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DOI:

[10.1016/j.ejmg.2018.09.003](https://doi.org/10.1016/j.ejmg.2018.09.003)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Pei, Y., Beaman, G. M., Mansfield, D., Clayton-smith, J., Stewart, M., & Newman, W. G. (2018). Clinical and genetic heterogeneity in Melkersson-Rosenthal Syndrome. *European journal of medical genetics*.
<https://doi.org/10.1016/j.ejmg.2018.09.003>

Published in:

European journal of medical genetics

Citing this paper

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Accepted Manuscript

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PII: S1769-7212(18)30394-X

DOI: [10.1016/j.ejmg.2018.09.003](https://doi.org/10.1016/j.ejmg.2018.09.003)

Reference: EJMG 3536

To appear in: *European Journal of Medical Genetics*

Received Date: 27 June 2018

Revised Date: 29 August 2018

Accepted Date: 9 September 2018

Please cite this article as: Y. Pei, G.M. Beaman, D. Mansfield, J. Clayton-Smith, M. Stewart, W.G. Newman, Clinical and genetic heterogeneity in Melkersson-Rosenthal Syndrome, *European Journal of Medical Genetics* (2018), doi: 10.1016/j.ejmg.2018.09.003.

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Clinical and genetic heterogeneity in Melkersson-Rosenthal Syndrome

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Keywords: facial nerve palsy, *FATP1*; fissured tongue; Melkersson Rosenthal syndrome, orofacial swelling, *SLC27A1*.

Abstract

Melkersson Rosenthal syndrome (MRS) is a rare autosomal dominantly inherited neurocutaneous syndrome characterized by a triad of facial (seventh cranial) nerve palsy, recurrent orofacial swelling and fissuring of the tongue. A recent report implicated a heterozygous missense variant in *SLC27A1* (*FATP1*) as the cause of this condition in members of an affected Chinese family. We undertook Sanger sequencing of this gene in 14 affected unrelated individuals affected by MRS. We did not detect any putative pathogenic variants. Our data indicates that there is both clinical and genetic heterogeneity in this condition and that the causative gene remains to be identified for the majority of cases.

1. Introduction

Melkersson-Rosenthal Syndrome (MRS, MIM155900) is a rare disorder characterised by a triad of clinical features, including recurrent facial nerve palsy, episodic orofacial swelling, and fissuring of the tongue (lingua plicata) (Melkersson, 1928; Rosenthal, 1931). Biopsy of the lip or tongue reveals non-caseating granuloma in affected individuals. There is marked variability in clinical presentation with the majority of affected individuals not manifesting all three features (Elias et al., 2013). Furthermore, there is intra- and inter-familial variability in the age of onset, frequency of inflammatory episodes and response to steroid treatment (Elias et al., 2013). The diagnosis is often made in a single individual in a family, but male to male vertical transmission is described consistent with an autosomal dominant inheritance pattern (Lygidakis et al., 1979). There is important clinical overlap with orofacial granulomatosis and oral Crohn's disease, both disorders characterised by non-caseating granulomata, but without concomitant facial nerve palsy or tongue fissuring (Wehl and Rauchenzauner 2018).

Through an exome sequencing approach in a single large Han Chinese family affected by MRS, Xu et al. (2017) reported a heterozygous missense variant in *SLC27A1* as the most likely causative variant. The proband presented with the diagnostic triad of a right-sided recurrent facial palsy, a fissured tongue and edema of her lower lip and cheek. The mother of the proband was considered affected on the basis that she had a fissured tongue without facial palsy or swelling. The uncle of the patient was unaffected and sequenced as a control. A heterozygous variant, c.68>G in *SLC27A1*, predicted to result in a missense substitution p.Pro23Arg, was identified in the two affected individuals, and not in the unaffected uncle or 200 healthy controls. *SLC27A1* encodes fatty acid transport protein 1 (FATP1) (Xu et al., 2016). The wild type and variant were expressed in human embryonic kidney cells (HEK293), resulting in a reduction in FATP1 levels in cells transfected with the variant and reduced long chain fatty acid (LCFA) uptake.

We therefore undertook a study to determine if novel or very rare variants in *SLC27A1* were present and could result in MRS in our cohort of affected individuals.

2. Patients and methods

Individuals were ascertained on the basis of the presence of the clinical features associated with a diagnosis of MRS: orofacial swelling, facial palsy and a fissured tongue. Ethical approval was obtained from the NHS (11/H1003/3) and from the University of Manchester. Each individual provided written informed consent to participate in the study.

Oligonucleotide primers were designed to amplify all 12 exons of *SLC27A1* (details available on request). Sanger sequencing was performed using the BigDye Terminator v3.1 kit (Life Technologies, CA, USA) according to manufacturer's instructions and resolved on an ABI3730 sequencer (Life Technologies, CA, USA). Results were analysed using SeqScape v2.5 (Life Technologies, CA, USA).

3. Results

We ascertained 14 individuals who had a minimum of two criteria – orofacial swelling, tongue fissuring, and facial nerve palsy (Table 1). Only five individuals had the full triad of features. In seven of the 14 affected individuals, there was a fissured tongue. Two individuals without orofacial swelling had a positive family history of facial palsy and fissured tongue. Four families had a history in at least one first-degree relative of two or more diagnostic features. Twelve (~85%) of the 14 affected individuals were female. The affected individuals came from six different countries. The age of onset (first episode) ranged from 7 to 58 years for orofacial swelling and 3 to 58 years for facial palsy. No individual had a history of other granuloma-related problems, notably sarcoidosis or inflammatory bowel disease.

No rare (minor allele frequency <2%) or novel coding variants in *SLC27A1* were identified in any of the cases.

4. Discussion

Our data indicate that variants in *SLC27A1* do not account for the majority of cases of MRS and support a concept of genetic heterogeneity. It is possible, but unlikely, that copy number or non-coding variants, not assessed by this analysis, affecting *SLC27A1* expression or function could result in the MRS phenotype in some of our cases. Notably in the control exome sequence database EXAC (<http://exac.broadinstitute.org>) of approximately 60,000 individuals, there is no skewing of the numbers of observed versus expected missense or loss of function variants, suggesting that *SLC27A1* tolerates variants in this gene and that they are not more likely to be associated with inherited disorders.

Our small cohort is similar to previous series in that there is a female preponderance (Elias et al., 2013), suggesting that hormonal influences may be relevant triggers for episodes of orofacial swelling or facial palsy. There is phenotypic variability with a wide spectrum at age of onset and presence of the key clinical features, which may indicate genetic heterogeneity or certainly genetic modifiers of clinical presentation. In contrast to our cohort, in other series affected individuals have described a number of co-morbidities (Elias et al 2013). The episodic nature of the condition with resolution between flares shares similarities with some cardiac or neurological disorders due to channelopathies or periodic auto-inflammatory disorders. The majority of these disorders are autosomal dominant and often due to activating mutations. Therefore, they are tractable for inhibitory therapeutic approaches. This extrapolation informs the prioritisation of variants for future gene discovery studies in MRS and provides stimulus to undertake this work.

Acknowledgments

We thank the patients and their families. The work was supported by funding from the Dowager Countess Eleanor Peel Trust and Manchester NIHR Biomedical Research Centre.

Conflict of Interest

The authors have no conflict of interest to declare.

ACCEPTED MANUSCRIPT

References

- Elias, M.K., Mateen, F.J., Weiler, C.R., 2013. The Melkersson–Rosenthal syndrome: a retrospective study of biopsied cases. *J. Neurol.* 260 (1),138–143.
- Lygidakis, C., Tsakanikas, C., Ilias, A., Vassilopoulos, D. 1979. Melkersson-Rosenthal's syndrome in four generations. *Clin Genet.*15(2), 189-192.
- Melkersson, E., 1928. Ett fall av recidiverande facialis pares i samband med ett angioneurotiskt ödem. *Hygiea* 90, 737–741.
- Rosenthal, C.1931. Klinisch-erbbiologischer Beitrag zur Konstitutionspathologie. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, 131(1), 475-501.
- Wehl, G., Rauchenzauner, M., 2018. A systematic review of the literature of the three related disease entities cheilitis granulomatosa, orofacial granulomatosis and_Melkersson_–Rosenthal_syndrome. *Curr Pediatr Rev.* May 14. (epub ahead of print)
- Xu, X.G., Guan, L.P., Lv,Y., et al., 2017. Exome sequencing identifies FATP1 mutation in Melkersson–Rosenthal syndrome. *J. Eur. Acad. Dermatol. Venereol.* 31(5), e230-e232.

Table 1

Clinical presentation for each MRS proband

Individual	Sex	Origin	Family history	Facial Palsy			Facial Swelling including lips, orbits, cheeks		Fissured Tongue	Treatment
				Age of onset (years)	Location	Recurrent	Age of onset (years)	Recurrent		
P1	F	UK	-	15	L	Y	15	Y	N	Steroid
P2	F	USA	-	20s	L	Y	20s	Y	Y	Steroid
P3	M	Serbia	-	58	U	N	58	Y	N	Steroid
P4	M	Spain	-	35	B	Y	35	Y	Y	Steroid
P5	F	UK	-	20s	R	N	7	Y	N	Steroid, Antihistamine
P6	F	Netherlands	-	12	B	Y	10	Y	N	Steroid
P7	F	Poland	-	14	B	Y	29	Y	N	Steroid
P8	F	UK	-	4	B	Y	20	Y	N	Steroid
P9	F	UK	-	8	B	Y	18	N	Y	Steroid
P10	F	UK	-	3	B	Y	27	Y	Y	Steroid
P11	F	UK	+	20s	B	Y	N/A	N/A	Y	No
P12	F	UK	+	12	B	Y	N/A	N/A	Y	Acyclovir
P13	F	UK	+	36	U	Y	16	Y	Y	Steroid
P14	F	UK	+	37	B	Y	37	Y	N	No

This table summarises the clinical features for ten singletons (P1 – P10), and the probands of four familial cases (P11 – P14).

F = female; M = male; U = unilateral; B = bilateral; R = right side; L = left side; Y = present; N = not present; N/A = not applicable.