expression dysregulation of cancer-prone genes in cells deriving from CdLS patients with concomitant cancer would support this notion. Some limitations do not allow us to draw a definitive conclusion. In fact, most CdLS patients are young, and reliable data for middle-aged and older individuals are not currently available. Further studies in larger populations need to be carried out in order to unravel the link between CdLS, cohesin complex, and cancer.

AUTHOR CONTRIBUTIONS

Maria M. Pallotta and Maddalena Di Nardo reviewed the literature and collected data, Juan Pie, Feliciano J. Ramos, Frank J. Kaiser, Ilaria Parenti, Raoul C. M. Hennekam, and Antonie D. Kline provided data, Antonio Musio took the main lead in writing the manuscript. All authors discussed the results and contributed to the final manuscript.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

Adane, B., Alexe, G., Seong, B. K. A., Lu, D., Hwang, E. E., Hnisz, D., Lareau, C. A., Ross, L., Lin, S., Dela Cruz, F. S., Richardson, M., Weintraub, A. S., Wang, S., Iniguez, A. B., Dharia, N. V., Conway, A. S., Robichaud, A. L., Tanenbaum, B., Krill-Burger, J. M., … Stegmaier, K. (2021). STAG2 loss rewires oncogenic and developmental programs to promote metastasis in Ewing sarcoma. *Cancer Cell*, *39*(6), 827–844.e10.

Banait, N., Fenton, A., & Splitt, M. (2015). Cornelia de Lange syndrome due to mosaic NIPBL mutation: antenatal presentation with sacrococcygeal teratoma. *BMJ Case Reports*, bcr2015211006. https://doi.org/10.1136/bcr-2015-211006

Bonino, J. A., & Sharma, P. (2006). Barrett's esophagus. *Current Opinion in Gastroenterology*, *22*(4), 406–411.

Charles, A. K., Porter, H. J., Sams, V., & Lunt, P. (1997). Nephrogenic rests and renal abnormalities in Brachmann-de Lange syndrome. *Pediatric Pathology and Laboratory Medicine*, *17*(2), 209–219.

Chico-Ponce de León, F., Gordillo-Domínguez, L. F., González-Carranza, V., Torres-García, S., García-Delgado, C., Sánchez-Boiso, A., Arenas-Huertero, F., Perezpeña-Diazconti, M., Eguía-Aguilar, P., Baqueiro-Hernández, C., Buenrostro-Márquez, G., Martínez-Rodríguez, S., Dhellemmes, P., & Castro-Sierra, E. (2014). Brachmann-Cornelia de Lange syndrome with a papilloma of the choroid plexus: analyses of molecular genetic characteristics of the patient and the tumor. A single-case study. *Child's Nervous System*, *31*(1), 141–146. https://doi.org/10.1007/s00381-014-2504-6

Cukrov, D., Newman, T. A. C., Leask, M., Leeke, B., Sarogni, P., Patimo, A., Kline, A. D., Krantz, I. D., Horsfield, J. A., & Musio, A. (2018). Antioxidant treatment ameliorates phenotypic features of SMC1A-mutated Cornelia de Lange syndrome in vitro and in vivo. *Human Molecular Genetics*, *27*(17), 3002–3011.

Davidson, I. F., Bauer, B., Goetz, D., Tang, W., Wutz, G., & Peters, J. M. (2019). DNA loop extrusion by human cohesin. *Science*, *366*(6471), 1338–1345.

Davidson, I. F., & Peters, J. M. (2021). Genome folding through loop extrusion by SMC complexes. *Nature Reviews Molecular Cell Biology*, *22*(7), 445–464.

Di Nardo, M., Pallotta, M. M., & Musio, A. (2022). The multifaceted roles of cohesin in cancer. *Journal of Experimental & Clinical Cancer Research*, *41*(1), 96.

DuVall, G. A., & Walden, D. T. (1996). Adenocarcinoma of the esophagus complicating Cornelia de Lange syndrome. *Journal of Clinical Gastroenterology*, *22*(2), 131–133.

Fazio, G., Massa, V., Grioni, A., Bystry, V., Rigamonti, S., Saitta, C., Galbiati, M., Rizzari, C., Consarino, C., Biondi, A., Selicorni, A., & Cazzaniga, G. (2019). First evidence of a paediatric patient with Cornelia de Lange syndrome with acute lymphoblastic leukaemia. *Journal of Clinical Pathology*, *72*(8), 558–561. https://doi.org/10.1136/jclinpath-2019-205707

Huisman, S., Mulder, P. A., Redeker, E., Bader, I., Bisgaard, A. M., Brooks, A., Cereda, A., Cinca, C., Clark, D., Cormier-Daire, V., Deardorff, M. A., Diderich, K., Elting, M., van Essen, A., FitzPatrick, D., Gervasini, C., Gillessen-Kaesbach, G., Girisha, K. M., Hilhorst-Hofstee, Y., … Hennekam, R. C. (2017). Phenotypes and genotypes in individuals with SMC1A variants. *American Journal of Medical Genetics. Part A*, *173*(8), 2108–2125.

Izumi, K. (2016). Disorders of transcriptional regulation: An emerging category of multiple malformation syndromes. *Molecular Syndromology*, *7*(5), 262–273.

Keijzers, G., Bakula, D., & Scheibye-Knudsen, M. (2017). Monogenic diseases of DNA repair. *The New England Journal of Medicine*, *377*(19), 1868–1876.

Kim, Y., Shi, Z., Zhang, H., Finkelstein, I. J., & Yu, H. (2019). Human cohesin compacts DNA by loop extrusion. *Science*, *366*(6471), 1345–1349.

Kline, A. D., Grados, M., Sponseller, P., Levy, H. P., Blagowidow, N., Schoedel, C., Rampolla, J., Clemens, D. K., Krantz, I., Kimball, A., Pichard, C., & Tuchman, D. (2007). Natural history of aging in Cornelia de Lange syndrome. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *145C*(3), 248–260.

Kline, A. D., Moss, J. F., Selicorni, A., Bisgaard, A. M., Deardorff, M. A., Gillett, P. M., Ishman, S. L., Kerr, L. M., Levin, A. V., Mulder, P. A., Ramos, F. J., Wierzba, J., Ajmone, P. F., Axtell, D., Blagowidow, N., Cereda, A., Costantino, A., Cormier-Daire, V., FitzPatrick, D., … Hennekam, R. C. (2018). Diagnosis and management of Cornelia de Lange syndrome: First international consensus statement. *Nature Reviews. Genetics*, *19*(10), 649–666.

Luzzani, S., Macchini, F., Valade, A., Milani, D., & Selicorni, A. (2003). Gastroesophageal reflux and Cornelia de Lange syndrome: Typical and atypical symptoms. *American Journal of Medical Genetics. Part A*, *119A*(3), 283–287.

Macchini, F., Fava, G., Selicorni, A., Torricelli, M., Leva, E., & Valade, A. (2010). Barrett's esophagus and Cornelia de Lange syndrome. *Acta Paediatrica*, *99*(9), 1407–1410.

Maruiwa, M., Nakamura, Y., Motomura, K., Murakami, T., Kojiro, M., Kato, M., Morimatsu, M., Fukuda, S., & Hashimoto, T. (1988). Cornelia de Lange syndrome associated with Wilms' tumour and infantile haemangioendothelioma of the liver: report of two autopsy cases. *Virchows Archiv A Pathological Anatomy and Histopathology*, *413*(5), 463–468. https://doi.org/10.1007/bf00716995

Nizon, M., Henry, M., Michot, C., Baumann, C., Bazin, A., Bessieres, B., Blesson, S., Cordier-Alex, M. P., David, A., Delahaye-Duriez, A., Delezoide, A. L., Dieux-Coeslier, A., Doco-Fenzy, M., Faivre, L., Goldenberg, A., Layet, V., Loget, P., Marlin, S., Martinovic, J., … Cormier-Daire, V. (2016). A series of 38 novel germline and somatic mutations of NIPBL in Cornelia de Lange syndrome. *Clinical Genetics*, *89*(5), 584–589.

Pallotta, M. M., Di Nardo, M., Sarogni, P., Krantz, I. D., & Musio, A. (2021). Disease-associated c-MYC downregulation in human disorders of transcriptional regulation. *Human Molecular Genetics*, *31*, 1599–1609.

Pei, R. S., Lin, C. C., Mak, S. C., Chi, C. S., & Chou, G. (2000). Barrett's esophagus in a child with de Lange syndrome: report of one case. *Acta Paediatrica Taiwanica*, *41*(3), 155–157.

Postema, F. A. M., Oosterwijk, J. C., & Hennekam, R. C. (2021). Genetic control of tumor development in malformation syndromes. *American Journal of Medical Genetics. Part A*, *185*(2), 324–335.

Ramos, F. J., Puisac, B., Baquero-Montoya, C., Gil-Rodriguez, M. C., Bueno, I., Deardorff, M. A., Hennekam, R. C., Kaiser, F. J., Krantz, I. D., Musio, A., Selicorni, A., FitzPatrick, D. R., & Pie, J. (2015). Clinical utility gene card for: Cornelia de Lange syndrome. *European Journal of Human Genetics*, *23*(10), 1431.

Revenkova, E., Focarelli, M. L., Susani, L., Paulis, M., Bassi, M. T., Mannini, L., Frattini, A., Delia, D., Krantz, I., Vezzoni, P., Jessberger, R., & Musio, A. (2009). Cornelia de Lange syndrome mutations in SMC1A or SMC3 affect binding to DNA. *Human Molecular Genetics*, *18*(3), 418–427.

Santoro, C., Apicella, A., Casale, F., La Manna, A., Di Martino, M., Di Pinto, D., Indolfi, C., & Perrotta, S. (2016). Unusual association of non-anaplastic Wilms tumor and Cornelia de Lange syndrome: case report. *BMC Cancer*, *16*(1). https://doi.org/10.1186/s12885-016-2402-2

Sarogni, P., Pallotta, M. M., & Musio, A. (2020). Cornelia de Lange syndrome: From molecular diagnosis to therapeutic approach. *Journal of Medical Genetics*, *57*(5), 289–295.

Sarogni, P., Palumbo, O., Servadio, A., Astigiano, S., D'Alessio, B., Gatti, V., Cukrov, D., Baldari, S., Pallotta, M. M., Aretini, P., Dell'Orletta, F., Soddu, S., Carella, M., Toietta, G., Barbieri, O., Fontanini, G., & Musio, A. (2019). Overexpression of the cohesin-core subunit SMC1A contributes to colorectal cancer development. *Journal of Experimental & Clinical Cancer Research*, *38*(1), 108.

Sato, A., Kajita, A., Sugita, K., Izumi, T., Fukuyama, Y., Funata, N., & Okeda, R. (1986). Cornelia de Lange syndrome with intracranial germinoma. *Acta Pathologica Japonica*, *36*(1), 143–149.

Schrier, S. A., Sherer, I., Deardorff, M. A., Clark, D., Audette, L., Gillis, L., Kline, A. D., Ernst, L., Loomes, K., Krantz, I. D., & Jackson, L. G. (2011). Causes of death and autopsy findings in a large study cohort of individuals with Cornelia de Lange syndrome and review of the literature. *American Journal of Medical Genetics Part A*, *155*(12), 3007–3024. https://doi.org/10.1002/ajmg.a.34329

Sugita, K., Izumi, T., Yamaguchi, K., Fukuyama, Y., Sato, A., & Kajita, A. (1986). Cornelia de lange syndrome associated with a suprasellar germinoma. *Brain and Development*, *8*(5), 541–546. https://doi.org/10.1016/s0387-7604(86)80101-2

Tate, K., Yoshida, H., Ishikawa, M., Shimizu, H., Uehara, T., & Kato, T. (2019). Endometrial carcinoma with an unusual morphology in a patient with cornelia de lange syndrome. *International Journal of Gynecological Pathology*, *38*(4), 340–345. https://doi.org/10.1097/pgp.0000000000000504

Terabayashi, T., & Hanada, K. (2018). Genome instability syndromes caused by impaired DNA repair and aberrant DNA damage responses. *Cell Biology and Toxicology*, *34*(5), 337–350.

Vial, Y., Lachenaud, J., Verloes, A., Besnard, M., Fenneteau, O., Lainey, E., Marceau-Renaut, A., Preudhomme, C., Baruchel, A., Cavé, H., & Drunat, S. (2018). Down syndrome-like acute megakaryoblastic leukemia in a patient with Cornelia de Lange syndrome. *Haematologica*, *103*(6), e274–e276. https://doi.org/10.3324/haematol.2017.178590

Vrouwe, M. G., Elghalbzouri-Maghrani, E., Meijers, M., Schouten, P., Godthelp, B. C., Bhuiyan, Z. A., Redeker, E. J., Mannens, M. M., Mullenders, L. H., Pastink, A., & Darroudi, F. (2007). Increased DNA damage sensitivity of Cornelia de Lange syndrome cells: Evidence for impaired recombinational repair. *Human Molecular Genetics*, *16*(12), 1478–1487.

Wright, M. J., Kline, A. D., Wolfgang, C. L., & Javed, A. A. (2022). Pancreatic neuroendocrine tumor in a 27-year-old patient with Cornelia de Lange syndrome: A case report. *Annals of Pancreatic Cancer*, *5*, 5.

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