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CLINICAL REPORT

Mutation profiling in South African patients with Cornelia de Lange syndrome phenotype

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Abstract

Background: Cornelia de Lange Syndrome (CdLS) presents with a variable multi-systemic phenotype and pathogenic variants have been identified in five main genes. This condition has been understudied in African populations with little phenotypic and molecular information available.

Methods and Results: We present a cohort of 14 patients with clinical features suggestive of CdLS. Clinical phenotyping was carried out and cases were classified according to the international consensus criteria. According to this criteria, nine patients had classical CdLS, one had non-classical CdLS and four presented with a phenotype that suggested molecular testing for CdLS. Each patient underwent mutation profiling using a targeted next generation sequencing panel of 18 genes comprising known and suspected CdLS causal genes. Of the 14 patients tested, pathogenic and likely pathogenic variants were identified in nine: eight variants in the *NIPBL* gene and one in the *STAG1* gene.

Conclusions: We present the first molecular data for a cohort of South African patients with CdLS. Eight of the nine variants identified were in the *NIPBL* gene, the most commonly involved gene in cases of CdLS. This is also the first report of a patient of African ancestry presenting with *STAG1*-related CdLS.

1 | INTRODUCTION

Cornelia de Lange syndrome (CdLS) presents with a highly variable clinical phenotype. Features range from mild to severe developmental delay and physical abnormalities including craniofacial and limb malformations (Kline et al., 2018). The diverse nature of this phenotype can partly be attributed to inter- and intragenic variability (Mannini et al., 2013). Pathogenic variants have been identified predominantly in five genes: *NIPBL*, *RAD21*, *SMC1A*, *SMC3* and *HDAC8*, accounting for approximately 70% of reported CdLS cases. It is not clear if this molecular profile can be expected in all population groups because the literature is dominated

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by genotype and phenotype information from North American and European population groups. More recently, mutations have also been identified in *BRD4, STAG1, KMT2A, SETD5, HDAC2, MAU2, ZMYND11, MED13L, PHIP, EP300* and *ANKRD11* (Aoi et al., 2019; Cucco et al., 2020; Olley et al., 2018; Parenti et al., 2020; Wagner et al., 2019). These are said to cause either CdLS or a CdLS-like phenotype. Additionally, a number of differential diagnoses exist for CdLS, which could account for the patients without an identified mutation. Although cases of these conditions can be clinically distinguished from classic cases of CdLS, a wide phenotypic spectrum exists, which make milder or atypical cases of CdLS more difficult to differentiate from other conditions.

The mutations identified in these genes have predominantly been small (<50 bp) variants, including frameshift, nonsense or splice site mutations, which are predicted to lead to truncated proteins or a loss of gene function (Mannini et al., 2013). Upon carrying out a phenotype–genotype correlation study Mannini et al. (2013), concluded that truncating mutations in *NIPBL* result in a more severe phenotype, while missense and in-frame deletions in *NIPBL* and *SMC1A/SMC3* result in a milder form of the disease. Interestingly, pathogenic missense mutations and in-frame deletions in the HEAT domain of the NIPBL protein result in a severe phenotype, suggesting that gene, mutation type and protein domain are all important in phenotype determination (Mannini et al., 2013).

To date, no molecular studies have been carried out on South African patients suspected to have CdLS, and only a few clinical case reports have previously been published on patients with African ancestry (Begeman & Duggan, 1976; Cicoria, 1974; Dowsett et al., 2019; Ptacek et al., 1963). Here, we report the phenotype and first molecular findings for a South African cohort of patients with CdLS or CdLS-like phenotype.

2 | PHENOTYPIC FINDINGS

The cohort for the study comprised 14 patients presenting with clinical features suggestive of a CdLS or a CdLS-like clinical phenotype. Patients were recruited from genetic clinics that were held in Johannesburg and Pretoria, Gauteng, South Africa. Patients were eligible to participate if they had been assessed by a medical geneticist who determined their clinical phenotype to be suggestive of CdLS.

Each patient underwent additional clinical phenotyping at the time of recruitment using a clinical tick sheet; the main clinical findings and scoring according to the international criteria are described in the table found in Table S1. Based on these criteria, 9/14 patients would be classified as class 1: having classical CdLS (patients 1, 3, 5, 7, 8, 9, 10, 12 and 14); 1/14 would be classified as class 2: having a non-classical form of CdLS (patient 11) and 4/14 patients would be classified as class 3: indicate evidence for molecular testing for CdLS (patients 2, 4, 6, 13). In some of these, in particular those classified as class 3, the score may have been due to insufficient clinical information having been recorded at recruitment. The most common phenotypic features in this cohort were long/curly eyelashes (14/14), microcephaly and synophrys (13/14), short stature (12/14), postnatal growth retardation, depressed nasal bridge and hirsutism (11/14). Consent for photographs was obtained from three of the 14 patients in this cohort (Figure 1).

3 | MOLECULAR FINDINGS

The 14 patients underwent mutation screening by means of a targeted gene panel. The genes included in this panel consisted of known causal genes, suspected causal genes and genes accounting for some common differential diagnoses (*NIPBL, RAD21, SMC1A, SMC3, HDAC8, PDS5A, PDS5B, SCC4, STAG1, AFF4, ANKRD11, ESCO2, KMT2A, TAF1, TAF6, SETD5, SMARCB1* and *ARID1B*). DNA was isolated from a peripheral blood sample. Library preparation was carried out using the Agilent SureSelect system, and sequencing was carried out on an Illumina MiSeq platform.

Pathogenetic or likely pathogenic variants were identified in nine of the 14 patients (Table 1) resulting in a yield of 64%. Eight of these were identified in the *NIPBL* gene and one was identified in the *STAG1* gene. Six variants were classified as pathogenic and three were classified as likely pathogenic according to the ACMG/AMP guidelines (Richards et al., 2015).

4 | DISCUSSION

Four small deletions were identified within the *NIPBL* gene in the present cohort, all predicted to cause a premature termination that should lead to a loss of gene function (patients 1, 3, 10 and 11). Three of these patients presented with classical CdLS while one (patient 11) presented with non-classical CdLS according to the guidelines established by Kline et al. (2018). The *NIPBL* c.2479_2480delAG variant, identified in patient 3, occurred in exon 10, one of the largest exons in the *NIPBL* gene. This variant was previously reported as pathogenic on the ClinVar database (ClinVar ID: 96336). The duplication identified in patient 13 (*NIPBL* c.7831dupA, p.Arg612LysfsTer20) results in a truncation in the NIPBL protein sequence similar to the small deletions, and this patient was classified as having a class 3 phenotype indicative of molecular testing according

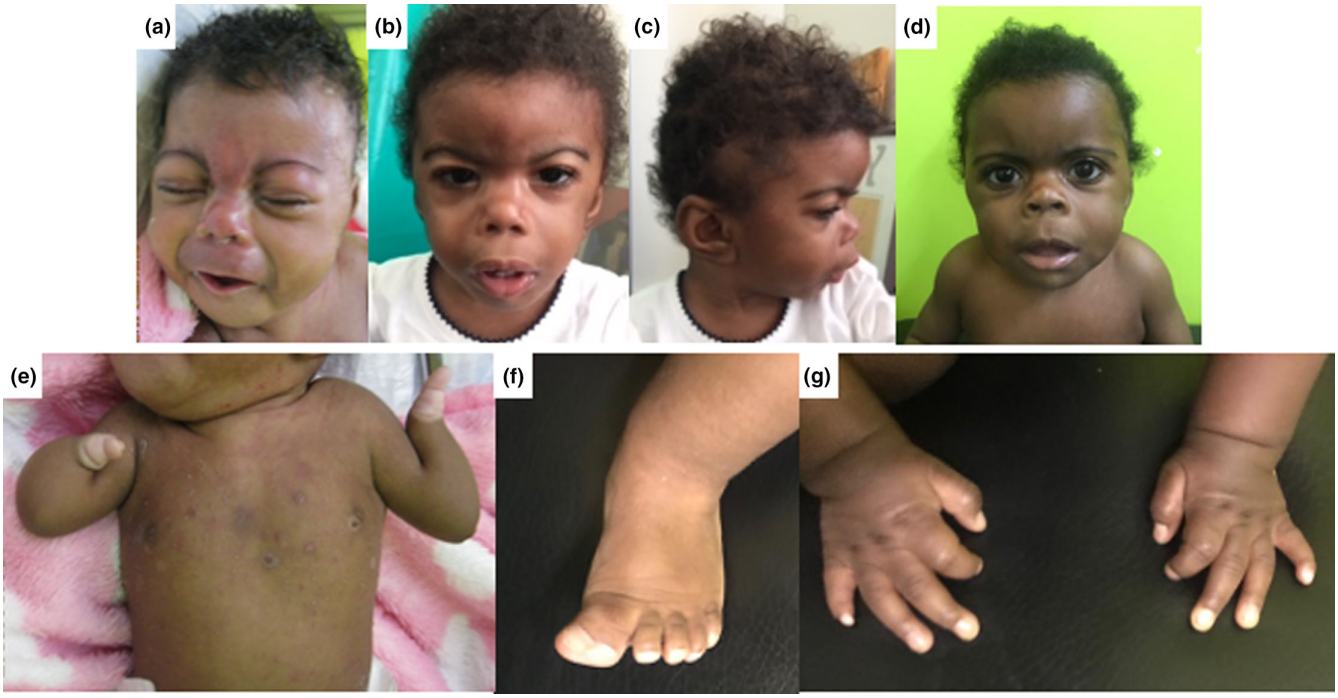

FIGURE 1 Images showing the phenotype of a subset of patients who tested positive for a *NIPBL* disease-causing mutation. Images a-d depicts the facial features of patients 1 (a); 9 (b, c) and 14 (d) with microcephaly, synophrys, depressed nasal bridge and long smooth philtrum being present in each. Images e–g depict the limb reduction defects in patients 1 (e) and 14 (f) showing a duplicated hallux and (g) brachdactyly and proximally inserted thumbs.

to the international guidelines (Kline et al., 2018). An essential splice site pathogenic variant was identified in patient 9 (*NIPBL* c.6955–2 A>C). The patient presented with a classical CdLS phenotype.

Two missense variants were identified within the cohort, in patient 4 (*NIPBL* c.3932G>A, p.Cys1311Tyr) and 14 (*NIPBL* c.5465A>G, p.Asp1822Gly), and both were classified as likely pathogenic. The described phenotype of patient 4 is not classical but does score as a class 3 according to the international guidelines (Kline et al., 2018). This is in accordance with multiple genotype–phenotype studies that conclude that missense mutations correlate to a milder CdLS phenotype (Mannini et al., 2013). Another missense variant that occurs within the same amino acid residue (*NIPBL* c.3931T>C, p.Cys1311Arg) as this variant observed in patient 4 has previously been classified as pathogenic (Tonkin et al., 2004). The patient reported by Tonkin et al. (2004) also presented with a mild CdLS phenotype similar to patient 4 in the present cohort.

The missense variant identified in patient 14 (*NIPBL* c.5465A>G, p.Asp1822Gly) falls within the HEAT domain of the NIPBL protein, which is usually associated with a more severe phenotype (Mannini et al., 2013). This agrees with the classical/class 1 phenotype observed in this patient. This variant has been identified previously and was reported as likely pathogenic on ClinVar (ClinVar ID: 159152).

A nonsense variant in the *STAG1* gene (*STAG1* c.17T>G, p.Leu6Ter) was observed in patient 6. This is the first report of a *STAG1* mutation in an African patient to date. Patient 6 was clinically diagnosed with CdLS and presented with a non-classical phenotype of CdLS. According to the findings described by Lehalle et al. (2017) and Yuan et al. (2019) patients with mutations in the *STAG1* gene present with an overlapping phenotype with CdLS but without the characteristic craniofacial features. Some of the overlapping features between patient 6 and other patients with a *STAG1* mutation include: intellectual disability, failure to thrive, low set and dysmorphic ears, clinodactyly, high nasal bridge, long curly eyelashes, hirsutism, deep set eyes and a depressed/broad nasal bridge. On review, the patient does not appear to have the broad nasal tip, downturned corners of the mouth, long and smooth philtrum, or the narrow vermillion border typical of CdLS. This is an emerging neurodevelopmental syndrome and it is unclear at this point whether *STAG1* mutations will fall within the spectrum of genes implicated in CdLS or whether they will be classified as a new cohesinopathy.

The genetic cause of ~30% of the patients with a clinical diagnosis of CdLS remains unknown after mutation screening in the *NIPBL*, *SMC1A*, *HDAC8*, *RAD21* and *SMC3* genes (Braunholz et al., 2015). We identified (likely) pathogenic variants in 9 out of the 14 patients screened, which corresponds to a detection rate of 64%. Five of the patients who had a pathogenic variant identified were classified as class 1, one was classified as class 2 and three were classified as class 3.

TABLE 1 Molecular findings and ACMG/AMP classification of the mutations identified in this study—all mutations were observed in a heterozygous state.

Patient number	Variant	HGVS nomenclature	Consequence	ACMG/AMP criteria applied	ACMG/AMP classification	ClinVar ID
1	*NIPBL* c.6027_6030delGTTC p.(Leu2009PhefsTer6)	NM_133433.4:c.6027_6030del	Frameshift	PVS1, PM2, PM6	Pathogenic	1697850[a]
3	*NIPBL* c.2479_2480delAG p.(Arg827GlyfsTer2)	NM_133433.4:c.2479_2480del	Frameshift	PVS1, PM2, PP5	Pathogenic	96336
4	*NIPBL* c.3932G>A p.(Cys1311Tyr)	NM_133433.4:c.3932G>A	Missense	PM5, PM6, PP3, PM2	Likely pathogenic	1697856[a]
6	*STAG1* c.17T>G p.(Leu6Ter)	NM_005862.3:c.17T>G	Nonsense	PVS1, PM6, PM2	Likely pathogenic	2578395[a]
9	*NIPBL* c.6955-2A>C	NC_000005.9:g.37051879A>C NM_133433.4:c.6955-2A>C	Canonical splice site	PVS1, PM2, PM6	Pathogenic	1697857[a]
10	*NIPBL* c.5639_5642delCAAC p.(Pro1880HisfsTer10)	NM_133433.4:c.5639_5642del	Frameshift	PVS1, PM2, PM6	Pathogenic	1697858[a]
11	*NIPBL* c.302_311delCAAGGAGTCC p.(Ala101ValfsTer18)	NM_133433.4:c.302_311del	Frameshift	PVS1, PM6, PM2	Pathogenic	1697859[a]
13	*NIPBL* c.7831dupA p.(Arg612LysfsTer20)	NM_133433.4:c.7834dup	Frameshift	PVS1, PM2, PP5	Pathogenic	1697860
14	*NIPBL* c.5465A>G p.(Asp1822Gly)	NM_133433.4:c.5465A>G	Missense	PM5, PM1, PP3, PM2, PP5	Likely pathogenic	159152

[a]First ClinVar entry for this variant generated in this study.

A limitation of this study was that copy number variant analysis was not performed. By including this type of test, the diagnostic yield may increase. Although the gene panel approach was appropriate for this cohort, exome- and genome level investigations are still warranted owing to the number of cases without a causative mutation in one of the known genes. This could potentially reveal other genes involved in CdLS and other disorders with CdLS-like features in African cohorts.

5 | CONCLUSION

This is the largest African cohort to undergo molecular studies for CdLS to date. The data collected from this study are not only in agreement with the literature already published on CdLS but will also add valuable African dysmorphology data to better direct testing for this condition in future (Hurst & Robin, 2020).

Our study has produced a baseline mutation profile of CdLS in South African patients, with mutations in *NIPBL* the most common, as elsewhere. An accurate, timely molecular diagnosis has a profound impact on the patient and their family which extends beyond improved clinical management (Joseph et al., 2016). This is particularly relevant in the South African State healthcare system where the diagnostic odyssey for rare disease patients is exacerbated by a significant lack of resources and access to specialist clinical care. A genetics-first approach could address this issue and improve diagnostic services for patients with CdLS phenotypes in Africa (Arnett et al., 2021). This is also the first case of a *STAG1*-related cohesinopathy in a patient of African ancestry and may indicate that mutations in other genes less commonly implicated in CdLS and its related phenotypes may be identified in the future within African populations.

AUTHOR CONTRIBUTIONS

Heather Seymour, Patracia Nevondwe and Maria Mudau designed the gene panel, performed the experiments and analyzed the data under the guidance of Nadia Carstens. Candice Feben, Careni Spencer, Engela Honey and Amanda Krause recruited and performed phenotyping on the patients. Candice Feben, Careni Spencer, Robyn Kerr, Zane Lombard, Nadia Carstens and Amanda Krause designed and supervised the study. Heather Seymour and Nadia Carstens wrote the manuscript, and all authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The variants described here were submitted to ClinVar and can be viewed under Organization ID 508172 or the ClinVar IDs recorded in Table 1. Data available on reasonable request from the corresponding author.

ETHICS STATEMENT

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M170761) and the Research Ethics Committee of the University of Pretoria (80/2018). Informed consent has been obtained from the patients and/or parents.

PATIENT CONSENT FOR PUBLICATION

Obtained using the guidelines developed by the Dysmorphology Subcommittee of the Clinical Practice Committee, American College of Medical Genetics (PMID: 11339658).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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