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## Clinical Letter

### Diagnostic next generation sequencing in neonatal erythroderma

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Dear Editors,

The list of differential diagnoses of neonatal erythroderma (NE) is long. Ichthyoses, immunodeficiencies and infections are the most frequent underlying causes while metabolic disorders, drugs and more rare causes such as atopic dermatitis, psoriasis and seborrheic dermatitis are the less frequent [1, 2]. Neonatal erythroderma is often accompanied by a collodion membrane. A correct diagnostic approach to neonatal erythroderma is difficult based on the clinical presentation alone. To our knowledge, this is the first report on the application of next generation sequencing (NGS) in a cohort of patients with NE as main inclusion criterium. This study revealed a variety of genetic diagnoses. Next generation sequencing was proven to be particularly valuable for detecting life-threatening disorders that are difficult to clinically recognize in the early stages in NE patients without a collodion.

To obtain a definite genetic diagnosis in 23 patients, NGS was performed prospectively (September 1, 2014–January 1, 2018) in 15 patients at birth and retrospectively in eight patients born before September 1, 2014 in which a definite diagnosis was not present yet. The NGS panel was regularly updated during the study. The last version of the NGS panel as present on January 1, 2018 was run on patients without a genetic diagnosis earlier in the study. Non-genetic diagnoses such as infections or drug-use were less plausible based on history, laboratory results and clinical characteristics. Informed consent was obtained from parents of the patients along with approval of the medical ethics committee.

A targeted NGS panel of 60 genes associated with neonatal erythroderma and collodion membrane was used (see Table S1 in the online supplement), based on extensive literature search. The gene panel comprised uniquely mapped coding regions of 60 genes from the built genome GRCh37/hg19 ([www.ncbi.nlm.nih.gov/assembly/2758](http://www.ncbi.nlm.nih.gov/assembly/2758)) as well as 50 bp flanks into intronic regions. The DNA was enriched using the SureSelect XT Target or Human All Exon v5 kit (Agilent Technologies B. V. Netherlands) and sequenced using the HiSeq2500 system on rapid run mode (Illumina, Netherlands) at a mean target depth of 100x. The reads were aligned to hg19 using BWA (BWA-MEM v0.7.5a); variants

were called using the GATK haplotype caller (v2.7-2). The correlation between the diagnosis and clinical presentation (erythroderma or collodion) was calculated using the odds ratio and chi-squared tests.

A genetic diagnosis was found in 70 % of the cases (16/23) (Table 1); 60 % in the prospective cohorts (9/15) and 88 % (7/8) in the retrospective cohorts, respectively. A collodion membrane was present in 14/23 patients (61 %) of which 12 (86 %) had an underlying type of ichthyosis. Mutations linked to ichthyoses were found in the genes: *TGM1* (4/14), *ALOX12B* (3/14), *PNPLA1*, *ABCA12*, *ALOXE3*, *KRT10* and *ALDH3A2* [1/14 each]. In two collodion patients, no definite genetic diagnosis could be made; variants of unknown significance (VUS) were found in *BTBD* and *ALOX12B*, which were unlikely to have contributed to the clinical presentation. In patients without a collodion membrane, an underlying diagnosis was made in 67 % of cases (6/9), with an underlying type of ichthyosis in 44 % (4/9). In two patients, mutations were found in *IL36RN* and *SPINK5*, defining: Deficiency of Interleukin-36 Receptor Antagonist (DITRA) and Netherton syndrome, respectively. In two patients, no pathogenic mutations could be found, and in one patient, a VUS in *C5* was found, which was unlikely to have contributed to the clinical presentation.

The obtained diagnostic yield of 60 % in the prospective group was higher compared to, for instance, NGS panels for other heterogeneous entities like primary immunodeficiencies (33–48 %) [3], hereditary anemias (45.8 %) [4] and monogenic liver diseases (17 %) [5]. This confirms the strong genetic etiology of neonatal erythroderma. Along with the genetic heterogeneity this demonstrates the relevance of performing NGS for NE.

Additionally, our results confirm that a form of ichthyosis is the most likely diagnosis in cases of NE accompanied by a collodion. In contrast, in patients without a collodion membrane, other diagnoses are more likely (OR 6, chi-squared: 0.03). In the patient with DITRA, the diagnosis resulted in a significant therapeutic change later on [6]. Since results are limited to a Dutch population, genetic differences are possible in other populations [7, 8]. A limitation in this study relates to the use of a targeted NGS panel: since causal genes, such as *SULT2B1*, were not known as related to ichthyosis and thus not included during the study, a higher yield in diagnostic outcome in our study population could have been achieved if open exome (WES; Whole Exome Sequencing) analysis had been performed. On the other hand, the patients lacking a genetic diagnosis might not have had a genetic basis for their NE.

In conclusion, this study underscores the relevance of the use of NGS to establish a diagnosis for patients with NE. In the absence of a collodion membrane, causes other than the relatively non-life-threatening ichthyoses, such as

**Table 1** Next generation sequencing outcome of (likely) pathogenic mutations in nine prospective (1–9) and eight retrospective (10–17) patients with neonatal erythroderma.

Patient	Collodion	Gene	Variant description	Protein	Status of mutation	Type of mutation	Clinical significance*	Diagnosis (inheritance)
1	Yes	ABCA12	NM_173076: c.609T>G	p.Trp2031Gly	Hom	Missense	Likely pathogenic	HI (AR)
2	Yes	ALOX12B	NM_001139.3: c.1463G>A	p.Arg488His	Hom	Missense	Pathogenic	SHCB (AR)
3	Yes	ALOX12B	NM_001139: c.1642C>T NM_001139: c.1349G>A	p.Arg548Trp p.Gly450Glu	Het Het	Missense Missense	Pathogenic VUS	LI* (AR)
4	Yes	ALOX12B	NM_001139: c.467_470dup NM_001139: c.1562A>G	p.His158fs p.Tyr521Cys	Het Het	Frameshift Missense	Pathogenic Pathogenic	ARCI (AR)
5	No	ALOXE3	NM_001165960.1: c.2285C>T	p.Pro762Leu	Hom	Missense	Pathogenic	ARCI (AR)
6	Yes	PNPLA1	NM_173676.2: c.488C>T	p.Pro163Leu	Hom	Missense	Pathogenic	ARCI (AR)
7	Yes	TGM1	NM_00359.3: c.877-2A>G	p.(?); (?)	Hom	Splice site	Pathogenic	ARCI (AR)
8	Yes	TGM1	NM_00359.3: c.968G>A	p.Arg323Gln	Hom	Missense	Likely pathogenic	SHCB (AR)
9	Yes	TGM1	NM_00359.3: c.857G>A; 857G>A	p.Arg286Gln	Hom	Missense	Likely pathogenic	SHCB (AR)
10	No	ABCA12	NM_173076: c.6440dup NM_173076.2: c.3180-6T>G	p.Gln2149fs p.(?)	Het Het	Frameshift Splice site	Pathogenic VUS	ARCI* (AR)
11	Yes	ALDH3A2	NM_000382.3: c.1297_1298del	p.Glu433fs	Hom	Frameshift	Pathogenic	SLS (AR)
12	Yes	ALOXE3	NM_001165960.1: c.1642T>C NM_001165960.1: c.2285C>T	p.Cys548Arg p.Pro762Leu	Het Het	Missense Missense	Likely pathogenic Pathogenic	ARCI (AR)
13	No	IL36RN	NM_173170.1: c.80T>C	p.Leu27Pro	Hom	Missense	Pathogenic	DITRA (AR)
14	Yes	KRT10	NM_000421.3: c.1468_1473delinsAGTTCCG	p.Gly490fs	Het	Frameshift	Likely pathogenic	Ichthyosis with confetti (AD)
15	No	SPINK5	NM_006846.3: c.649C>T NM_006846.3: c.724G>T	p.Arg217 *p.Glu242*	Het Het	Nonsense Nonsense	Likely Pathogenic	NS (AR)
16	Yes	TGM1	NM_00359.3: c.1472C>T	p.Thr491Met	Het	Missense	Pathogenic	LI* (AR)
17	No	DSG1	NM_001942.2: c.382C>T	p.Arg128*	Het	Nonsense	Pathogenic	SAM* (AR)

Abbr.: AD, autosomal dominant; AR, autosomal recessive; ARCI, autosomal recessive congenital ichthyosis; DITRA, deficiency of interleukin receptor-36 antagonist; Het, Heterozygous; HI, Harlequin ichthyosis; Hom, Homozygous; LI, Lamellar ichthyosis; N/A, Not Available; NGS, Next Generation Sequencing; NS, Netherton syndrome; SAM, severe dermatitis, atopic diathesis and metabolic syndrome; SHCB, self-healing collodion baby; SLS, Sjögren-Larsson syndrome.  
\*According to AMCG guidelines 2015 [10]; \*\*Clinically conform diagnosis; \*\*\*No genetic diagnosis; \*\*\*\*2<sup>nd</sup> mutation (large deletion) was detected elsewhere, but not with current NGS method.

immunodeficiencies, metabolic disorders or DITRA, are possible. In newborns, these might be detected through genetic evaluations at an earlier stage than onset of clinical signs. Immunodeficiencies such as Omenn syndrome can be present with congenital erythroderma but without typical associated systemic symptoms such as a failure to thrive, infections and fever [9]. These life-threatening conditions require immediate and adequate therapy, which can be facilitated by rapid NGS diagnostics. This is now feasible for newborns with NE.

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## Conflict of interest

None.

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