MALTA (MYH9 Associated Elastin Aggregation) Syndrome: Germline Variants in MYH9 Cause Rare Sweat Duct Proliferations and Irregular Elastin Aggregations

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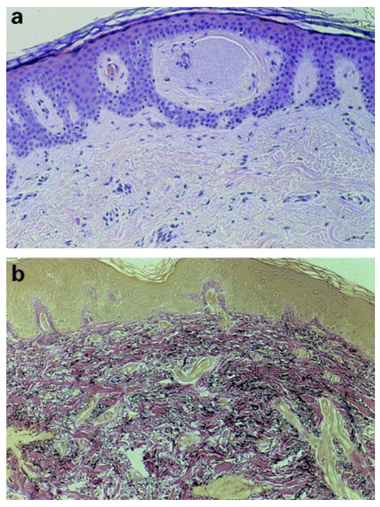
INTRODUCTION

Syndromes with overlapping histopathological features pose challenges for diagnosis and treatment. These include:

- 1961: **Nicolau-Balus syndrome** was characterized by the irregular distribution of elastin fibers, where individuals with the phenotype had benign cutaneous lesions, including atrophodermia vermiculata, multiple syringomata, and milia (Nicolau and Balus, 1961)
- 1981: **Rombo syndrome** was described with a similar phenotype (Michaëlsson et al.,1981), with elastin distribution in these cases appearing like “swathes of steel wool” in some areas of the dermis (van Steensel et al., 2001)
- 2010: Several cases of the same elastin distribution but with the additional feature of **sweat duct proliferations** were described, with similar morphology to **microcystic adnexal carcinoma (MAC)** but no malignant behaviour. (Schaller et al.. 2010)

These conditions may shed light on the common genetic pathology of sweat duct tumours.

In this study, five families with clinical and histopathological features that show similarities to Nicolau-Balus and Rombo syndromes where microcystic adnexal carcinoma (MAC)-like ductal proliferations were present, suggesting a common genetic basis. This study thus elucidates this possible common genetic basis.



(a) Photomicrograph showing clumping of hyaline-like material directly below the epidermis and in the papillary dermis, a lymphocytic infiltrate around proliferating vessels, and hyalinization of collagen (haematoxylin and eosin; original magnification ×100).
(b) A highly irregular distribution of elastin is seen throughout the dermis, with clumping in some areas (van Giesson stain; original magnification ×40).
(van Steensel et al., 2001)

OBJECTIVES

This study aims to explore if the Nicolau-Balus and Rombo syndromes share a common pathology and have shared genetics.

METHODOLOGY

6 participants from 3 families (Family 1,2,3) diagnosed with sweat duct proliferations resembling microcystic adnexal carcinoma (MAC).

6 participants from 2 families (Family 4,5) diagnosed with Rombo syndrome

Germline whole-exome sequencing data analyzed using an optimized in-house variant call file generation pipeline to generate and identify 732 rare protein-affecting variants of MYH9.

MYH9 codes for a non-muscle myosin, NMMIIA, which harbored protein-affecting variants that segregated with phenotype in each family.

2 more affected and 2 unaffected members from Family 3 additionally selected for further segregation analysis by Sanger sequencing.

Targeted Sanger sequencing for MYH9 variants

Hence, the term MALTA (MYH9 Associated eLasTin Aggregation) syndrome is proposed to reflect the common underlying genetic basis of these diseases.

Protein structure of NMMIIA analyzed using Mechismo (mechanistic protein structure prediction tool) to assess the MYH9 variants identified in the context of key functional elements of the protein.
4 of the 5 identified variants clustered in the NMIIA myosin head.

Using Mechismo to analyze 42 variants linked to MYH9-related platelet disorder (MRPD) to try to understand how variants of MYH9 could cause two distinct phenotypes (MALTA vs MRPD).

Two tumors from case 2-1(Nicolau-Balus syndrome) stained for NMMIIA. Tumor DNA was extracted from formalin-fixed paraffin-embedded material and underwent somatic exome sequencing. 245 protein-affecting somatic variants that reside within known oncogenic genes were analyzed.

Table 1. MALTA Families Analyzed and *MYH9* Variants Identified in Each Family

Family	Proband Gender[1]	Initial Diagnosis of Proband	Dermatological Features in Proband: MAC-Like Ductal Proliferations	Irregular Elastic Fiber Distribution	Atrophodermia Vermiculata	Syringomas	Proband Platelet Count and Volume	Total Number of Family Members Sequenced[2]	*MYH9* Variant	Amino Acid Change	Variant Effect Predictor Consequence	Segregation	Variant Identification
1	Male (9)	MAC-like ductal proliferations	Yes	Yes	Yes	Yes	Normal	1 (0)	c.2012C>T	p.C671Y	Missense variant	Sporadic	Exome sequencing
2	Female (9)	Nicolau-Balus syndrome/MAC-like ductal proliferations	Yes	Yes	Yes	Yes	Normal	2 (0)	c.1767_1769delITCCI	p.M589_D590delinsI	Inframe deletion	Not available	Exome sequencing
3	Male (17)	MAC-like ductal proliferations	Yes	Yes	Yes	Yes	Normal	7 (2)	c.5492_5499delGGCTGCCT	p.Q1831Lfs*20	Frameshift deletion	Yes	Exome sequencing
4	Male (7)	Rombo syndrome	No	Yes	Yes	ND	Unknown	5 (1)	c.706G>T	p.G236C	Missense variant	Yes	Targeted sequencing
5	Male (24)	Rombo syndrome	Yes	Yes	Yes	No	Unknown	1 (0)	c.694_695delinsAA	p.S232N	Inframe indel	Sporadic	Targeted sequencing

Abbreviations: MAC, microcystic adnexal carcinoma; MALTA, *MYH9* associated elastin aggregation; ND, not determined.
[1]Age at diagnosis.
[2]Number of unaffected.

ACKNOWLEDGEMENTS

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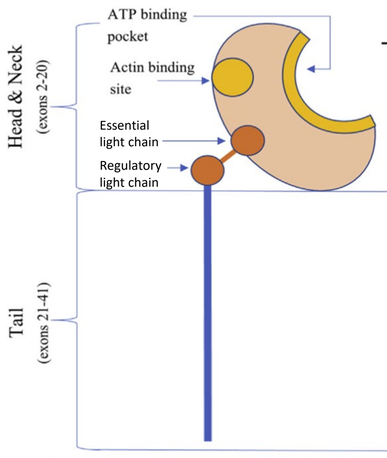
RESULTS

- MYH9 variants may lead to MALTA phenotype by affecting key binding sites which may influence the kinetic activity or binding affinity of myosin to its substrates. None of these variants had previously been observed in the phase 3 of the 1000 Genomes Project or the Genome Aggregation Database.

Family - associated Variant identified	Effect	Location
1 - Missense variant c.2012C>T	predicted to be deleterious to protein function	within ATP-binding domain
2 - Inframe deletion c.1767_1769delTCC	unknown	affects actin-binding region
3 - Frameshift variant	loss of key acetylation and phosphorylation sites	at the end of the tail domain
4 - Missense variant c.706G>T Single amino acid change	predicted to be deleterious to protein function	within ATP-binding domain
5 - Variant c.694_695delinsAA Single amino acid change	affects interaction affinity of ADP to myosin, predicted to be deleterious to protein function. [consistent with RaptorX (online binding site prediction tool to predict ligand interaction sites)]	magnesium-binding domain that facilitates ADP release in myosin motors

- MYH9-related platelet disorder (MRPD) is associated with MYH9 variants, causing enlarged platelets. It is not associated with dermatological findings. In contrast to MALTA, most MRPD-associated variants were located in the myosin tail (25 of 42 variants [60%]), and were predicted to affect the binding regions for calcium-binding proteins and the formation of heterodimers with myosins.

Germline *MYH9* Variants Cause Irregular Elastin



	Exon	MALTA variants	MRPD variants
Head & Neck (exons 2-20)	2	0	11
	6	1	0
	7	1	0
	11	0	2
	15	1	0
	16	1	0
	17	0	4
Tail (exons 21-41)	21	0	1
	22	0	1
	25	0	1
	26	0	1
	27	0	1
	28	0	1
	31	0	8
	32	0	1
	33	0	2
	39	1*	1
	40	0	1
	41	0	6*

All variants are missense or inframe except those indicated by *, which are protein truncating.

MALTA variants and MYH9-related platelet disorder variants mapped to the exons of MYH9 non-muscle myosin. Differential distribution of variants according to MALTA and MRPD is seen across the head and tail. In the tail region, more MRPD variants are found compared to MALTA variants.

- 3 of 5 cases of MALTA exhibited no MRPD features (history of hearing impairment or bleeding irregularities, platelet size, platelet counts). Thus, different pathogenic variants in MYH9 could affect different tissue types and result in two distinct phenotypes as seen in MALTA and MRPD.
- In skin fibroblasts, expression of NMMIIA increases during dermal wound healing and scar tissue remodeling, during which extracellular matrix components including elastin are secreted. NMMIIA has been shown to increase in expression as the elasticity of the dermis decreases. Possibly explaining the proliferative phenotype in MALTA syndrome.
- Staining in the Nicolau-Balus syndrome tumor was ubiquitous in healthy skin and in other benign adnexal lesions. One identified variant from exome sequencing was a heterozygous missense variant in the receptor tyrosine kinase proto-oncogene RET, predicted to be deleterious and damaging in SIFT and PolyPhen respectively.

CONCLUSIONS

- Genetic analysis has shown that Nicolau-Balus syndrome, Rombo syndrome, and similar syndromes involving MAC-like ductal proliferations are one disorder with a common genetic aetiology; the authors propose for these disorders to be referred to as MALTA (MYH9 Associated eLasTin Aggregation Syndrome).
- The phenotype of MALTA syndrome may be explained by the role of NMMIIA (encoded by MYH9) found in fibroblasts which contribute to dermal wound healing and scar tissue remodelling.
- Despite similar genetic aetiologies, the features of MALTA syndrome *differ significantly* from **other MYH9-related disorders** including MRPD, with no overlapping phenotype.
- Staining of tumours for NMMIIA compared to healthy skin and benign lesions was ubiquitous. The role of nonmuscle myosins (affected by variants in MYH9) in tumorigenesis provides an avenue for future exploration.

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